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Content

Assessing Efficacy Of Neuroaid In Improving Functional Outcome In Intracranial Haemorrhage And Traumatic Brain Injury

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Abstract

Introduction and Objective

NeuroAiD, a combination of natural products, is used to improve recovery after ischemic stroke. Its neurorestorative properties in preclinical model of traumatic brain injury (TBI) makes it attractive for treatment of brain injuries. We aimed to evaluate the safety and potential efficacy of NeuroAiD in brain injuries in the real-world setting.

Materials and Methods

The NeuroAiD Safe Treatment (NeST) Registry (clinicaltrials.gov NCT02536079) is a registry that provides information on use and safety of NeuroAiD in clinical practice. We analysed anonymized information of TBI and intracerebral haemorrhage (ICH) patients in the NeST Registry (www.neuroaid.com/en/nest/main/index). Patients who consented are prospectively entered using online forms for baseline and follow-ups. Data collected include demographics, diagnosis, medical history, modified Rankin Score (mRS), Glasgow Coma Scale (GCS), National Institute of Health Stroke Scale (NIHSS), compliance and side effects.

Results

Seventy-two subjects from Malaysia were included in the NeST registry. 51 with ICH (mean age 58.65±13.96 years; female 18) and 21 with TBI (mean age 38.24±15.42 years; female 4). Median GCS for ICH patients were 15(range 3-15) at baseline, 15 (3-15) at month (M) 1, 15 (3-15) at M2 and 15 (1-15) at M3. Median NIHSS for TBI patients were 10 (0-33) at baseline, 6(0-31) at M1, 5(0-29) at M2 and 4.5 (0-28) at M3. mRS improved over time for both TBI and ICH patients (figures). One patient with Sjogren's reported side effect (skin rash/lip ulcer) at day 35 of NeuroAiD intake deemed unrelated to the treatment.

Conclusion

NeuroAiD was safe in TBI and ICH patients with improved overall functional, neurological and cognitive measures.

Keywords: NeuroAiD, neurorestorative, traumatic brain injury, intracranial haemorrhage, safety

1.0 Introduction

Following brain injuries, a cascade of injury which results from mechanical disruption of haematoma leading to neuronal and glial ischaemia, oedema, and cell necrosis. Products released from haematoma cause the release of oxygen free radicals and inflammatory chemicals leading to further insult [1, 2]. After a few days, clot resolution will take place and neurological function may recover, which may not be complete. The recovery process, involves resolution of clot, reduction of the acute injury, neuroplasticity of surviving neurons, and possibly neurogenesis [3]. The brain can regenerate and restore the loss neuronal circuits following a traumatic insult. However, the homeostatic balance of antioxidants and toxic reactive free radicals are impaired, resulting in secondary injury, which hinders recovery [4].

MLC601 (NeuroAiD I™) consists of 14 natural ingredients and MLC901 (NeuroAiD II™) is a combination of 9 herbal components are widely used in China and in many Asian and European countries. Both formulations are collectively referred as 'NeuroAiD' in this registry. NeuroAiD efficacy and safety are supported by preclinical and clinical studies. The neuroprotective and neuroproliferative properties of NeuroAiD have been extensively elucidated in in vitro and in vivo experiments using animal and cellular models of focal and global ischaemia as well as traumatic brain injury models.[5-9].

The clinical data on NeuroAiD are most well reported in stroke. Evidently, an international, multicentred, randomised placebo controlled clinical trial provided evidence of its benefits on the long-term functional outcome persisting overtime up to 18 months with an excellent safety profile [10,11]. More subjects on MLC601 improved to functional independence compared to placebo among subjects receiving persistent rehabilitation up to M3. The larger treatment effect of MLC601 was sustained over 2 years when MLC601 was combined with rehabilitation, suggesting MLC601 was beneficial and had sustained effects on neuro-repair processes after stroke [12]. A recently published pilot study with MLC901 (NeuroAiD ™ II), a simplified formulation of MLC601, has revealed significant improvements in complex attention (P = 0.04, d = 0.6) and executive functioning (P = 0.04, d = 0.4) at 6 months in the MLC901 group compared with controls[13].

Since 2001 when it was marketed in China, there have been minimal serious side effects reported to date with the use of NeuroAiD. The common side effects reported from NeuroAiD were mostly mild and transient. Excellent clinical safety has been demonstrated in published clinical trials which reported the more common adverse events (AEs) being gastrointestinal symptoms (nausea, vomiting, discomfort, diarrhoea, dry mouth), and headache [14-19] .Safety studies in humans have shown that NeuroAiD, given alone or combined with aspirin, had no effect on clotting and coagulation[18] .Furthermore, there was no effect on haematological, haemostatic and biochemical parameters, and/or ECG in normal patients and patients with stroke, even when started within 48 h of stroke onset [20-22].

The primary objective of NeuroAiD Safe Treatment (NeST) Registry is to evaluate the use and safety of NeuroAiD in the real-world setting. We hypothesized that this registry will be able to demonstrate the safety effects of NeuroAiD in the heterogenous group of patients who are actually taking open-label NeuroAiD.

2.0 Materials and Methods

2.1 Study Design

The NeuroAiD Safe Treatment (NeST) Registry (clinicaltrials.gov NCT02536079) is a product-specific and safety outcome registry [23]. Patient participation is entirely voluntary, and an agreement is obtained before participation (Figure 1). We analysed anonymized information of TBI and intracerebral haemorrhage (ICH) patients in the NeST Registry (www.neuroaid.com/en/nest/main/index) where the principal investigator has sole access to. Patients consented are prospectively entered using online forms for baseline and follow-ups. Data collected include demographics, diagnosis, medical history, modified Rankin Score (mRS), Glasgow Coma Scale (GCS), National Institute of Health Stroke Scale (NIHSS), compliance and side effects. The registry was approved by the Ethical Committee of Hospital University Kebangsaan Malaysia.

2.2 Participants and Procedure

The decision on the use of NeuroAiD is made following discussion between the participant and the physician and only then will the option of the participation in the registry be considered. Inclusion criteria were: (i) male or female; (ii) any age; (iii) any patient who is taking or has been prescribed NeuroAiD for any duration as judged by the physician and/or the participant (iv) diagnosed with intracerebral haemorrhage or traumatic brain injury at any time at point of admission, (v) patient consented to be included in the registry and allows retrieval and analysis of data in accordance with local requirements. Exclusion criteria, on the other hand were: (i) unwillingness to participate; (ii) contraindication to NeuroAiD.

The assessments were done at baseline, followed by month-1, month-2 and month-3 using the National Institute of Health Stroke Scale (NIHSS), Glasgow Coma Scale (GCS), Modified Rankin Score (mRS) and Short Orientation Memory Concentration Test (SOMCT). Baseline assessments were performed in the ward, and the following monthly assessments were done during the neurosurgery clinic appointment, supervised by the principal investigator. Side effects are enquired during each follow-up and any side effects reported are recorded into the online database.

2.3 Treatment

Each 400 mg capsule of MLC601 contains nine herbal ingredients (extracts of *Radix astragali, Radix salvia miltiorrhizae, Radix paeoniae rubra, Rhizoma chuanxiong, Radix angelicae sinensis, Carthamus tinctorius, Prunus persica, Radix polygalae* and *Rhizoma acori tatarinowii*) and five non-herbal components (*Hirudo, Eupolyphaga seu steleophaga, Calculus bovis artifactus, Buthus martensii* and *Cornu saigae tataricae*). MLC901 contains only the herbal extracts. The product is available in capsule form and administered orally or the contents may be diluted in water and administrated via a gastric tube. The usual dosage is 4 capsules three times a day for MLC601 and 2 capsules three times a day for MLC901. The treatment duration is 3 months. The capsules should be kept sealed and stored below 30°C in a dry place until opened for administration.

NeuroAiD is manufactured according to applicable control measures that ensure the consistency and quality of the product from batch to batch and adhere to good manufacturing practice. The active ingredients and finished product are subjected to full quality control testing for safety.

All participants are allowed to receive standard care and other therapies and treatments, including (but not limited to) blood pressure control, rehabilitation and other types of care deemed appropriate and as prescribed by their physician. There is no restriction to the use of any other treatment as recommended by the treating physician, although they should be recorded in the database.

3.0 Results

Seventy-two subjects from Malaysia were included in the NeST registry. 51 with ICH (mean age 58.65±13.96 years; female 18) and 21 with TBI (mean age 38.24±15.42 years; female 4). mRS improved over time for both TBI and ICH patients (Figures 2a and 2b). Median GCS for ICH patients were 15(range 3-15) at baseline, 15 (3-15) at month (M) 1, 15 (3-15) at M2 and 15 (1-15) at M3. Median NIHSS for TBI patients were 10 (0-33) at baseline, 6(0-31) at M1, 5(0-29) at M2 and 4.5 (0-28) at M3 (Figure 3,4, and 5). NeuroAiD was safe in TBI and ICH patients with improved overall functional, neurological and cognitive measures.

For ICH, at the end of treatment (M3), there were 28 (54.9%) patients and for TBI, there were 14 patients (66.67%) that was follow-up. The reasons for drop out cases in both pathologies were due patients claiming that they have achieved full recovery or unspecified reasons hence defaulted further follow-ups. 6 patients (8.33%) passed away due to other causes deemed not related to the treatment of NeuroAiD. One patient with Sjogren's reported side effect (skin rash/lip ulcer) at day 35 of NeuroAiD intake deemed unrelated to the treatment.

4.0 Discussion

Our analyses demonstrate systematically the monitoring and evaluation of the safety of NeuroAiD in clinical practice, given in ICH and TBI in the heterogenous population. We limited the inclusion criteria to increase the generalisability of this current analysis. The analysis will supplant the acknowledged limitations of what is known about the safety profile of NeuroAiD at the time of authorization and conduct of systematic clinical trials in a homogenous population in a controlled setting. We will continue to include more patients in the future and hope to further solidify our hypothesis. There are still scope for consistency in quality and type of data included, addition of value to registry with more data pertaining to long-term and functional outcomes, more information on prehospital care and emergency medical services, and complications as well as other obstacles born out of logistics and other measures that augment the efficacy of registry data in clinical and epidemiologic translational researches[24].

Given the complexity in the recovery processes after brain injuries like ICH and TBI, there is an increasing evidence that strategy using combination therapies compromising more than one active ingredient can represent a better strategy[9]. NeuroAiD has a formula in which various ingredients act as neurorestorative agent targeting different pathways in the brain injury cascade. With so many failed neuroprotective trials[25], this herbal medicine could be a new promising neurorestorative therapy to support in the management of brain injuries.

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6.0 Appendix

Figure 1: Study Design

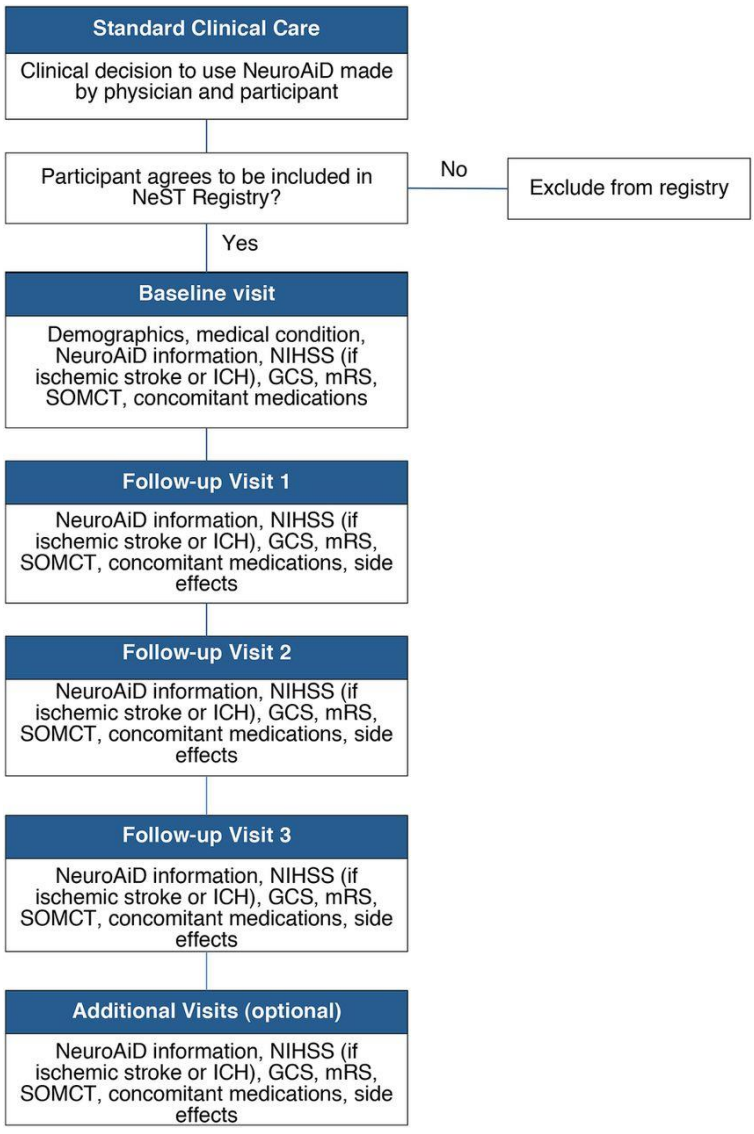
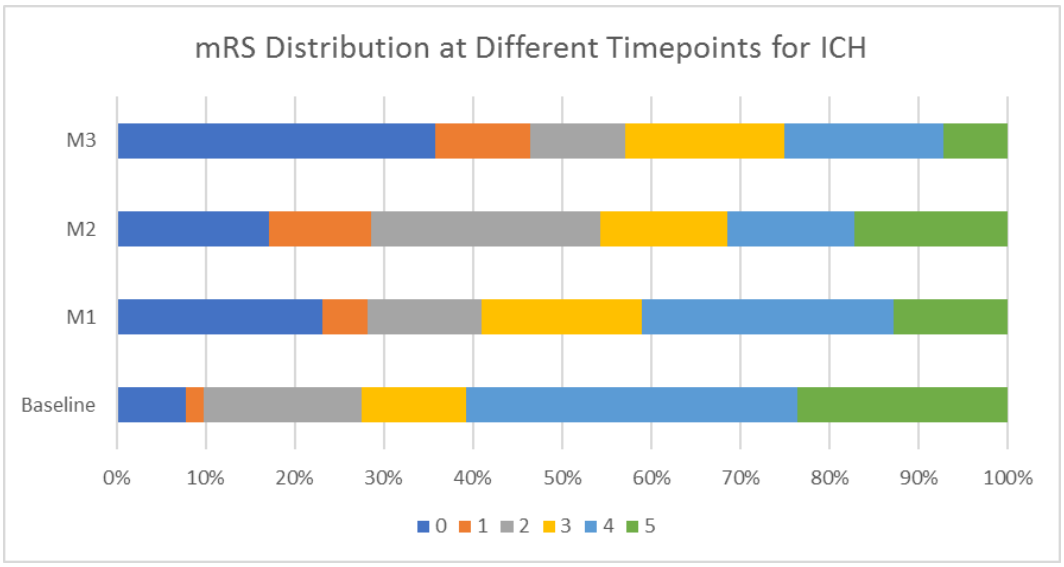


Figure 2: mRS Distribution at different timepoints for a. ICH and b. TBI

a.



b.

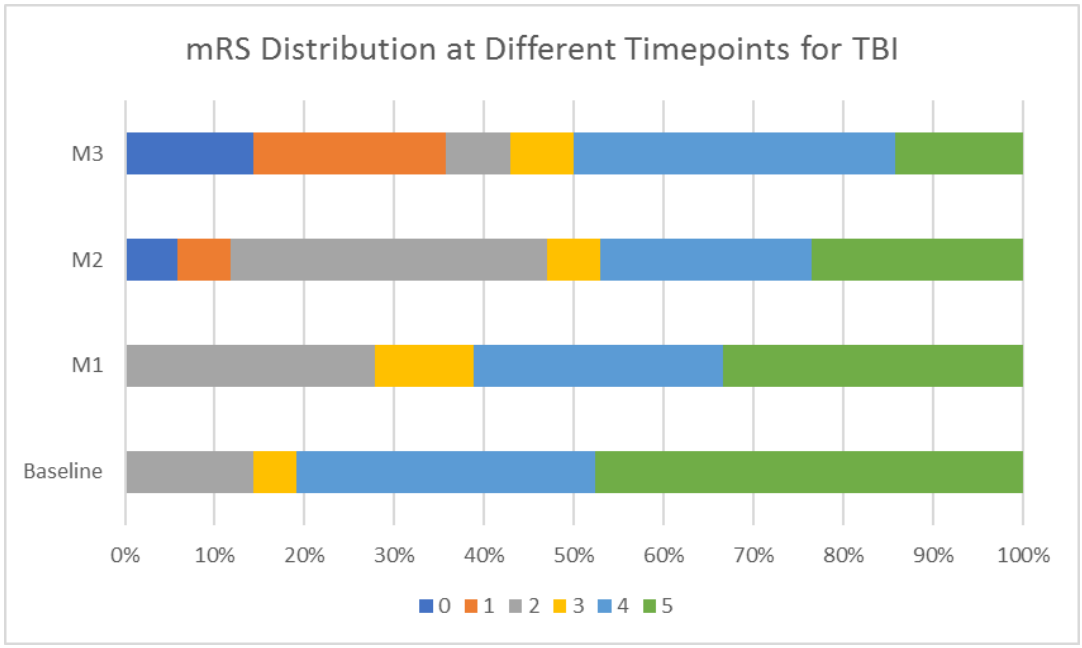
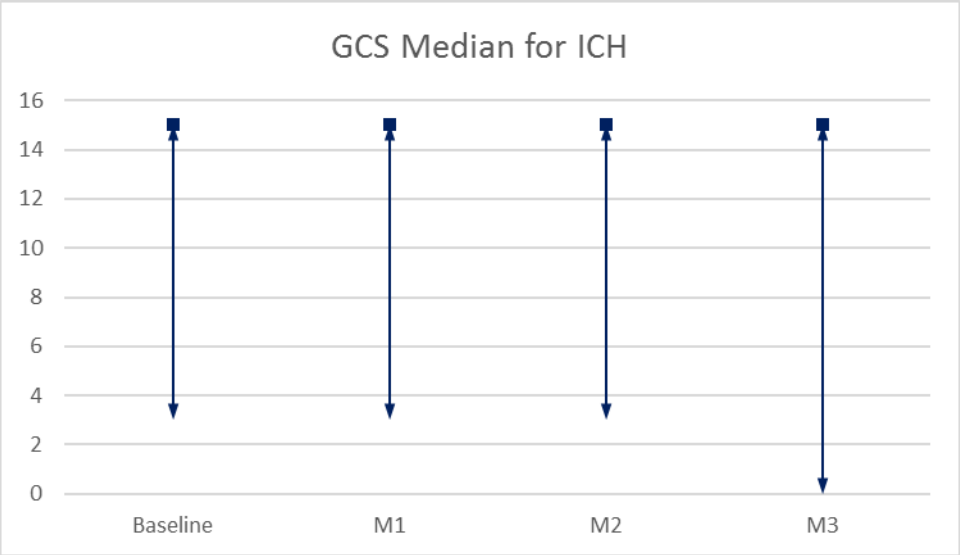


Figure 3. Median GCS a. ICH and b TBI

a.



b.

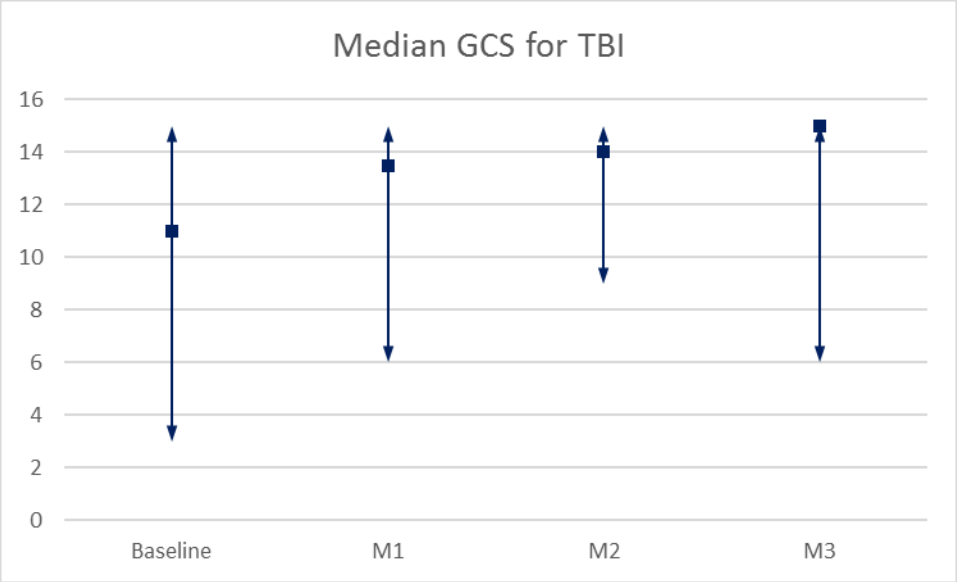
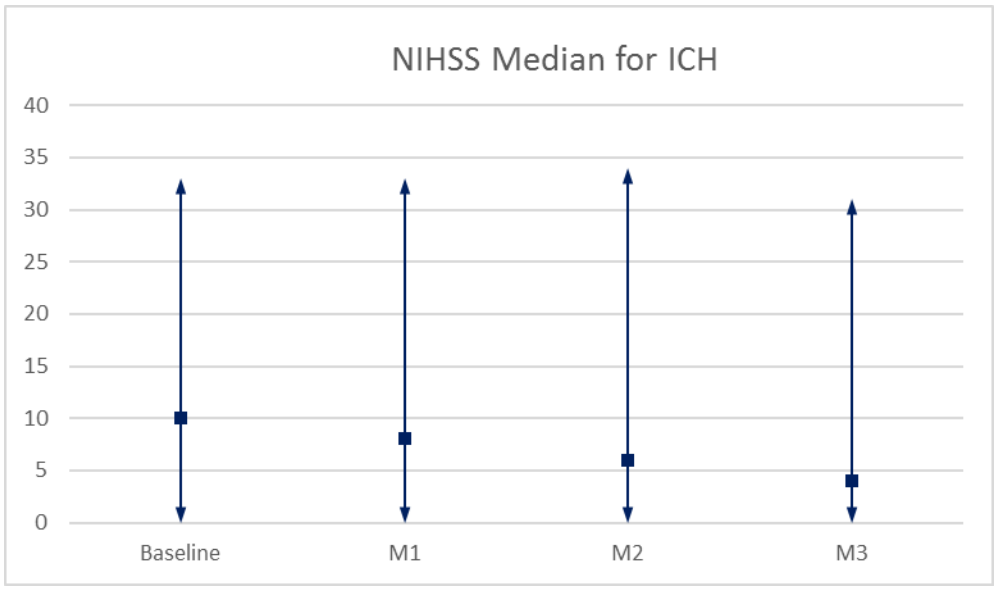


Figure 4. Median NIHSS a. ICH and b. TBI

a.



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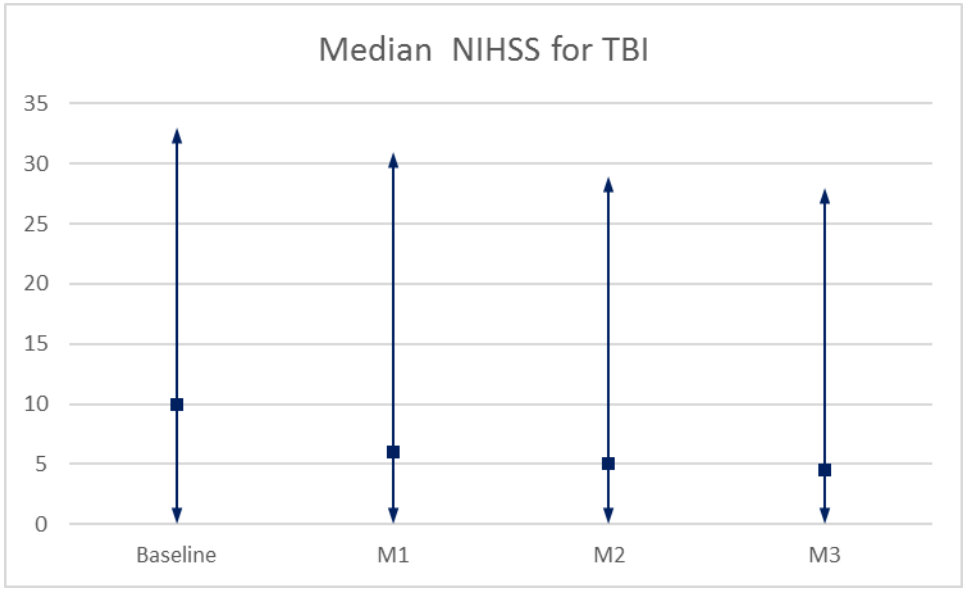
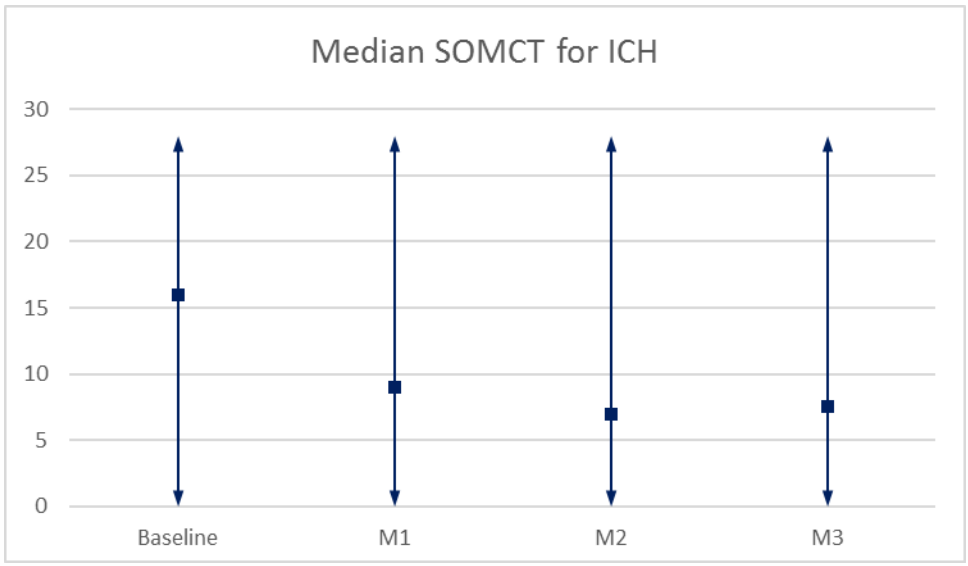


Figure 5. Median SOMCT a. ICH and b. TBI

a.



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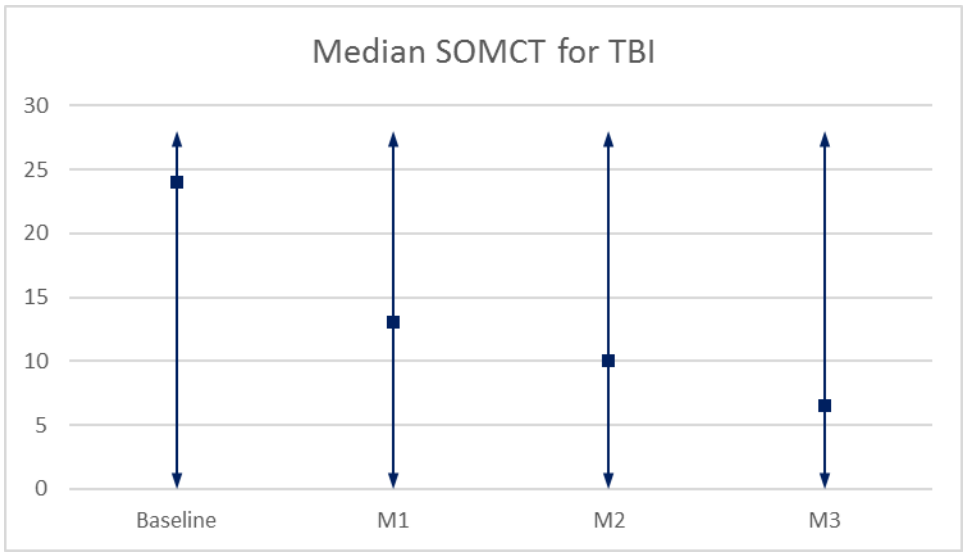

Augmented Reality Display For Pedicle Screw Insertion Using A Novel Machine Vision Image Guided System: Pre-Clinical Study And Initial Clinical Findings

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Abstract

Purpose

Augmented Reality (AR) can display virtual tool overlay onto real-world imaging. We tested the feasibility of a novel AR display on Machine Vision Image Guided System (MvIGS) as an adjunct during cervical and thoracolumbar instrumented fusion with preclinical and initial clinical results.

Materials and Methods

Preclinical testing was performed on spinal phantoms with fine cut CT scan. C2 pars and C3-S1 pedicle screw insertions were simulated bilaterally (n=48). Optimal starting point was determined by the operating surgeon to allow the greatest angular tolerance. For each screw, an optimal trajectory, followed by 4 near-breach trajectories was identified in both radiological and AR displays (240 trajectories). Comparisons of mean breach angles between radiological and same-side AR camera, for each of the left and right sides of the spine were analyzed by non-parametric Mann-Whitney-U test. Initial clinical experience included 5 patients with 28 screws' trajectories shown as adjunct AR display for untracked instruments.

Results

(mean ± SD)	**Left Pedicle**				**Right Pedicle**			
Direction	**Medial**	**Lateral**	**Superior**	**Inferior**	**Medial**	**Lateral**	**Superior**	**Inferior**
Radiological	11.3±6.4°	16.5±7.6°	24.3±11.3°	21.1±9.4°	10.8±4.3°	16.1±8.9°	27.5±8.1°	20.7±7.3°
AR	8.7±7.8°	32.1±30.8°	35.4±21.5°	38.7±26.7°	8.4±5.2°	20.0±21.3°	57.3±25.4°	27.1±15°
p-value	-	-	0.023	0.013	-	0.035	<0.001	0.045

Table 1: Directional angular breach tolerances were analyzed for right-handed surgeons.

Conclusions

AR display for angular tolerance in pedicle screw insertion showed either equivalent or larger angles than radiological display. AR display may be a useful adjunct for spinal instrumented fusion, especially for untracked surgical instruments.

Keywords: pedicle screw insertion, augmented reality, neurosurgical navigation, infrared tool tracking, spine.

1. Introduction

Pedicle screw insertion represents a common procedure in spine surgery.
Although considered as a basic tool in the armamentarium of a spine surgeon, misplacement rate have been reported ranging from 3 to 55% for thoracic spine, and 5 to 41% for lumbar spine using standard free-hand techniques[1-4].
Pedicle screw misplacement may result in a wide spectrum of consequences, from totally asymptomatic events, to dramatic ones[1].
In the last decades several technological advancements have been brought to the operating room in order to decrease its incidence and improve the outcome. Among them, the neuronavigation represents the most important one, playing an important role in both cranial and spine surgery[2].
Several studies have been published showing that pedicle screw placement accuracy using 2D navigation is higher than when a free hand technique or preoperative CT scan navigation are used[5-8].
Although this technology is extremely accurate, especially when tracked tools are used, the result of the trajectory seen in post-operative imaging is not necessarily equally correct. Nevertheless, considering there is very little room for error in pedicle screw insertion, especially in the thoracic region, the likelihood for screw misplacement is high, even when navigation is used.
Recently, important advancements have been done with the advent of the augmented reality (AR). AR refers to when users experience the surrounding real world with computer generated content superimposed onto their view. AR requires some sort of hardware like a computer screen with a camera attached or a smartphone.
Today, there are countless commercially available phone apps and computer programs which are considered an AR experience, some of which will be employed in this study.
The aim of this study is to report our preliminary results using an augmented reality technology for pedicle screw insertion.

2. Materials and Methods

At Sunnybrook Health Sciences Centre, a novel AR display on Machine Vision Image Guided System (MvIGS) was introduced in 2018. It is used as adjunct during spinal instrumented fusion. The system includes a light head which contains two cameras and an infrared (IR) tracker which overlook the surgical site.
Preclinical data was collected using a phantom to simulate real surgical conditions.
Pedicle screw insertion was simulated from C2 to S1, on both sides. For each screw 5 trajectories were registered: the correct one, followed by superior, inferior, medial and lateral breaches. Using this data, we were able to calculate the two α angles (α_1 and α_2) and the two β angles (β_1 and β_2) with respect to the correct screw trajectory per each screw.
The range between the two α angles and the two β angles create a safe zone, whereas the breach trajectories represent the limitation of the safe zones. Passing these outlined areas will result in a breach.
A total of 240 measurements were taken from levels C2 to S1 between both the left and right-side pedicles. All trajectories included in the phantom experiments were completed by a single surgeon. Each level of the spine was reregistered prior to navigation such that the accuracy of the recorded trajectories would be maintained throughout the experiment.
For the clinical data, 24 screws were inserted in 5 patients, for a total of 140 trajectories. Eleven screws were placed in the cervical spine, 6 screws were placed in the thoracic spine, 6 screws in the lumbar spine, and 1 screw in the sacrum.
Again, prior to any measurements, each level of the spine was reregistered to maintain the same level of accuracy throughout the procedure.

3. Results

(mean ± SD)	**Left Pedicle**				**Right Pedicle**			
Direction	**Medial**	**Lateral**	**Superior**	**Inferior**	**Medial**	**Lateral**	**Superior**	**Inferior**
Radiological	11.3±6.4°	16.5±7.6°	24.3±11.3°	21.1±9.4°	10.8±4.3°	16.1±8.9°	27.5±8.1°	20.7±7.3°
AR	8.7±7.8°	32.1±30.8°	35.4±21.5°	38.7±26.7°	8.4±5.2°	20.0±21.3°	57.3±25.4°	27.1±15°
p-value	-	-	0.023	0.013	-	0.035	<0.001	0.045

Table 1: Directional angular breach tolerances were analyzed for right-handed surgeons.

In the phantom experiments, we found that the radiological angles are the largest angles compared to the left and right cameras for 13 out of 96 sets of measurements, resulting in only about 13% of the time. Similarly, in the clinical results, we only found 4 instances of the same phenomena out of 51 sets of data, which is approximately 8% of the time.

These findings tell us that in almost all cases, the camera angles created a larger safe zone than the areas proposed by the radiological angles. This observation is true in both the phantom and clinical results.

The magnification effect found between the radiological angles and the camera angles further explain the difficulty surgeons' experience. When navigation is lost while inserting pedicle screws, it is easy to see why surgeons may recall the trajectory incorrectly because of the change in the magnitude.

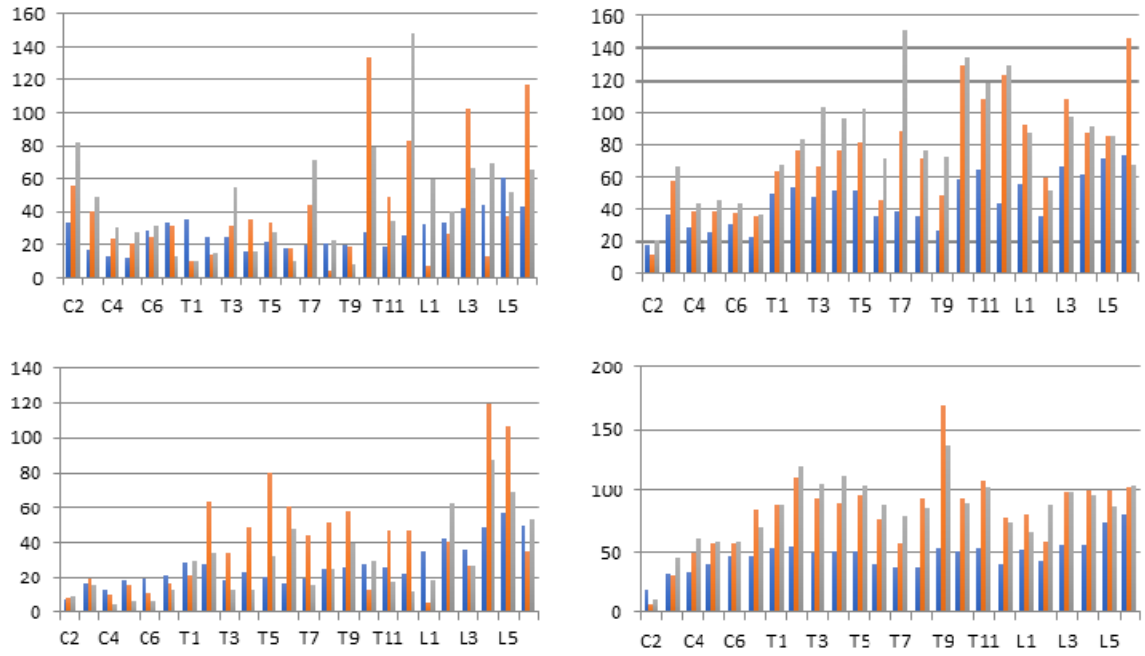


Figure 1: Phantom Data collected from C2 to S1. Graphs from left to right are Left Alpha, Left Beta, Right Alpha, Right Beta. Blue, Orange and Grey bars represent radiological, left camera and right camera angles.

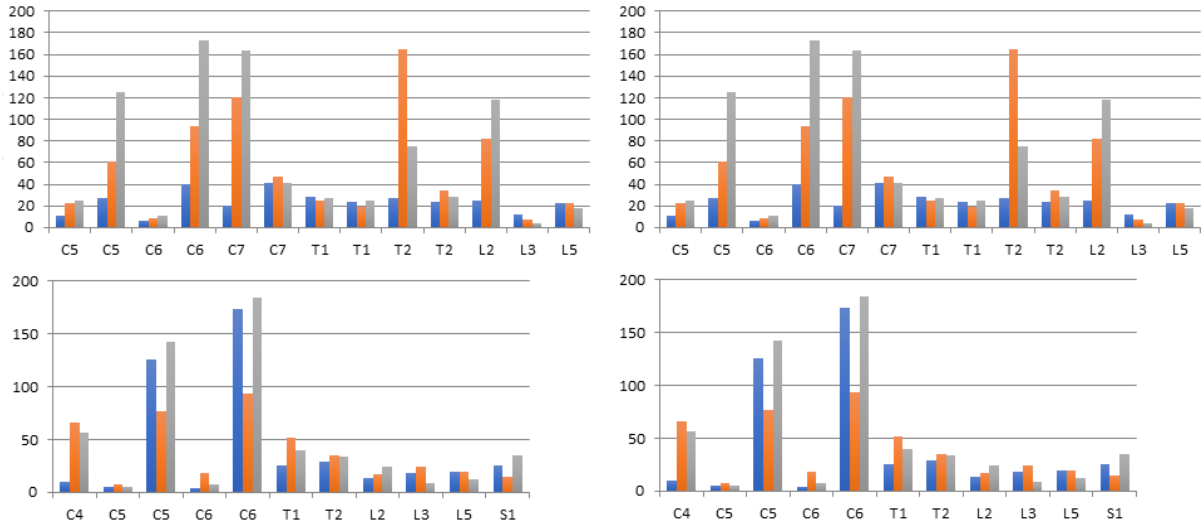


Figure 2: Clinical Data collected from C2 to S1. Graphs from left to right are Left Alpha, Left Beta, Right Alpha, Right Beta. Blue, Orange and Grey bars represent radiological, left camera and right camera angles.

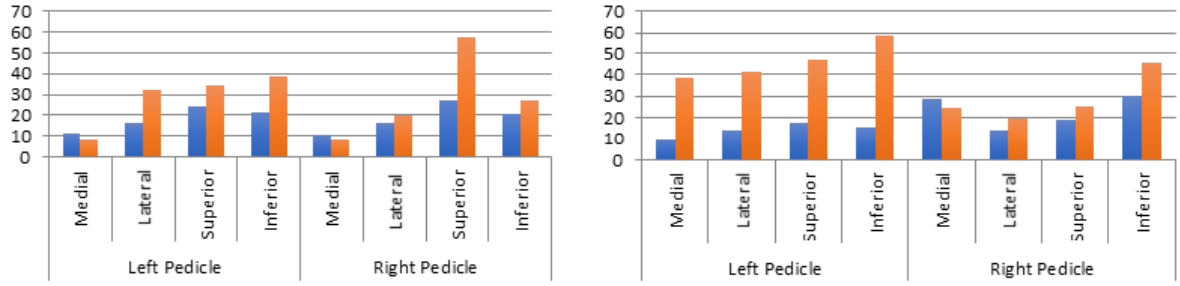


Figure 3: Mean Phantom (left) vs Mean Clinical (right) Radiological Angles and Camera Angles. Blue and orange bars represent radiological and camera angles respectively.

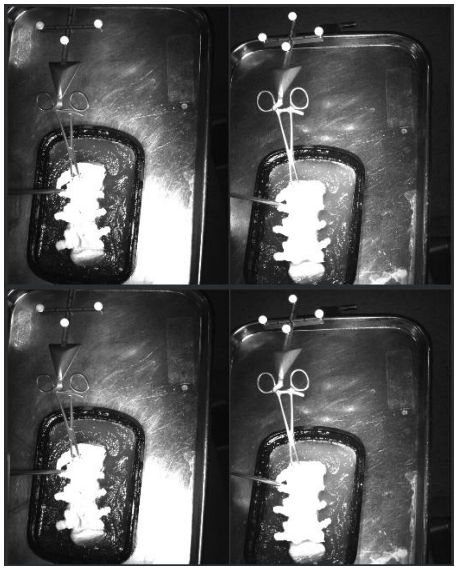
4. Discussion

Surgical navigation devices are not always used in the operating room even though they offer incredible accuracy. Many systems are not created to operating in tandem with the existing workflow presented in the operating room. By creating systems which are not convenient nor user friendly, surgeons tend to opt out of using navigation during surgery on a regular basis. Commercially available systems also do not connect the information shown in the CT scans with the location of the tool tip directly onto the surgical site, creating a constant need to look up and down to ensure the correct trajectory is being used. Constantly changing views from the surgical site to the navigation screen can potentially move the tool tip on the submillimeter level without the surgeon knowing. Because of this workflow, a submillimeter accurate system does not yield resulting trajectories with the same accuracy. Another caveat with existing surgical navigation devices is that the tools themselves are not compatible between devices from different companies. This inconvenience demands that surgeons must use tools from the same manufacturer, which can be quite limiting depending on the available surgical suite.
This is the first study which aims to maintain the benefits of surgical navigation when tracking is unavailable for various reasons. Safe zones are shown on top of the surgical site as an augmented reality view to maintain the level of accuracy surgeons receive with navigation.

4.1 Limitations of the Study

In the clinical cases, the location of the surgical navigation device changes within the room which is normal during set up for these devices. Unlike the phantom experiments, the location and orientation of the MvIGS light head was predictable. However, as part of the user instructions, the surgeon must align the cameras in the light head to be parallel to the spinous processes of the patient. These instructions ensure that the rotation of the light head is less distorted in the camera angles. In general, this distortion cannot be fully eliminated, making some discrepancies between the phantom and clinical data. It is apparent that if there is an obvious distortion in the light head orientation, the other camera view will compensate for the change. i.e. if the left camera angle is very small, the right camera angle will be very large.

One grave cause for misleading information from the overhead view includes angles which move along the same axes perpendicular to the image plane of the cameras. These two may appear to look exactly the same on the overhead view, but radiologically, those angles can be very different. The camera angles alone are not always enough to make safe insertions. Surgeons are instructed to keep the light head within working range of the IR camera. The two camera views look incredibly similar because the light head is just barely within usable range. When the views look too much alike, it is almost as if the information presented is monocular, making it unreliable for navigation.



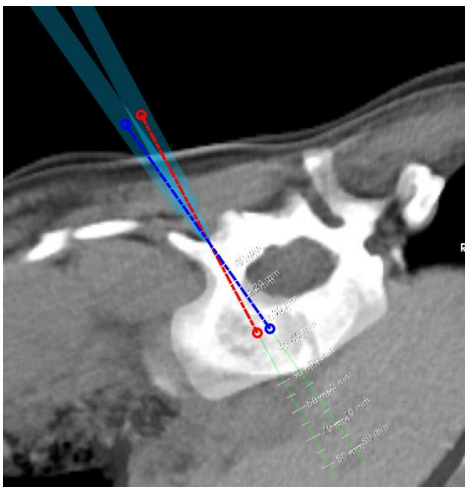


Figure 4: Two different trajectories which may appear to be the same in overhead camera views are separated by 6.8 degrees. The top camera angles are shown through the red line and the bottom view is shown in blue. This difference is indistinguishable in the overhead view.

Other causes for unreliable AR views would be the common causes which prevent proper navigation. Situations where the tools are not in view of the tracker, improper registration, and damaged or missing reflective markers on the IR tracked tool are all causes of poor practice when using any surgical navigation system. These cautions are standard and must always be followed for all navigation devices.
From this study, we propose a novel solution to assist surgeons without disrupting the operating room workflow during neurosurgery when using navigation. Using AR, surgeons can overlay the intended trajectory directly onto the surgical site using the overhead cameras in the 7D MvIGS system. This eliminates the need to remember trajectories and provides a systematic path for untracked tools when navigation is unavailable.

5. Conclusion

An AR trajectory system was used to inform users of potential medial, lateral, superior and inferior breaches. The breach trajectories were used to show the boundaries of the safe zone in both axial and sagittal views. Throughout all levels of the spine, there appears to be a magnification effect between the safe zones in the radiological views and the angles observed in the left and right camera views. In phantom and clinical experiments, the radiological angles were larger 13% and 8% of the time respectively. This change in magnitude can potentially be a cause of incorrect trajectories when surgeons are required to recall the tool position when navigation is unavailable. When the MvIGS light head is on the boarder of the working distance, it appears that the two camera images look very similar to one another which are detrimental for navigation. The overhead view effectively becomes a monocular view rather than stereoscopic, which make the AR view unreliable. Future initiatives would be to determine the accuracy of using the AR navigation system to guide pedicle screw placement into a spine phantom as well as a thorough statistical analysis to ensure significance in the data. To ensure a true 3D experience, further implementation of this technology on a head mounted display would be further intuitive and eliminate the need for two separate camera views.

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A Randomized Controlled Trial (RCT) Comparing Endoscope-Assisted And Craniotomy Evacuation In Spontaneous Intracerebral Hematoma

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Abstract:

Objective:

This study was done to determine and compare the hematoma evacuation rate, operating time and functional outcome of patients with spontaneous ICH by mRS, treated by endoscope-assisted evacuation with that of craniotomy.

Materials and Methods:

We have studied 40 patients of spontaneous ICH diagnosed by non-contrast CT scan of brain. In 20 patients endoscope-assisted and in another 20 patients craniotomy evacuation was done. Follow up CT scan was done within 24 hrs of surgery to compare with pre-operative scan. Data were analyzed by demographic variable (age, sex), clinical (GCS at admission, on 3rd postoperative day and at discharge), hematoma evacuation rate and operating time. Follow up was done at 3 months and outcome was measured by modified Rankin scale (mRS).

Results:

The mean (SD) age of endoscope-assisted group and craniotomy group was found 57.9(9.9) years and 52.2(11.7) years respectively. Male sex was predominant. There was no statistically significant difference ($p > 0.05$) between two groups regarding age, sex, improvement in GCS and mortality rate. Mean operating time was 1.23(0.47) hrs in endoscope-assisted group and 2.15(0.56) hrs in craniotomy group. Hematoma evacuation rate was better in endoscope-assisted group 74(11) % than in craniotomy group 65(13) %. There was statistically significant difference regarding operating time, hematoma evacuation rate and outcome in both groups ($p <0.05$).

Conclusion:

This study revealed that endoscope-assisted procedure has better outcome and hematoma evacuation rate than craniotomy.

Key words:

Endoscope-assisted, hematoma evacuation, spontaneous ICH.

Introduction:

Intracerebral hemorrhage (ICH) is a common disease with an incidence ranging from 11 to 23 cases per 100,000 per year. Although it accounts for only 10 to 15% of all strokes, it is the fatal stroke subtype with mortality up to 40%[1]. Risk factors include age, hypertension, and history of coronary artery disease, previous stroke or TIA, cigarette smoking, alcohol consumption, low serum cholesterol, low dose aspirin and oral contraception[2].

According to etiological aspects primary or spontaneous hemorrhage can be distinguished from secondary hemorrhage. Primary hemorrhages are spontaneous hemorrhages, which are mainly caused by arterial hypertensive diseases. Secondary hemorrhages are due to traumatic, tumorous or pharmacological causes[1]. Cerebral amyloid angiopathy is a common cause of ICH in the elderly, which is not associated with arterial hypertensive disease[3].

Lobar hemorrhage incorporate primary hemorrhages into the occipital, temporal, frontal and parietal lobes (including ICH arising from cortex and sub-cortical white matter), as opposed to hemorrhage of deep structures (e.g. basal ganglion, thalamus and infratentorial structures). It accounts for 10-32 % of non-traumatic ICH. With large hemorrhages, it may be difficult to make a distinction between lobar and deep ICH. Lobar hemorrhages may also have a more benign outcome than ganglio-thalamic hemorrhages [4].

Understanding the pathophysiology and the natural history of ICH is of utmost importance as it provides the basis for identifying potential therapeutic targets. ICH results from vessel rupture and blood extravasation in the brain parenchyma, leading to hematoma formation, mechanical disruption and tearing of neighboring blood vessels, leading to growth of the hematoma and culminating in cessation of neuronal function. This primary insult is followed by a cascade of secondary events including edema formation, precipitated by the growing mass of blood and toxic effects of blood degradation products, over the ensuing days-to-weeks resulting in delayed (secondary) neuronal injury [5]. The classic presentation of ICH is the progressive onset of focal neurological deficits over minutes to hours with accompanying headache, nausea, vomiting, decreased level of consciousness and elevated blood pressure[6].

Several factors influence the extremely poor outcome associated with spontaneous ICH, such as the level of consciousness at presentation, volume of parenchymal hemorrhage, volume of intraventricular hemorrhage (IVH), and the extent of cerebral damage[7]. Hematoma expansion has been identified as one of the most important determinants of early neurological deterioration and poor outcome in primary ICH[8].

The selection of the approach (the frontal and temporal approach) for putaminal ICH is an important issue. In patients with ICH volume less than 50 ml it is not difficult to evacuate the hematoma through the shortest distance from the cortical surface to the hematoma. However when the hematoma is larger than 50 ml, the shape usually became elliptical .The frontal approach was recommended in these cases due to its involving non-eloquent regions and providing better visualization that may result in maximal hematoma evacuation[9].

Endoscope-assisted ICH evacuation performed in the early stage was associated with a minimal rebleeding rate (0%-3.3%) compared with the traditional craniotomy method (5%-10%). Other advantages of the endoscope-assisted method include low complication rate, less operative time, less blood loss, improved evacuation rate, and early recovery of the patients[10].

Methods and Materials:

This was a Randomized Controlled Trial (RCT) carried out at the department of Neurosurgery, Dhaka Medical College Hospital, Dhaka, Bangladesh from January, 2015 to June, 2016. We have studied 40 diagnosed patients of Spontaneous ICH admitted or referred, who fulfill the selection criteria. Variables were patient's age, sex, GCS at admission, on 3rd post-operative day and at discharge, operating time, hematoma evacuation rate and mRS (Modified Rankin Scale) at three months.

Patients with age 30 to 75 yrs, GCS 8 to 13 and hematoma volume > 30 ml in ganglio-thalamic region and a subcortical hemorrhage > 30 ml with significant mass effect were included. Patients having GCS ≤ 7 and >13 and

hematoma volume > 62 ml were excluded from the study. Patients with purely intraventricular hemorrhage and cerebellar hemorrhage also excluded.

For the purpose of study we subdivided GCS into groups: < 8, 8-10, 11-13 and >13. The ABCs method was adopted to measure the hematoma volume: Volume (ml) = (A× B ×C)/2[11]. The hematoma evacuation rate was calculated and presented by percentage as: Preoperative hematoma volume (ml) - Post-operative volume/Pre-operative volume[12]. Both group received best available medical treatment along with surgery.

For endoscope-assisted evacuation we used 4-mm 0 degree rod-lens endoscope and sheath was prepared from outer covering of 3-cc syringe having inner diameter 10 mm and length 5.5 cm, proximal end was beveled to prevent brain injury. Sheath was fitted with an obturator having diameter 9 mm. We used sucker nozzle diameter 2-4 mm as per needed.

All surgical procedures were performed under general anesthesia. For patients with ganglio-thalamic ICH either "frontal" or "temporal" approach[13] was used in order to provide the shortest distance between the cortical surface and the hematoma on the preoperative CT scan. In patients with lobar hemorrhage the corridor that traverses the shortest distance to the hematoma (judging from the preoperative CT scan) was used. A linear skin incision (3–4 cm in length) is created. A 1.5- to 2.0-cm burr hole[9] is then created with the dura opened as a U-shaped flap[14] (Fig-1).

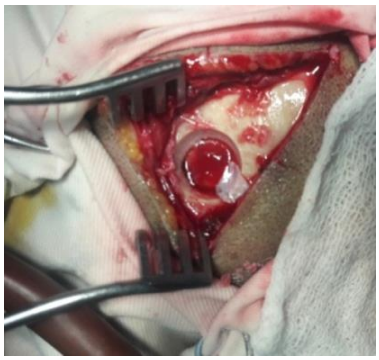


Fig 1: Burr hole and U-shaped flap of dura

With a small corticotomy or trans-sulcus we introduced obturator loaded sheath down to the depth measured by brain cannula and length estimated from the preoperative CT scan up to entry into the clot cavity. The most distal part of the hematoma was evacuated first by help of sucker and as the sheath is gradually withdrawn the residual hematoma pushed into the tip of the sheath as the brain expands. The hematoma is evacuated by manipulating the suction through the working space within the sheath[9]. Orientation was that the telescope up and sucker nozzle down for aerial view.

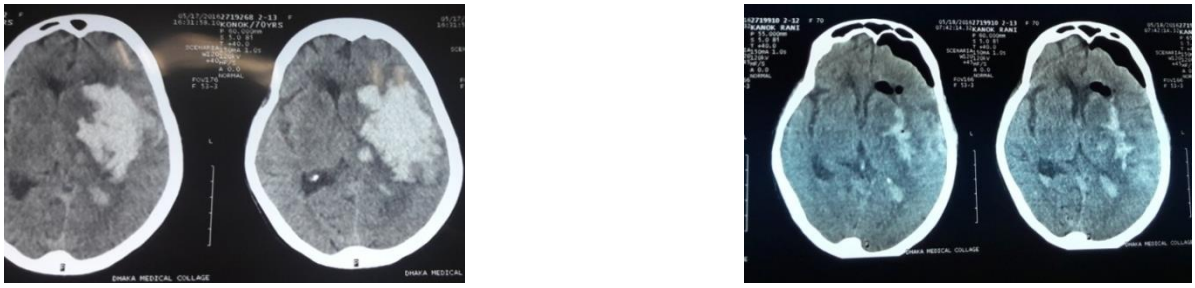
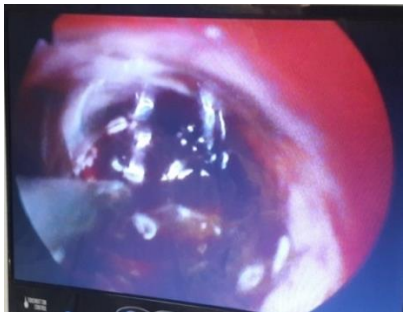


Fig 2: Pre-operative and Post-operative CT scan of Brain in Endoscope- assisted evacuation



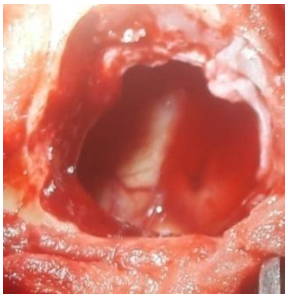


Fig 3: Endoscopic view of hematoma

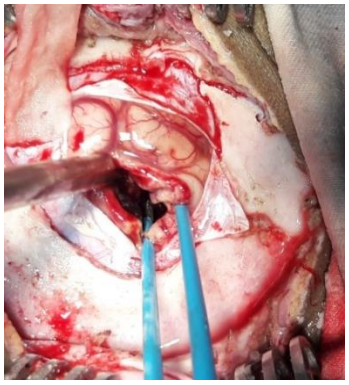


Fig 4: Hematoma cavity

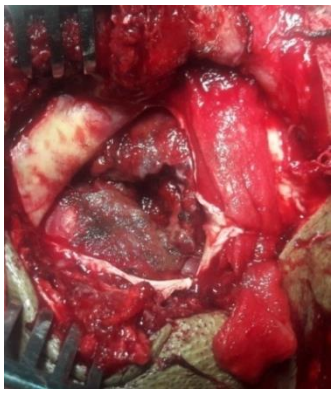


Fig 5: Craniotomy and evacuation

Fig 6: Trans-sylvian evacuation

In craniotomy group pterional craniotomy was done in ganglio-thalamic ICH and by trans-sylvian dissection (Fig: 6) hematoma was evacuated. In case of lobar hematoma craniotomy done after brain mapping over the preferred site (Fig: 5). Dura was opened by circulate incision. Hematoma was evacuated with suction equipment.

Results:

Table I

Distribution of Study population according to Sex in both groups (n=40)

Sex	**Group**		**p value**
	Endoscope- assisted group (n=20)	**Craniotomy group (n=20)**	
Male	15 (75.0)	16 (80.0)	0.705^{ns}
Female	5 (25.0)	4 (20.0)	
Total	20 (100.0)	20 (100.0)	

Table I shows, there was male predominance with 75% in the endoscope-assisted group with 80% in the craniotomy group. No statistically significant difference was observed.

Table- II

Distribution of Study population according to age in both groups (n=40)

Age (years)	Group		p value
	Endoscope -assisted group (n=20)	Craniotomy group (n=20)	
≤40	1 (5.0)	3 (15.0)	
41 – 50	4 (20.0)	9 (45.0)	
51 – 60	9 (45.0)	3 (15.0)	
>60	6 (30.0)	5 (25.0)	0.110^{ns}
Total	20 (100.0)	20 (100.0)	
Mean ± SD	57.9 ± 9.9	52.2 ± 11.7	
Range (min=max)	34 – 75	35 – 72	

Table II shows age limit was 30 to 75 years no patient found in the study below 34 years. There is no statistical significant difference in age distribution among both groups (p>0.05).

Table III

Duration of operating time in hours in both groups (n=40)

Duration of operation (hours)	Group		p value
	Endoscope assisted group (n=20)	Craniotomy group (n=20)	
Mean ± SD	1.23 ± 0.47	2.15 ± 0.56	$<0.001^{s}$
Range (min - max)	0.5 – 2.0	1.0 – 3.0	

Table III shows that surgical operating time is significantly shorter in endoscope-assisted group than craniotomy. Mean time is 1.23(0.47) hrs in endoscope-assisted group and 2.15(0.56) hrs in craniotomy group. There is statistically significant difference in two groups regarding operating time (p<0.001).

Table IV

Distribution of Study population by GCS in both groups

GCS	Group		p value
	Endoscope assisted group	Craniotomy	
Pre operative GCS			
8 -10	19 (95.0)	18 (90.0)	0.548
11-13	1 (5.0)	2 (10.0)	
GCS on 3rd POD			
< 8	2(10.0)	2(11.8)	0.476
8-10	5 (25.0)	5 (29.4)	
11-13	8 (40.0)	9 (52.9)	
>13	5(25.0)	1(5.9)	
GCS on discharge			
10	1(6.3)	0.0	
11-13	5(31.3)	8 (61.5)	0.214
>13	10 (62.5)	5 (38.5)	

Table IV: No statistically significant difference was observed regarding improvement of GCS

Table V

Hematoma evacuation rate in both groups (n=40)

Hematoma evacuation rate (%)	Group		p value
	Endoscope assisted group (n=20)	Craniotomy (n=20)	
Mean ± SD	74 ± 11	65 ± 13	0.036^{s}
Range (min - max)	55 – 89	30 – 87	

Table V shows hematoma evacuation rate in both groups. Mean evacuation is 74(11) % in endoscope-assisted group and 65(13) % in craniotomy group. There is statistically significant difference between two groups regarding hematoma evacuation rate ($p<0.05$). It was calculated from the formula that utilizes pre-operative and post-operative hematoma volume.

Table VI

Distribution of Study population according to mRS in 3 months follow up.

mRS	Group		p value
	Endoscope assisted group (n=16)	Craniotomy (n=13)	
No symptoms	6 (37.5)	2 (15.3)	
No significant disability despite symptoms	4 (25.0)	1 (7.7)	0.034[s]
Slight disability	6 (37.5)	5 (38.5)	
Moderate disability	0 (0.0)	5 (38.5)	

Table VI shows distribution of patients according to modified Rankin Scale (mRS) at 3- months follow up. Moderate disability of mRS scale was more frequent in craniotomy group (38.5%) that is absent in endoscope-assisted group. A good number of patients (10) had no symptoms and no significant disability despite symptoms in endoscope-assisted group. There is statistically significant difference regarding outcome in both groups ($p<0.05$)

Discussions:

Analysis of age distribution showed mean (SD) age of endoscope-assisted group and craniotomy group were found 57.9(9.9) and 52.2(11.7) years respectively. There were a good number of patients between 51 to 60 years age group in endoscopy group and 41 to 50 years age group in craniotomy group. A study done by Ibrahim (2016) observed mean age of the patient was 56.5 years in the endoscopic group and 51.4 years in the craniotomy group[15], which is comparable with the current study.

Male sex was found predominant in both group .The distribution of male was 75% and 80% in endoscope-assisted and craniotomy group respectively. Zhang et al. 2014[16] conducted a study in 51 patients divided in endoscopy group (21) and craniotomy (30) group, of them total 38 was male and 13 was female that was not statistically significant.

In our study hematoma was located in ganglio-thalamic region in 9(45%) patients in endoscope-assisted group and 8(40%) patients in craniotomy group. Parietal ICH was present in 6(30%) in endoscope-assisted group and 7(35%) in craniotomy group. Ibrahim (2016) observed in his study: in 13 patients hematoma was lobar (parietal lobe) in endoscopic group and it was in 11 patients in craniotomy group[15].

In this study, GCS on admission was 8-10 in 19(95%) patients and 11-13 in 1(5%) patient in endoscope-assisted group.GCS was 8-10 in 18(90%) patients and 11-13 in 2(10%) in craniotomy group. In 3rd post-operative day GCS improved to 11-13 in 8(40%) patients and >13 in 5(25%) patients and deteriorate in 2 patients in endoscope-assisted group. In craniotomy group GCS improved to 11-13 in 9(52.9%) patients, >13 in 1(5.9%) patients and deteriorate in 2 patients. Wang et al .2015[12] observed that the median preoperative GCS score was 8 and median GCS score 1 week after surgery was 11. In this study 3 patients died from craniotomy group before 3rd post-operative day. At discharge 10(62.5%) patients from endoscopy group found to be a GCS score >13 and 5(38.5%) patient from craniotomy group had the GCS >13. Four patients from endoscope-assisted group and anther four patients from craniotomy group died before discharge.

Mean pre-operative hematoma volume was 46 ± 8 ml in endoscopy group and 47 ± 8 ml in craniotomy group. Hematoma evacuation rate was 74 ± 11 % in endoscope-assisted group and 65 ± 13 % in craniotomy group.

There is statistically significant difference between two groups ($p<0.05$). Ibrahim (2016) observed median preoperative volume was 56.8 ml in endoscopic group and 64.83 ml in craniotomy group[15].

Mean operating time was 1.23(0.47) hrs in endoscope-assisted group and 2.15(0.56) hrs in craniotomy group. There was statistically significant difference between two groups ($p<0.05$). In a study by Zhang et al .2014 operating time was 76.48 ±14.92 min in the neuroendoscopy group, significantly shorter than 175±26.13 min in the craniotomy group ($p<0.00001$)[16].

In our study 4 patients died from endoscope-assisted group (20%) and 7 patients died from craniotomy group (35%). Ibrahim (2016) observed that mortality rates were 36.8% for the endoscopy group and 63.2% for the craniotomy group which was statistically significant ($p<0.05$)[15].

In our study 6 (37.5%) patients had no symptoms (mRS-0), 4 (25%) patients had no significant disability despite symptoms (mRS- 1), 6(37.5%) had slight disability (mRS- 2) in endoscope assisted group. In craniotomy group 2 (15.3%)) patients had mRS score -0, 1 (7.7%)) patients had mRS score 1, 5 (38.5%) had mRS score 2 and 5 (38.5%) patients had mRS score 3. No patient found to develop moderate severe disability and severe disability in both groups. There is statistically significant difference in outcome in both groups ($p<0.05$). Zhang et al. 2014 observed no statistically significant difference in mRS in endoscopy (3.57±1.66) and craniotomy (3.88±2.14) group ($p=0.56$)[16].

Conclusion:

This study revealed that hematoma evacuation rate was better in endoscope-assisted group and had less operating time than craniotomy. Outcome is better in endoscope-assisted group than in craniotomy group. Endoscope-assisted hematoma evacuation may be a promising minimally invasive technique in spontaneous intracerebral hematoma.

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Biomarker Potential Of Mitochondrial DNA In Aneurysmal Subarachnoid Hemorrhage

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Abstract

Aneurysmal subarachnoid hemorrhage (SAH) accounts for a very low proportion of all strokes (5%), but is accompanied with high morbidity and mortality. Half of the patients with SAH die and a significant proportion of the survivors suffer disability. While obliteration of the bleeding aneurysms from the circulation by neurosurgical clipping and endovascular coiling are relatively commonplace in most neurosurgical units, patients nevertheless deteriorate days after SAH due to post-SAH complications. The major post-SAH complications are cerebral vasospasm, seizures, delayed ischemic neurological deficits, acute and chronic hydrocephalus, delayed cerebral ischemia, cortical spreading depression, and infections. Renewed interest in the role of inflammation during early and delayed brain injury after SAH have led to exploration of different inflammatory mediators at both the CNS and systemic level. These mediators may have biomarker potential and include damage-associated molecular pattern molecules (DAMPs), cytokines, and immune cells. These can serve as diagnostic and prognostic markers of different post-SAH complications and clinical outcomes and may facilitate administration of aggressive treatment and critical management of patients at increased risk. Among different DAMPs, mitochondrial DNA (mtDNA) has been recognized as an alarmin due to its ability to upregulate inflammation via Toll-like receptor 9. Here, we briefly review the biomarker potential of cell free circulating mtDNA in the context of post-SAH complications and clinical outcome.

Keywords: Neuroinflammation, cGAS-STING, TLR-9, DAMPs, complications, brain injury

Introduction

Aneurysmal subarachnoid hemorrhage (SAH) is a devastating disease with high rates of morbidity and mortality 1. Although SAH accounts for a very low proportion of all strokes (5%), half of the patients with SAH die and a significant number of survivors may develop lifelong disability 1,2. While obliteration of the bleeding aneurysms from the circulation by neurosurgical clipping or endovascular coiling are relatively commonplace in most neurosurgical units, patients nevertheless deteriorate days after SAH due to post-SAH complications 3,4. The major post-SAH complications are cerebral vasospasm (CVS), seizures, delayed ischemic neurological deficits (DINDs), acute and chronic hydrocephalus, delayed cerebral ischemia (DCI), cortical spreading depression, and infections 3-5. The brain injury after SAH occurs in distinct phases, namely early brain injury (within 72 hours of SAH) and delayed brain injury (over 3–14 days later) 1,6,7. Renewed interest in the role of inflammation during early and delayed brain injury after SAH has led to explorations of different inflammatory mediators at both the CNS and systemic level 8. These mediators, such as damage-associated molecular pattern molecules (DAMPs), cytokines, and immune cells, may have biomarker potential. These can serve as diagnostic and prognostic markers of different post-SAH complications and clinical outcomes and can facilitate administration of aggressive treatment and critical management of patients at increased risk.

DAMPs, also known as alarmins or danger signal molecules, are released from damaged, stressed, and necrotic cells and can upregulate inflammation via their ligation to pattern recognition receptors (PRR) such as Toll-like receptors (TLRs) on immune cells 9,10. Numerous endogenous molecules, such as High mobility group box-1 (HMGB-1), ATP, S100B, uric acid, IL-1α, IL-33, DNA, and extracellular matrix proteins behave as DAMPs

when released extracellularly in an unsequestered form outside their place of context 11,12. Among different DAMPs, mitochondrial DNA (mtDNA) has been recognized as an alarmin due to its ability to upregulate inflammation via TLR-9 ligation and activation 13. Here, we briefly review the biomarker potential of cell-free circulating mtDNA in the context of post-SAH complications and clinical outcome.

1.1. Mitochondrial DNA

Mitochondria, the power house of cells, have many features similar to ancestral bacteria due to their endosymbiotic nature 14,15. In recent years, various potential DAMP molecules have been recognized to originate from mitochondria, such as N-formyl peptides, mitochondrial transcription factor A (TFAM), cardiolipin, and hypomethylated/ non-methylated mtDNA. These molecules are released upon cell stress, injury, and necrosis 15. DNA is known to mount a potent immune response even before its genetic role was appreciated 16,17. mtDNA bears CpG motifs resembling those of bacteria and is recognized by TLR-9 in the endosomal compartment of the cell 13. Accumulating evidence now suggests that mtDNA can bind and activate innate inflammatory immune responses through several PPRs, such as the NLRP3-, NLRC4-, AIM2-inflammasome complex and cGAS-STING in addition to TLR-9 18,19.

1.2. Mitochondrial DNA in inflammatory diseases

The ability of mtDNA to induce inflammation is highlighted by induction of TNF secretion from splenocytes that leads to arthritis upon injection in joints of mice 20. Circulating mtDNA has been shown to induce inflammation due to TLR-9 activation on immune cells 13. The levels of mtDNA in systemic circulation are elevated in several diseases, including sepsis 21, trauma 22,23, meningitis 24, HIV infection 25, acute myocardial infarction 26, autism 27, hepatic transplantation 28, and hemodialysis 29. Several studies have shown mtDNA as a potential biomarker of different neoplastic conditions, such as prostate cancer 30, germ cell cancer 31, and breast cancer 32. However, in the case of CNS diseases such as Alzheimer's disease, Creutzfeldt-Jakob disease, Parkinson's disease, multiple sclerosis, and meningitis, only a limited number of studies have shown elevated circulating cell-free mtDNA and its biomarker and prognostic potential 24,25,33-38.

1.3. Mitochondrial DNA in SAH

In the context of SAH, detailed investigations on mtDNA both in the CSF and systemic circulation are lacking. A single study investigated the levels of mtDNA in both CSF and systemic circulation from 21 SAH patients by employing quantitative PCR for the mitochondrial gene ND2 39. A significant elevation in CSF mtDNA levels on admission has been shown to associate with poor clinical outcome. However, plasma mtDNA levels have shown delayed elevation in patients with poor clinical outcome 39. On admission, CSF levels of mtDNA independently predicted poor clinical outcome with a cutoff value of 31.4 ng/ml (sensitivity 89% and specificity 100%) 39. We have also found significant elevation of different mtDNA genes (such as D-Loop and Cytochrome c oxidase subunit-1) over 2 weeks after SAH and a significant delayed elevation of Cytochrome B 40.

Discussion

Aneurysmal SAH has devastating consequences among other stroke subtypes due to its high rates of mortality and morbidity and its prevalence in individuals at a relatively younger productive age 1. Treatment of bleeding aneurysms by neurosurgical clipping or endovascular coiling does not prevent life-threatening complications as described above. The emergence of the early and delayed brain injury concept with an emphasis on the critical role of inflammation during these phases has significantly changed the direction of post-SAH research from a CVS reversal paradigm 1,41-44. A number of studies highlight the systemic upregulation of different pro-inflammatory cytokines 45-47. More than 75% of SAH patients develop a systemic inflammatory response syndrome characterized by fever, leukocytosis, and raised CRP values 8,43. Therefore, investigations in the role of inflammation during post-SAH complications are promising in identifying therapeutic targets and biomarkers.

DAMPs represent important endogenous triggers of innate immune activation after their release from stressed, damaged, and necrotic cells 9,10. In recent years, DAMPs have been recognized along with their cognate

receptors to initiate and sustain inflammation. mtDNA also represent an important DAMP, for which various other PRRs such as the NLRP3-, NLRC4-, AIM2-inflammasome complex and cGAS-STING in addition to TLR-9 have been recognized (Boyapati, West and Shadel 18,19. Extracellular cell-free circulating mtDNA levels are elevated in different CNS diseases 24,25,33-38. However, detailed investigations on mtDNA in the systemic circulation of SAH patients and their associations with various post-SAH complications and clinical outcome are still lacking. Until now, only a single study has investigated mtDNA levels and revealed a delayed increase in plasma mtDNA levels in patients with poor outcome 39. Therefore, detailed studies emphasizing the biomarker potential of systemic mtDNA for post-SAH complications and clinical outcome are warranted. To date, the diagnostic and prognostic markers for various post-SAH complications and clinical outcome are either nonspecific or have not been validated. Therefore, there is a need to establish and validate biomarkers in SAH through large and multicenter clinical investigations. Biomarkers are not only useful in identifying the patients at increased risk of developing different complications and in facilitating aggressive treatment and management measures, but may also serve as therapeutic response monitors as they are surrogates of ongoing inflammation.

Conclusion

mtDNA represent an important DAMP that has a biomarker potential for post-SAH complications and clinical outcome and warrants further large multicenter investigations.

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Conflicts of interest

The authors declare no conflict of interest.

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Case Series: Cerebral Toxoplasmosis

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Abstract

Toxoplasmosis is a disease that results from infection with the Toxoplasma gondii parasite, one of the world's most common parasites. It is often subclinical except in patient whom are immunocompromised where severe infection may occur. We report a case series of 3 patients, who were admitted for intracranial lesions and were subsequently diagnosed as cerebral toxoplasmosis. These patients were initially treated as cerebral abscesses based on findings of brain imaging and were managed with intravenous antibiotics. Two of these patients deteriorated requiring decompressive craniectomy and lesionectomy. The third patient underwent a craniotomy and lesion excision as her lesion continued to increase in size despite being treated with an extended duration of antibiotics. All three of these patients proved to be diagnostic dilemmas and revealed the challenges of managing toxoplasmosis in immunocompromised individuals.

Introduction

Toxoplasmosis is an opportunistic infection caused by an obligate intracellular protozoan parasite, Toxoplasma gondii. In adults, toxoplasmosis is subclinical, but a severe infection can occur in patients who are immunocompromised, especially those with acquired immunodeficiency syndrome (AIDS). We report 3 patients whom were initially admitted to our department for intracranial lesions. They were later found to have cerebral toxoplasmosis. Due to a low clinical suspicion and based on history with no high risk behaviour, these patients were initially treated as cerebral abscess and managed with antibiotics based on the brain imaging findings.

Case Series

Patient A was a 45 year old lady with no known medical illness or high risk behaviour. She presented with a history of fever for one week which was associated with painful facial swelling especially over the nose and cheek region. On admission she was alert with GCS 15, fever (39.5^0C) and tachycardic (heart rate being 127 beats per minute). Her initial total white count was 3.0. A CT brain showed a vague right frontal lesion ~ 1x2cm (Fig. 1A). She was treated as right frontal abscess secondary to possible paranasal sinusitis. Her fever subsided antibiotics. However a repeat CT imaging done 3 week later showed an increase in size of the right frontal lesion (Fig.1B). She showed no improvement despite being on antibiotics for a long duration of time and therefore underwent elective right craniotomy and lesion excision. Intraoperatively, the lesion was solid and yellowish.

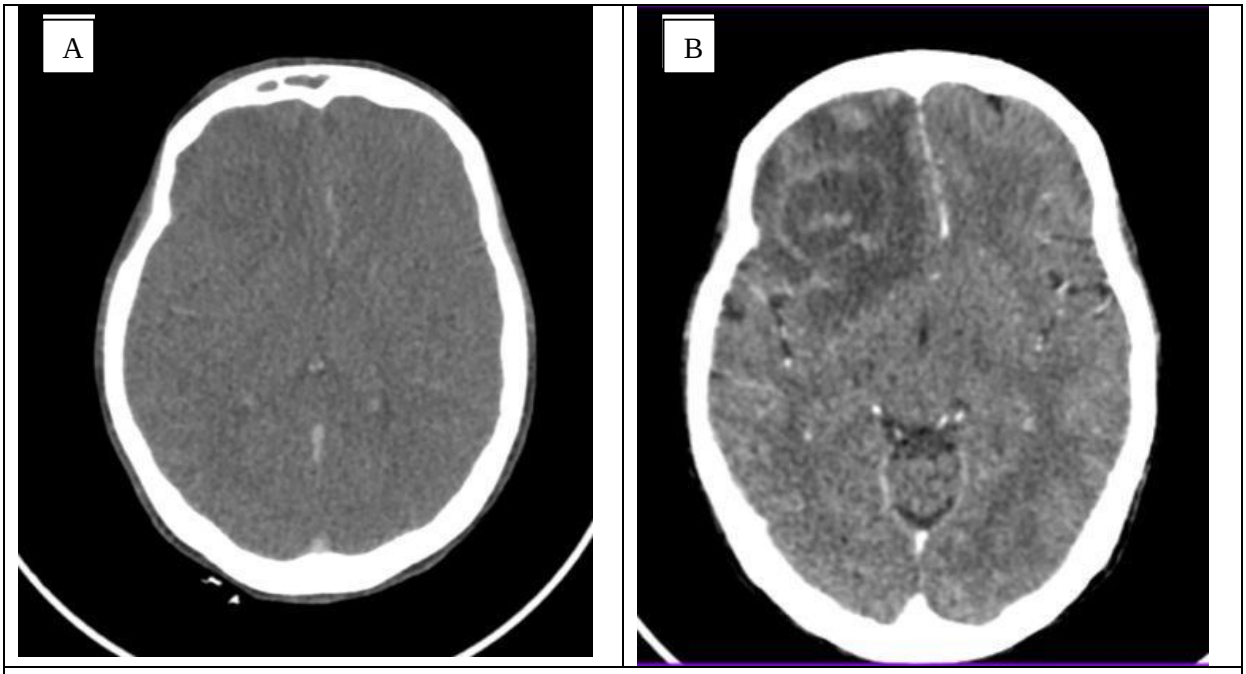

FIGURE 1
(A) Vague ring frontal ring enhancing lesion (1.5cm x 2.0cm)
(B) Right enhancing lesion increasing in size (2.5cm x 2.5cm)

Patient B was a 27 year old gentleman with a positive history of Tuberculosis contact. He had been experiencing on and off headaches for one month and a week of nausea and vomiting. He eventually presented to the emergency department after an episode of generalised tonic clonic seizures. He denied any other constitutional symptoms such as fever, night sweats, chronic cough and loss of weight. He was alert on admission with a GCS of 15 with normal vital signs. His Mantoux test was negative and his ESR was 50. CXR and CT thorax done were normal. An MRI brain performed showed a left temporal lesion with perilesional edema (Fig. 2.)

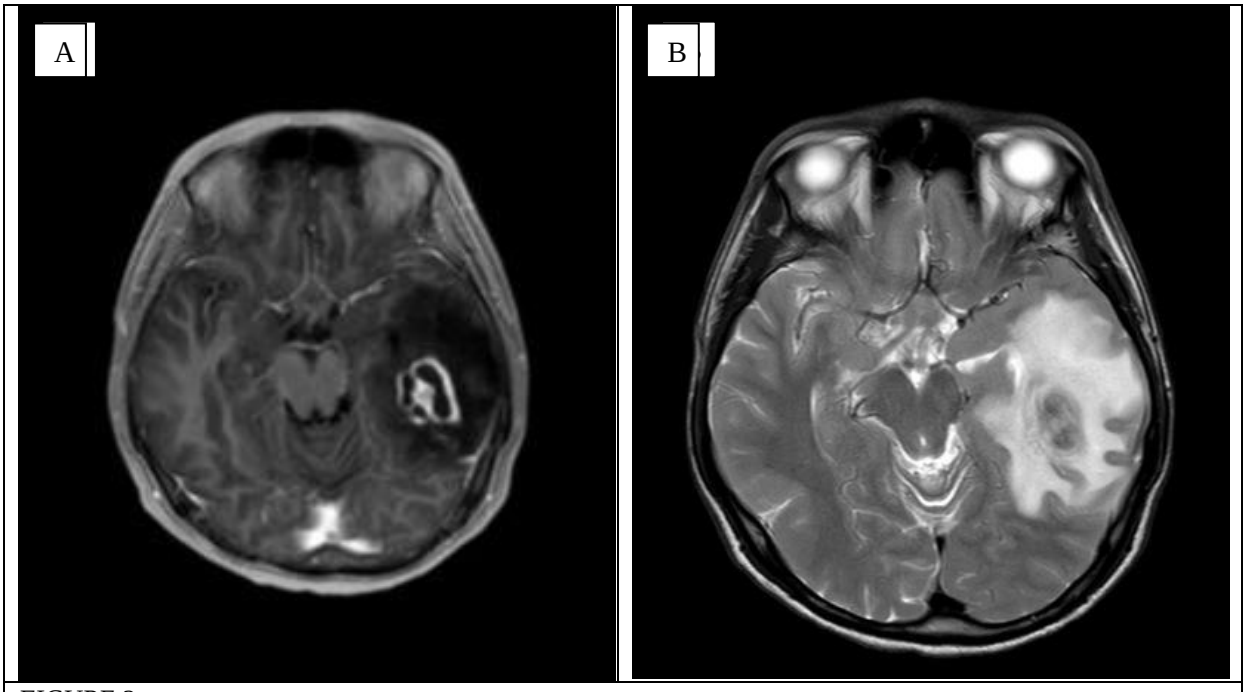

FIGURE 2
(A) MRI brain T1 with contrast noted ring enhancing lesion over the left temporal region (1.5 x 1.5cm)with central target sign

(B) MRI brain T2 noted the lesion causing extensive perilesional edema

He was started on anti-TB medications due to high clinical suspicion. One week later the patient deteriorated with repeat imaging showing worsening edema and midline shift. He underwent an emergency left decompressive craniectomy and lesionectomy. Intraoperatively, the lesion found was soft and yellowish (Fig.3B)

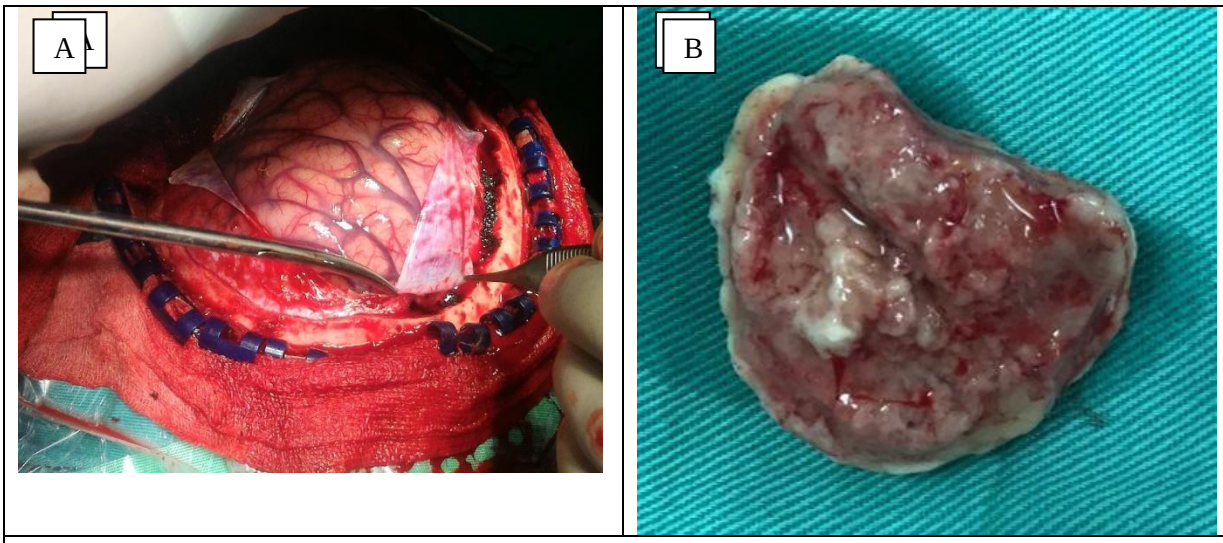

FIGURE 3
(A) Intraoperative image of brain edema despite left decompressive craniectomy
(B) Intraoperative image of the lesion appearing soft and yellowish

Patient C was a 25 year old gentleman who presented with a ten day history of fever which was associated with nausea and vomiting for five days. He had also been unable to talk for three days. Further history from his family suggested that he had no history high risk behaviour. He was clinically aphasic on admission with a GCS of E3V1M5 with his pupils bilaterally 3 mm reactive. His vital sign were stable. CT brain imaging found multiple left frontal lesions with perilesional edema. (Fig.4A) He deteriorated the same day and underwent left decompressive craniectomy. An intraoperative biopsy was taken. The lesion was vascular, soft and greyish. The following image is his post-operative MRI brain findings (Fig.4B).

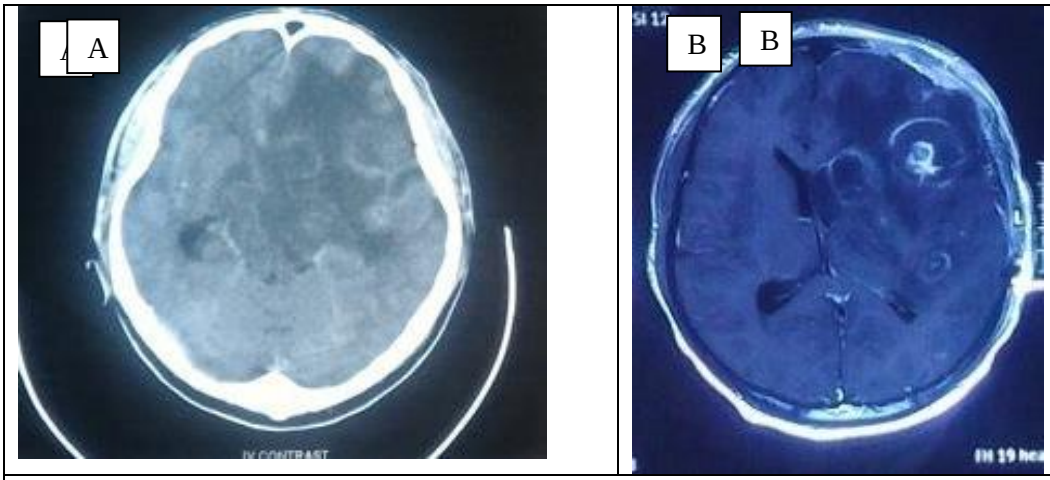

FIGURE 4
(A) CT brain plain axial view done noted multiple lesion over the left frontal region with perilesional edema
(B) MRI brain with contrast axial view done postoperatively noted multiple well defined ring enhancing lesion with typical target sign seen

All the lesions taken intraoperatively were sent for histopathology and revealed brachyzoites that stained positive for toxoplasma. (Fig 5B). Postoperatively, upon further investigation, all patients were tested positive for HIV.

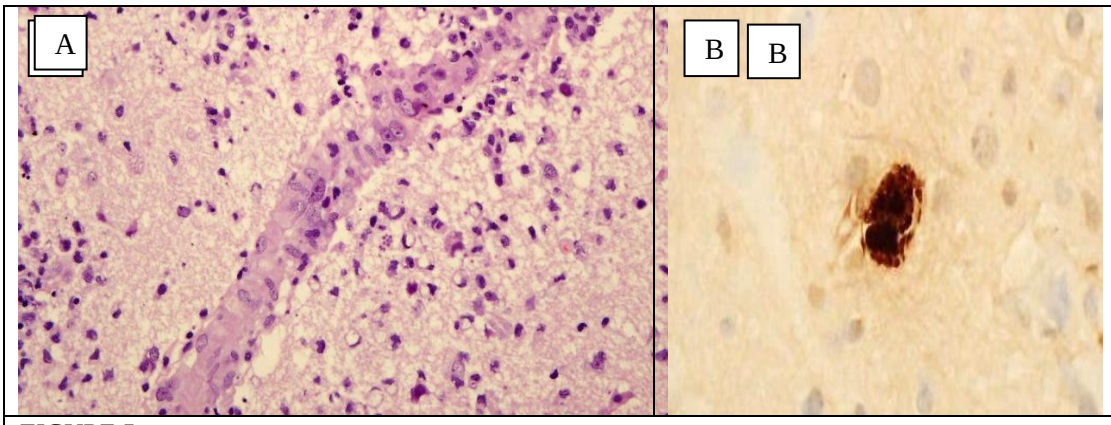

FIGURE 5
(A) Low power field notes small blood vessels infiltrated by inflammatory cells, composed of histiocytes mixed with lymphocytes and a few neutrophils
(B) Within these inflammatory infiltrates small brachyzoites that stained positive for toxoplasmosis stain were seen

Demographics of these patients have been summarized in the table below (Tab 1).

TABLE 1

	PATIENT A	**PATIENT B**	**PATIENT C**
Age	45	27	25
Sex	Female	Male	Male
Presentation symptoms	Fever for 1 week associated with painful facial swelling (nose and cheek)	Generalized tonic clonic seizure (first onset) with history of TB contact	Less responsive with preceding history of fever for 10 days
Consciousness	Alert	Alert	Drowsy
TW	3.0	-	-
ESR	-	50	120
Initial Impression	Right frontal abscess secondary to paranasal sinusitis	Left temporal tuberculoma	Left multiple frontal abscess
Outcome	Survival	Deceased	Deceased
Retroviral screening	Positive	Positive	Positive

Demographic of the 3 patients (age, presentation symptoms, consciousness, impression, outcome of patient with their retroviral screening)

Discussion

Toxoplasmosis accounts for 50 to 70% of intracranial lesions in patients with AIDS. Most patients are given medical treatment and neurosurgical consultation for biopsy is sought if the diagnosis is in doubt.

Toxoplasmosis gondii is an obligate intracellular protozoan parasite that causes toxoplasmosis. Reactivation of latent cyst occurs in immunocompromised host leading to severe infection which are life threatening. Based on Veeranoot et al, the incidence of toxoplasmosis in HIV patients in Malaysia is high with Toxoplasma (IgG) seroprevalence antibody reported to be of 21 to 44.8%.1

Commonly patients present with headache associated with fever, altered mental status, visual disturbance, seizure, cranial nerve abnormalities and sensory disturbance.Motor weakness and speech disturbance are common signs. These symptoms and signs are non-specific and physician should have low

threshold for suspicious of toxoplasmosis in immunocompromised patients whom are febrile. It is often life threatening if the infection is not treated accordingly.

Proper history taking and physical examination are crucial in making a diagnosis. The physician's choice of imaging should be guided by findings from a thorough history and physical examination.[2] The common differential diagnosis would include primary central nervous system (CNS) lymphoma, progressive multifocal leukoencephalopathy, HIV encephalopathy, cytomegalovirus encephalitis, toxoplasma encephalitis, and tuberculoma are the leading diagnosis in developing countries.

The areas of the central nervous system most commonly affected include the basal ganglia, corticomedullary junction, white matter, and periventricular regions.[3] In plain CT brain images, toxoplasmosis appears as multiple hypo to isodense lesion with surrounding edema. Calcification are commonly seen in congenital toxoplasmosis which a rare entity in immunocompromised patient.[3] With contrast, the lesion may shows variable rim enhancement from smooth with thin to solid wall or ill defined eccentric rim.[5]

One of our patients, had multiple contrast enhancing ring lesions with mass effect due to cytotoxic edema caused by the infection. The midline shift has resulted in impaired consciousness of the patient. As his family was unaware and therefore unable to give history of the high risk behaviour, the patient was treated as cerebral abscess until the serology for HIV came back positive.

Meanwhile on MRI brain, toxoplasmosis appears as a hypointense lesion in T1-weighted image with peripheral hyperintensity (which aids in differentiating from CNS lymphoma). On contrast CT the lesions show rim like enhancement with surrounding hypointense area (due to edema).

Vastava et al who studied the imaging characteristics of toxoplasmosis in immunocompromised patients concluded that radiating enhancement in cortical/subcortical regions having very few nodular or ring enhancing lesions--quite different from those in the immunocompromised patients.[6]

CNS lymphoma like toxoplasmosis has predilection for the basal ganglia and at times may be multiple. CNS lymphoma are usually more locally infiltrative (eg: butterfly like spread), more enhancing and has periventricular distribution.[3]

Diagnosis of tuberculous meningitis (TBM) depends upon the detection of the tubercle bacilli in the CSF. Impaired consciousness, seizures, disseminated intravascular coagulation, and signs and symptoms of meningitis with or without spinal fluid changes are all characteristic. Every patient with TBM should preferably be evaluated by imaging with contrast enhanced CT either before or within the first 48 hours of treatment. TBM would have been possible in this case, since it is usually more common in the younger population. TBM is characterised by diffuse brain oedema and demyelination, which are usually extensive, unlike the findings of the patient's brain MRI. Microscopically, TBM is characterised by microvascular necrosis with perivascular macrophage reaction and demyelination along with focal glial nodules in the white matter and occasional haemorrhagic lesions.

A high index of suspicion for toxoplasmosis should be considered in immunocompromised febrile patient. When the absolute CD4 count is less than 100 u/L an incidence of toxoplasmosis reported being 10-34%.[3] Confirmation can be obtained by the high titre IgG anti toxoplasma antibodies. Thus, initiation of prophylaxis treatment for opportunistic infections and their prompt recognition and treatment are the only economically viable options in Malaysia and other developing countries.[2]

Surgical intervention is limited in the form of diagnostic biopsy if the is no response to prophylactic treatment and decompressive craniectomy if the patient has intractable intracranial hypertension.As our case shows, the procedure may have an immediate effect on reducing intracranial hypertension. Agrawal et all recommends that decompressive craniectomy be considered for patients with intractable intracranial hypertension secondary to various causes, infective or otherwise, and suggest it may result in an improved outcome. However, the morbidity is still high as patient may have other illness due to the immunocompromised state. Our patient was referred to infectious disease team for combine management.

Summary

In summary, Toxoplasmosis accounts for 50 to 70% of the cases of intracranial mass lesions in patients with AIDS. Most patients are given medical therapy with neurosurgical consultation for biopsy if the diagnosis is doubtful. These 3 cases reveal the diagnostic dilemma and challenges in management of toxoplasmosis in an immunocrompromised patient as symptoms and signs are non-specific. Thus, a high index of suspicion and prompt diagnosis of HIV is important in the management of toxoplasmosis.

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Chronic Pituitary Dysfunction In Patients With Traumatic Brain Injury – Long Term Follow Up Required In Patients With Cognitive And Mood Disorders

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Abstract

Background: Traumatic brain injury is one of the most common causes of mortality in young adults, with significant long term physical disability, behavioral and neuropsychological deficits. The dysfunction is unrecognized in most traumatic brain injuries. Earlier it was considered to be a rare cause of hypopituitarism. But, in recent times, the surge in the incidence of pituitary dysfunction due to Traumatic Brain Injury is because of increased number of Road Traffic Accidents and increased awareness on the same.

Objective: The main aim of this study was to know the incidence of pituitary dysfunction due to traumatic brain injury and factors influencing the incidence and severity of dysfunction; to determine the prevalence of the dysfunction in patients with cognitive and mood disorders, and to analyze their relationship with endocrine abnormality.

Methods: We have done pituitary hormonal evaluation in 60 patients with traumatic brain injury who met the criteria. Hormonal evaluation was done, first within 24 hours of hospital admission and after 6 months and 1 year of follow up. Cognitive and neuropsychological evaluation done.

Results: Anterior pituitary dysfunction was the most common and observed in 45% of patients of traumatic brain injury in acute phase, and the deficiency persisted at 6 months of follow up. Gonadotropin deficiency was observed in 27% of the patients, and recovered in 21% on follow up and most of the patients suffered with loss of libido and infertility. ACTH deficiency was observed in 32% of the patient in acute phase, glucocorticoid supplementation initiated in immediate post injury period, and recovery was noted in majority. TSH deficiency was observed in 17% of patients, thyroid supplements given for long period, and resolved completely after 6 months. Growth hormone deficiency in 18%, Transient diabetes insipidus in 12%, Cognitive and behavioral abnormalities in 18% were observed.

Conclusion: Alterations in pituitary hormones may be observed post injury in acute phase, the most common dysfunction being gonadotropin and somatotropin deficiency, followed by cortisol and thyrotropin deficiency. Assessment of cortisol is vital in acute phase, as cortisol deficiency if detected, and treated on time, can be life-saving. Long term follow-up regarding hormonal dysfunction is needed in patients with persistent cognitive and mood disorders following head injury. An adequate replacement therapy is of paramount importance.

Key words: Traumatic brain injury, Hypopituitarism, Hypogonadism, Cognitive dysfunction, Fatigability.

Introduction

Traumatic Brain Injury is one of the most common cause of mortality in young adults, with significant long term physical disability, behavioral and neuropsychological deficits. The dysfunction is predominantly a medical problem of the young male because of male to female ratio is 5:1, and in about 60% of the head trauma cases had occurred at the age of 11–29 year[1]. The single decade most a risk is the third. Thereafter, the frequency declines progressively. Even though the majority of patients develop symptoms of hypopituitarism relatively early, may became clinically evident at any time after the accident, and 15% of patients are diagnosed 5 or more years after the trauma[2].

The existence of neuroendocrine dysfunction following traumatic brain injury (TBI) has recently attracted considerable attention, especially since untreated hormonal disorders counteract the recovery from physical and mental sequelae of head injured patients. The spectrum of neuroendocrine dysfunction is wide ranging, from an isolated deficiency including diabetes insipidus to panhypopituitarism, with a broad spectrum of combinations not as selective as in pituitary tumors. Diagnosis of pituitary dysfunction is particularly important as subtle clinical manifestations of head injury are reminiscent of some hormonal deficiencies. The type of trauma is diverse, but in about three fourths of the cases, it is represented by road traffic accidents.

Currently, there is an urgent need for longitudinal studies to provide information on the degree to which pituitary deficiencies in TBI patients are transient or persistent, to define risk factors resulting in pituitary dysfunction, and to distinguish between the impact of brain damage and subsequent intensive care treatment and long-term hormonal and neuropsychological dysfunctions. The present study provides the results of a prospective longitudinal study with meticulous radiological and repetitive clinical and endocrinological assessment in the acute phase after TBI and a long-term follow-up examination with a dynamic neuroendocrine testing and neuropsychological examination.

1.1. Aims and objectives:

The main aim of this study was to determine the prevalence of pituitary dysfunction presenting with cognitive and/or mood complaints and/or fatigability late after a mild traumatic brain injury (TBI) and factors influencing the incidence and severity of dysfunction; to determine the prevalence of the dysfunction in patients with cognitive and mood disorders, and to analyze their relationship with endocrine abnormality.

1.2. Material and methods:

We have done pituitary hormonal evaluation in 60 patients with traumatic brain injury who met the criteria. The first evaluation done within 24 hours of hospital admission. Reassessment done after 6 months & 12 months of follow up. We analyzed the patients based on demographics, imaging, GCS, GOS; cognitive and neuropsychological evaluation done during recovery.

Imaging: CT & MRI brain.

Pituitary hormonal assessment: Anterior & Posterior pituitary hormones.

Pituitary hormones Screening protocol:

ACTH:

1. Morning basal serum cortisol in acute phase on day1,
2. 1-4 days post injury measures on every patient,
3. 5-10 days post injury measures on clinically suspicious patients.

1. Reassess ACTH and TSH deficiencies before discharge.
2. Treat ACTH and TSH deficiencies

1. Reassess at 6 months.
2. Treat ACTH, TSH, FSH/LH deficiencies as appropriate

1. Reassess at 12 months. 2. Clinical evaluation.

Cognitive and Neuropsychological evaluation: MOCA (Montreal Cognitive Assessment) and EBIS questionnaire

Follow up: Hormonal assessment and GOS.

Inclusion Criteria[3,4]:

1. All TBI patients who need hospitalization in Neurosurgery units and ICU monitoring in particular, regardless of severity, should be screened in acute phase and at 12 months follow up.
2. Those with a history of complicated mild TBI, moderate or severe TBI, who experience clinical signs and/or symptoms associated with hypopituitarism should be screened.
3. Complicated TBI is defined by the presence of at least one of the following conditions:
   a. Need for hospitalization for more than 24 hours
   b. Need for ICU monitoring and/or need for any neurosurgical intervention.
   c. Presence of acute pituitary hormone changes during the first 2 weeks after TBI (ACTH deficiency and/or Central DI)
   d. Any anatomical changes on initial CT or MRI

Exclusion criteria:

1. Mild TBI patients who are discharged from emergency units
2. Who have no loss of consciousness and/or post traumatic amnesia of less than 30 minutes
3. TBI patients in a chronic vegetative state with low life expectancy
4. Who have pre-existing dyshormonogenesis
5. Who died or lost follow up

1.3. Results:

Among 60 patients, 48 were males and 12 were females. Mean age of presentation is 31.6 years. Most common mode of injury was road traffic accidents with 86.6% incidence, followed by fall and assault. Patients GCS was recorded at the time of admission and graded as Complicated mild TBI [n= 15 (25%)], Moderate TBI [n= 28 (47%)], Severe TBI [n= 17 (28%)].

Anterior pituitary dysfunction was the most common and observed in 45% (27) of patients in acute phase, and the deficiency persisted at 1 year follow up. ACTH deficiency was seen in 15% and manifested as Hypotension, Hyponatremia & Apathy; Glucocorticoid supplementation given immediately in intensive care unit and recovery noted in 74% at 1 year of follow-up. FSH/LH deficiency seen in 11.6%, presented with Loss of libido and infertility; sex hormone supplementation given and 71.4% recovered at 1 year. TSH deficiency seen in 8.3%, hypothyroidism resolved completely after 6 months with thyroid hormone supplementation. ADH deficiency seen in 11.6% manifested as Diabetes Insipidus and vasopressin supplementation given, complete recovery seen after 6 months. Growth hormone deficiency seen in 10%, no supplementation given. Cognitive and behavioral abnormalities were observed in 18.3%, required long-term neuropsychological rehabilitation. (Table.1 & 2)

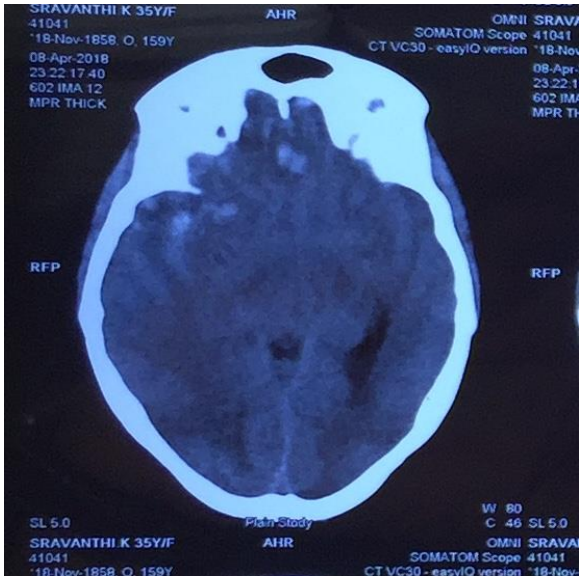
Clinical presentation:

1. Loss of libido and infertility – 11.6%
2. Hypotension, Hyponatremia & Apathy – 15%
3. Hypothyroidism – 8.3%
4. Diabetes insipidus – 11.6%

5. Cognitive and behavioral abnormalities – 18.3%

Management – Hormonal supplementation:

1. ACTH deficiency – Glucocorticoids
2. Hypothyroidism – Thyroid hormones
3. Diabetes Insipidus – Vasopressin
4. Growth Hormone deficiency – No supplementation required up to 1 year
5. Cognitive and behavioral abnormalities – Psychosocial rehabilitation



"Fig. 1": CT brain showing basifrontal and temporal hemorrhagic contusion with obliteration of cistern spaces.

Table. 1: Incidence of hormonal deficiencies

Type of deficiency	Complicated mild TBI n= 15 (25%)	Moderate TBI n= 28 (47%)	Severe TBI n= 17 (28%)
ACTH deficiency (15%) n = 9	2	4	3
FSH/LH deficiency (11.6%) n = 7	1	3	3
TSH deficiency (8.3%) n = 5	2	1	2
ADH deficiency (11.6%) n = 7	2	2	3
Growth hormone def (10%) n = 6	2	2	2
Cognitive & Behavioral abnormalities (18.3%) n = 11	3	3	5

Table. 2: Manifestations of hormonal deficiencies, management and follow up

Type of deficiency	Acute Phase	Chronic Phase	Treatment	Follow up
ACTH deficiency (15%)	Hypotension Hyponatremia	Apathy	Glucocorticoid supplementation	74% recovered at 1 year
FSH/LH deficiency (11.6%)	Loss of libido	Infertility	Sex steroid hormones supplementation	71.4% recovered at 1 year
TSH deficiency (8.3%)	Hypothyroidism	Hypothyroidism	Thyroid supplements	Resolved after 6 months
ADH deficiency (11.6%)	Diabetes insipidus	Diabetes insipidus	Vasopressin	Resolved completely
Growth hormone def (10%)	No manifestations	No manifestations	Not required up to 1 year	86% recovered at 1 year
Cognitive & Behavioral abnormalities (18.6%)	Fatigability, irritability	depression	Psychosocial rehabilitation	Needs long term treatment

Table. 3: Comparative analysis

Type of deficiency	Tanriverdi F et al, n=30 (2008)	Kleindiest et al, (n=23) 2009	Tanriverdi F et al, n= 25 (2013)	Present study n=60 (2017-18)
ACTH deficiency	20% (1yr), 6.6% (2yr)	48% (2yr)	16% (1yr), 4% (3yr), 4% (5yr)	15%
FSH/LH deficiency	3.3% (1yr), 0 (3yr)	5% (2yr) (High Prolactin 5%)	8% (1yr), 4 (3yr), 0 (5yr)	11.6%
TSH deficiency	6.6%, 0 (3yr)	5% (2yr)	4% (1yr), 0 (3yr), 0 (5yr)	8.3%
ADH deficiency	-	-	-	11.6%
Growth hormone	43.3% (1yr), 23.3% (3yr)	39% (2 yr)	44% (1yr), 23% (3yr), 28% (5yr)	10%

Cognitive & Behavioral abnormalities	-	-	-	18.6%

1.4. Discussion:

TBI-induced hypopituitarism was first reported approximately 95 years ago[5]. Until recently, neuroendocrine dysfunction after TBI was thought to be an uncommon disorder; however, two cornerstone papers published in 2000 drew attention to TBI-induced pituitary dysfunction and stimulated new research[6,7]. Although the frequency of chronic hypopituitarism after TBI varies widely between the studies, most report a range of 15%–50%[8,9]. The frequency of pituitary dysfunction varies according to the severity of trauma, type of trauma, time elapsed since trauma, study population, study design, endocrine testing, and the criteria used to diagnose anterior pituitary hormone deficiency[10].

In a meta-analysis by Schneider et al that included 1,015 TBI patients from ten cross-sectional and four prospective studies, the pooled prevalence of anterior hypopituitarism has been reported as 27.5%. The most common pituitary hormone deficiencies found in the majority of the studies were growth hormone and gonadotropin (follicle-stimulating hormone/luteinizing hormone [FSH/LH]) deficiencies. The pooled prevalence of hypopituitarism in mild, moderate, and severe TBI was estimated to be 16.8%, 10.9%, and 35.3%, respectively. These data clearly show that although the risk of developing hypopituitarism is highest in patients with severe TBI, the risk is substantially high in mild TBI even comparable with moderate TBI. However, it is important to mention that all patients with mild TBI included in the meta-analysis needed hospitalization and neurosurgical intervention[11]. In present study, anterior pituitary dysfunction was observed in 45%; the most common dysfunction being gonadotropin and somatotropin deficiency, followed by cortisol and thyrotropin deficiency. The prevalence of hypopituitarism in Complicated mild TBI, Moderate TBI, Severe TBI was 25%, 47%, and 28%.

In a recent systematic review of 27 studies that evaluated all pituitary axes, 31% of the patients had long-term hypopituitarism, as defined by at least one anterior pituitary hormone deficiency[12]. In contrast, in one study, hypopituitarism was reported to be rare, in unselected head trauma patients admitted to emergency departments, and it was concluded that routine pituitary screening in these patients is unlikely to be cost-effective. However, most of the patients in that study had mild TBI and do not need hospitalization and/or neurosurgical intervention, and most were discharged directly from the emergency service[13]. It is tempting to speculate that when the extremely high number of people suffering TBI is taken into account, even low rates of hypopituitarism, such as 1%, translate into a large number of patients with TBI-induced pituitary dysfunction. There is an insufficient number of prospective studies in the literature.

Only three, long-term prospective studies have evaluated pituitary function for longer than 12 months[14,15,16]. In the study by Kleindienst et al, 23 patients with mild, moderate, or severe TBI were screened during the acute phase and at 24–36 months after their injury. In the chronic phase, 48% of the patients had ACTH deficiency and 39% had growth hormone deficiency[16]. In the 3-year prospective study of 30 patients (63% with mild TBI) by Tanriverdi et al 23.3% had growth hormone deficiency and 6.6% had ACTH deficiency 3 years after TBI[14]. The longest prospective study, performed by the same research group, evaluated 25 patients (64% with mild TBI and 36% with moderate or severe TBI) 1, 3, and 5 years after TBI. Although most of the pituitary hormone deficiencies improved over time, there were significant rates of pituitary hormone deficiency 5 years after TBI (28% growth hormone, 4% ACTH, and 4% gonadotropin)[15]. The main limitation of these prospective studies was the low numbers of patients screened. The statistical analysis of present study was comparable with the long term prospective studies and needs to follow up for longer duration. (Table. 3)

1.5. Conclusion:

In TBI patients with persistent cognitive disorders, fatigability or mood disorder, the risk of anterior pituitary deficiency is high and justifies a systematic pituitary assessment with specific reference tests. According to the current literature, approximately 15%–20% of TBI patients may develop chronic hypopituitarism, which clearly suggests that TBI-induced hypopituitarism is a frequent problem, in contrast with previous assumptions. Long term follow-up regarding hormonal dysfunction is needed in patients with

persistent cognitive and mood disorders, apathy and sexual dysfunction. An adequate replacement therapy is paramount importance.

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Comparative Study Between Local And Intravenous Dexamethasone On Postoperative Pain After Elective Lumbar Spine Surgery: A Randomized Controlled Study

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Abstract

Background: severe postoperative pain is commonly associated with spine surgeries. Improved functional outcome, early ambulation, early discharge, and preventing the development of chronic pain have been linked to adequate control of pain in this period.

Aim: we intended to compare between local and intravenous dexamethasone on postoperative pain after elective lumbar spine surgery.

Settings and Design: This is a prospective randomized controlled double-blinded clinical study.

Patients and Methods: 180 patients, aged 18-45 years with physical status classes I and II of the American society of Anesthesiologists were studied. Scheduled elective lumbar spine surgery under general anesthesia were randomly divided into three study groups. Each group contains 60 patients: (Group I): received 16 mg dexamethasone IV drip. (Group II): received 16 mg dexamethasone subcutaneous injection around the scar after skin closure. (Group III): received 500 ml saline infusion. Patients were observed for postoperative pain for 48 hours by using the visual analog scale, duration of analgesia and any side effects.

Statistical Analysis Used: one-way ANOVA test and Chi-square test were.

Results: A highly significant difference between placebo and local infiltration groups and between placebo and intravenous groups was detected regarding postoperative need for fentanyl. A statistically significant difference was found when comparing local infiltration and intravenous groups as regards postoperative consumption of fentanyl.

Conclusion: local dexamethasone infiltration was found more effective than intravenous administration in postoperative pain management after elective spine surgery.

Keywords: dexamethasone, postoperative pain, spine surgery

Introduction

Spine surgeries often needs a lot of dissection of subcutaneous tissues, bones, and ligaments that result in a significant degree of postoperative pain. [1] Satisfying pain relief is, therefore, an important factor of patients' postoperative care. Adequate pain mangement in these patients is aggravated as many of these patients suffered a lot from chronic pain and managed with traditional analgesics or narcotics. The preexisting pain along with long-term consumption of analgesics and opioids alter pain perception in these patients thereby complicating pain management.[2,3] Effective pain control facilitates early mobilization as well as expedites hospital discharge. Chemical mediators such as substance P, hydroxytryptophan, bradykinin, serotonin, and prostaglandins are released as a result of tissue damage that results in stimulation of the A (delta) and C nerve fibers and thus results in pain perception.[4]

Postoperative pain has been managed with multimodal analgesia approaches. One of these is the injection of dexamethasone [5]. Postoperative pain, nausea and vomiting induced mainly by acute inflammation caused by tissue damage. Therefore, dexamethasone is mainly useful in minimizing pain, nausea, and vomiting due to its powerful anti-inflammatory effect. Dexamethasone is the most potent anti-inflammatory drug with a long half-life and is considered safe for less than two weeks duration even in amounts above physiological doses [6].

Glucocorticoids have an understood mechanism of action, however, some suggested theories of action include: Inhibitory effect on release of inflammatory mediators (prostaglandin, bradykinin), “pain threshold” reduction

prevention which results after surgeries and tissue swelling reduction caused by anti-inflammatory effects and thus inhibit nerve compression by inflammatory tissue [7].

Both systemic administration of Dexamethasone [8,9] and local infiltration [10] can decrease scores of postoperative pain and average consumption of analgesics, as well as treat postoperative nausea and vomiting.

The aim of the current study is to compare between Local and intravenous dexamethasone on postoperative pain after elective lumbar spine surgery.

Patient and methods:

Our institute's ethical committee approved this randomized prospective double-blinded controlled study to be implemented at Fayoum university hospital for two years (from February 2016 till May 2018) on 180 patients Scheduled for elective lumbar spine surgery after obtaining a written informed consent for anesthesia was obtained from every patient and the nature of our study and the complications have been explained to them.

Inclusion criteria included patients aged 18 - 60 years, Weighted 55 - 85 Kg and with patients physical status ASA classes I and II Scheduled for elective lumbar spine surgery**.**

Exclusion criteria included Patients with anemia (hemoglobin concentration<10gm.dl), systemic hypertension, significant cardiovascular diseases, renal diseases, chronic pain, diabetes mellitus, and hepatic diseases.

Patients were randomly divided into three equal groups by the use of computer-generated random numbers. Group I included 60 patient injected with 16 mg Dexamethasone IV drip on 500 cc saline (dexamethasone sodium phosphate USP 8mg/ 2ml amp. EIPICO pharmaceutical Egypt). Group II included 60 patient injected 16 mg Dexamethasone subcutaneously around the scar of the operation after closure of skin and Group III received Placebo as infusion with 500 cc saline intravenously.

Parameters of primary outcome were VAS score and the patients' need for further analgesics. Other settings were hemodynamic changes and occurrence of side effects or complications.

The visual analog scale (VAS) is a psychometric response scale which can be used in questionnaires. It measures subjective characteristics or attitudes that cannot be measured directly. Responding to a VAS item is indicated by specifying the level of agreement by respondents to a statement by admitting a position along a continuous line between two end-points.

This continuous (or "analog") aspect of the scale differentiates it from discrete scales such as the Likert scale. Visual analog scales have high metrical characteristics than separate scales; thus a more full range of statistical methods can be applied to the measurements.

Statistical analysis:

We calculated the sample size by using the G power program 3.1.9.2. Data were analyzed using SPSS version 16 (SPSS Inc., Chicago, IL). Results are declared as the mean ± standard deviation for continues (pain severity, MAP, HR, RR, and number and percentage of qualitative variables as morphine). Comparison of quantitative data between groups was made using ANOVA followed by post hoc test (LSD). Within-group comparison at each time follow up was done using measurement of analysis of variances repeatedly (ANOVA)." Mauchly test for checking sphericity condition as a prerequisite assumption was conducted. In conditions were this assumption was not satisfactory, multivariate Wilk's λ test was used. < 0.05 was considered as statistically significant.

Results:

One hundred eighty patients were included in our study and were randomly divided into three groups; each group has 60 patients. There was no statistically significant difference between the study groups as regards the demographic data: (sex, age, weight, height, ASA) as shown in (Table 1).

Table 1: demographic data:

		Group I	Group II	Group III	*p*-value
Age (years.)		28.5±7.2	32.35±9.2	30.2±9.6	0.38
Weight (Kg)		72.8±7.3	71.1±6.7	73.5±7.6	0.55
Sex	Male	51 (85%)	42(70%)	45 (75%)	0.52
	Female	9 (15%)	18(30%)	15 (25%)	
ASA physical status	I	54(90%)	54 (85%)	54 (85%)	0.86
	II	6(10%)	6 (15%)	6 (15%)	
Duration of surgery (min.)		77.5±28.6	67.8±28.8	68±28.5	0.51

*Data were presented as mean, and SD except for age and ASA were presented as numbers and percent. SD = standard deviation ASA= American Society of Anesthesiologists.

The mean blood pressure, heart rate, and respiratory rate show no statistically significant difference between the three groups when measured at 30 minutes up to 24 hours postoperatively (table 2).

Table 2: hemodynamic characteristics of the study groups

		G I	GIII	GIIII
Mean Blood pressure (mmHg)	30 min	83.17±4.94	80.75±4.4	83.3±6.4
	1h	85.5±5.4	84.4±6.4	85. 5±6.9
	4h	92.67±7.48	91±5.29	92.16±6.4
	6h	93.67±4.8	92.08±7.2	95.8±5.2
	12h	92.5.75±5.9	88.7±9.05	94.3. ±6.5
	24h	96±6.5	88.17±9.35	93.167±5.6
Heart rate	30 min	71.52±8.2	76.48±7.9	75.7±8.56
	1h	71.5±7.1	74.75±13.39	80±88.01
	4h	81,75±8.59	79.25±6.26	85.75±8.95
	6h	81.25±7.57	84±6.62	89.4±8.15
	12h	87±6.96	83.55±5.7	89.75±6.88
	24h	91.12±5.42	81.92±8.2	91.25±7,8
Respiratory rate	30 min	14.45±1.67	14.8±1.7	15.65±1.36
	1h	14.5±1.74	15.48±1.39	15.95±1.64
	4h	16.3±1.54	15.45±-1.74	17.1±1.9
	6h	16.65±1.65	16,55±1.67	17.75±1.27
	12h	17.85±1.53	16.45±1.96	18.5±1.52
	24h	18.7±1.4	16.7±1.36	21.5±13.7

*Data are presented as mean ± SD. P > 0.5 insignificant Intergroup comparison by Post hoc test Bonferroni test. intragroup comparison by repeated measure ANOVA showed significant values changes across time.

The VAS score difference was highly significant among patients in the placebo group when compared to those in the other two groups (table 3).

Postoperative morphine needs showed a highly significant difference between placebo and local infiltration groups at 1 hour up to 24 hours postoperatively (table 3).

Postoperative morphine needs showed a highly significant difference between placebo and IV groups at 1 hour up to 6 hours postoperatively. (table 3).

The needs for morphine postoperatively showed a significant difference between local infiltration and IV groups at 4, 12 and 24 hours postoperatively. (table 3).

The occurrence of nausea was significantly different between IV and placebo groups (table 4).

No significant difference was detected between the three study groups regarding the occurrence of wound and chest infections (table 4).

Table 3: Comparison of pain score and need for morphine between groups

		G I	GII	GIII	P values		
					P I & II	PI&III	P II& III
VAS	30 min	0	0	0	>0.99	>0.99	>0.99
	1h	0.25±.78	0.22±-89	2.3±2.1	0.99	0.00	0.00
	4h	2.8±1.6	3.25±1.49	5.25±2.23	0.84	0.00	0.00
	6h	4.12±1.22	4.45±1.6	6.95±2.29	0.99	0.00	0.00
	12h	5.58±1.5	4.7±1.7	7.7±1.7	0.063	0.00	0.00
	24h	7.7±1.6	3.7±1.57	8.45±1.8	0.07	0.017	0.00
Morphine use*	30 min	0	0	0	>0.99	>0.99	>0.99
	1h	2(5.0)	1(2.5)	20(40.0)	0.99	0.001	0.001
	4h	6(15.0)	15(37.5)	34(85.0)	0.022	0.00	0.001
	6h	29(72.5)	26(62.5)	40(100.0)	0.46	0.001	0.001
	12h	39(97.5)	29(72.5)	40(100.0)	0.001	0.26	0.001
	24h	40(100.0	6(15.0)	40(100.0)	0.00	0.99	0.00

*Data are presented as mean ± SD and presented as Number (percent).

Table 4 postoperative follow up and complications among the study groups.

	G I	GIII	GIIII	P values		
				P I & II	PI&III	P II& III
Nausea*	10(25.0)	15(37.5)	21(52.2)	0.227	0.01	0.177
Chest infection*	6(15.0)	6(15.0)	12(30.0)	0.99	0.108	0.108
Wound infection*	5(12.5)	2(5.0)	9(22.5)	0.24	0.23	0.023

*Data are presented as mean ± SD and presented as N(%).

Discussion:

In our study, results showed that the sensation of pain was markedly diminished in both IV administration of dexamethasone and local subcutaneous infiltration of wound techniques and the postoperative needs for analgesics up to 24 hours postoperatively without effects on postoperative injury or chest infection.

This result was proved by the markedly lower VAS score and less needs for postoperative morphine in both IV and local infiltration dexamethasone groups when compared to the placebo group.

Strong anti-in bflammatory characteristics of dexamethasone were attributed to the introduction of "dexamethasone induced postoperative pain reduction" theory. Although it is not clear how dexamethasone works as an analgesic, decrease in cyclooxygenase and lipoxygenase production, via inhibition of peripheral phospholipase appears to play the main role [11].

Proinflammatory factors and cytokine production in damaged tissue can be decreased in locally infiltrated dexamethasone group via lipocortin 1, a glucocorticoid-inducible protein that has been recognized as an important endogenous mediator of glucocorticoids' anti-inflammatory activities [12]. This then reduces local

edema and decreases pain at the surgical site. Furthermore, inhibiting phospholipase enzyme has a major role in pain relieve by the absorbed plasma dexamethasone from local tissue [13].

Cardoso et al. carried out a randomized, double-blinded, placebo-controlled study to evaluate the effect of a single preoperative dose of Dexamethasone on the postoperative period after cesarean section (CS). They studied 70 women with a full term pregnancy randomized to receive either dexamethasone 10mg in 100 ml of isotonic saline, intravenously or 100 ml of isotonic saline (placebo) before surgery. They found that patients who received dexamethasone at some time during the period of study had a lower pain at rest and on movement and pain scores were lowered by dexamethasone in the first day postoperatively after CS with spinal anesthesia by morphine. [14].

Shahraki et al. conducted a double-blind prospective randomized clinical trial was performed on 60 patients' candidate for elective cesarean section. Patients were randomly classified into two groups: A (received 8 mg IV Dexamethasone) and B (control received 2 ml normal saline). Significant differences were detected in terms of pain severity ($P < 0.001$), MAP ($P = 0.048$) and HR ($P = 0.078$; marginally significant), which were lower in cases group than the control group so they found that IV Dexamethasone post-operative pain severity and analgesic consumption could be reduced efficiently also the vital signs were improved after CS [15].

In 2015 a meta-analysis was published Li et al. to assess the effect of local analgesia on pain intensity reduction when injected via wound catheters. They evaluated Nine RCTs with 512 patients. Cumulative morphine consumption was lower in LA group compared with placebo group in the first 12 h (SMD = -0.736, 95% CI (-1.105, -0.368)), 24 h (SMD = -0.378, 95% CI (-0.624, -0.132)) and 48 h after surgery (SMD = -0.913, 95% CI (-1.683 to -0.143)). Lower morphine consumption was monitored in the first six hours after surgery, but significant reduction could not reach the common standard significant level. In the LA group compared with placebo group, significant reduction of pain scores was achieved at 12 hours but not six hours postoperatively. At 24 hours and 48 hours postoperatively, the pain score was lower, but significant reduction could not reach the common standard significant level. They concluded that wound infiltration with LA could reduce morphine requirements but not pain scores after CS [16].

A.M.Maged et al. compared local and intravenous dexamethasone on postoperative pain and recovery after CS and the results were similar to our achievement [17].

Subjective over objective assessment of pain was considered the main limitation in our study along with non-reporting the effect of the drugs on nausea and vomiting and inability to follow up the vital signs for more than 24 hours.

To our knowledge, this study is the only one done to compare the effects of both IV and local dexamethasone on postoperative pain after elective lumbar spine surgery. We found that the sensation of pain and postoperative needs for analgesics were markedly reduced by IV administration of dexamethasone and local subcutaneous infiltration of wound up to 24 hours postoperatively without any detected complications.

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Correlation Of Appearance Of MRI Perinidal T2 Hyperintensity Signal And Eventual Nidus Obliteration Following Photon Radiosurgery Of Brain Avms

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Abstract

The present work aims at studying the MRI-defined changes following photon radiosurgery of AVMs and to specifically correlate the appearance of perinidal T2 hyperintensity signal with the eventual angiographic obliteration of AVM nidus in response to stereotactic radiosurgery (SRS).

This retrospective study included 62 patients with brain AVMs who received photon SRS treatments between 2004 and 2017. The follow up period extended for ≥2 years following SRS.

Of the 30 AVMs with both MRI evidence of non-visualized nidus and angiographic verification of complete nidus obliteration, 20 (66.7 %) AVMs were associated with prior MRI evidence of appearance of perinidal T2 hyperintensity signal on an average of 12 months (range; 6-45 months) after radiosurgery. Lower Spetzler-Martin grade ($p = 0.013$), smaller AVM volume ($p = 0.017$), and appearance of post-SRS perinidal T2 hyperintensity signal ($p = 0.007$) were the statistically significant independent predictors of AVM obliteration.

Since the SRS-induced hemodynamic changes within the AVM nidus had initiated the cascade of subsequent formation of perinidal vasogenic brain edema, the appearance of perinidal high T2 signal in the post-SRS follow up MRIs would be a valuable prognostic sign of eventual angiographic obliteration of the AVM nidus following photon radiosurgery.

Keywords: AVM, radiosurgery, linac, gamma knife, hyperintensity.

Introduction

The desired goal of radiosurgery treatment of brain AVMs is complete obliteration of the AVM nidus without radiation-related complications. Such complications are attributed to the delivery of clinically significant radiation doses to normal brain tissues lying immediately adjacent to the AVM nidus or embedded within the nidus itself. [1-3] As the radiosurgery target volume increases, the volume of normal tissue receiving clinically significant dose rapidly increases, and consequently the higher the complication rate. [4-6] So, the selection of patients with cerebral AVMs for the radiosurgery treatment should be based on weighing the benefits versus the risks of radiosurgery, with respect to the natural history and to those of other treatment modalities (i.e., microsurgery and endovascular surgery). [7,8] The AVM angioarchitecture should be kept in consideration when making radiosurgery treatment decisions to avoid the adverse radiation effects. [6]

Kjellberg et al. [9] and Kjellberg [10] first described the latency period of 6 months to 3 years after radiosurgery before achieving complete obliteration of the AVM nidus. However, Cohen-Inbar et al. [2], recently reported that documentation of AVM obliteration can extend to as much as 5 years after radiosurgery.

Magnetic resonance imaging (MRI) is a noninvasive radiological study for accurate evaluation of AVM patency as well as the changes in the surrounding brain parenchyma after radiosurgery. [11-13] In approximately 30% of patients treated with radiosurgery for AVMs, follow up neuroimaging studies demonstrated transient changes, namely a high signal region on T2-weighted spin-echo MRI in areas surrounding the target and that had previously appeared normal. [11,14-17] These changes are usually observed 6-18 months after radiosurgery and are frequently transient.[15,18]

The purpose of the current work is to study the MRI-defined changes following photon radiosurgery of AVMs and to specifically correlate the appearance of perinidal T2 hyperintensity signal with the eventual angiographic obliteration of AVM nidus in response to radiosurgery treatment.

Material and Methods

Based on the availability of clinical and neuroimaging follow up data for a minimum of 24 months after SRS treatments, a combined study series of 62 patients with 62 AVMs were included in the present retrospective study (2004-2017). The Linac series (Alexandria Linac Radiosurgery Center, Egypt) included 21 patients/AVMs and the Gamma knife (GK) series (Koto Memorial Gamma Knife Center, Japan) included 41 patients/AVMs. The combined study series included 44 males and 18 females and the patients' age ranged between 10 and 73 years (mean=34 years). The demographics of the studied patient population are summarized in *"Tab. 1"*.

The study was approved by the Committees of Medical Ethics at both the Alexandria University in Egypt and the Koto Memorial Hospital in Japan.

Tab.1: Characteristics of the combined series of 62 patients with SRS-treated AVMs

Characteristic	***Cases***
Gender (Male/Female)	*44/18*
AVMs location:	
Superficial	*36*
Deep	*15*
Cerebellar	*9*
Brain stem	*2*
Spetzler-Martin grade:	
Grade I	*7*
Grade II	*19*
Grade III	*22*
Grade IV	*12*
Grade V	*2*
Prior treatment(s):	

None	*42*
Surgery	*5*
Embolization	*10*
Surgery + Embolization	*5*
Radiosurgery treatment:	
Linac-based SRS	*21*
Gamma knife-based SRS	*41*

1.1. Radiosurgery treatment

In the Linac-based SRS, 21 patients with 21 AVMs, averaging 5.71 cm^3 in volume (range; 0.46-18.04 cm^3), were treated with 1-2 isocenters, with an average prescribed marginal dose of 18.14 Gy (range; 12-25 Gy), to the average isodose line of 80% (range; 75-85%). The mean maximum target dose was 30.08 Gy (range; 19.28-49.98 Gy). The higher maximum doses are observed in the cases (n=3) treated with multiple isocenters. In such treatment plans, the inevitable hot spots resulted in inhomogeneous dose distributions, unlike the typical homogeneous dose distributions in single isocentric treatments of most of the cases (n=18).

In the GK-based SRS, 41 patients with 41 AVMs, averaging 4.22 cm^3 in volume (range; 0.02-23.8 cm^3), were treated with an average prescribed marginal dose of 19.13 Gy (range; 11-22 Gy), to the average isodose line of 50.98% (range; 48-63%). The mean maximum target dose was 37.53 Gy (range; 22-45 Gy).

The details of the radiosurgery dosimetry are presented in *"Tab. 2"*.

Tab.2: Radiosurgery dosimetry in the 62 studied cases with SRS-treated AVMs

SRS modality / ***Dosimetry***	***Linac-based SRS*** *(n=21)*	***GK-based SRS*** *(n=41)*
Target volume (cm^3) • *Mean* • *Range*	*5.71* *0.46-18.04*	*4.22* *0.02-23.8*
Marginal target dose (Gy) • *Mean* • *Range*	*18.14* *12-25*	*19.13* *11-22*
Marginal isodose line (%) • *Mean* • *Range*	*80* *75-85*	*50.98* *48-63*
Maximum target dose (Gy) • *Mean* • *Range*	*30.08*	*37.53*

	19.28-49.98	*22-45*
No. of isocenters	*1-2*	-

1.2. Post-radiosurgery follow up

The post-radiosurgery follow up period ranged from 24 to 141 months (mean = 54 months). Both clinical and radiological follow up were performed at regular intervals every six months after SRS. The study included only patients with available follow up MRIs for at least 2 years post-radiosurgery. Patients with less than 24 months of available complete clinical and radiological follow up data were excluded from the present study. Once MRI evidence of AVM nidus obliteration was observed, then, a confirmatory cerebral angiography was obtained to document complete nidus obliteration. The post-radiosurgery MRIs were also reviewed for evidence of newly developed perinidal T2 changes, namely; white mater hyperintensities (high signals) in either T2-weighted MRI or FlAIR (Fluid-Attenuated Inversion Recovery) MRI sequences.

1.3. Statistical analysis

Patient, AVM, radiosurgery, and post-radiosurgery variables were assessed as covariates in a Cox proportional hazards regression analysis to determine factors associated with obliteration, each reported with hazard ratio (HR) and 95% confidence interval (CI). Covariates with P <0.05 in the univariate analysis were entered into a multivariate model to identify independent predictors of obliteration. All statistical tests were 2 sided. Statistical significance was defined as P <0.05.

Results

In the Linac-SRS series (n = 21 patients/AVMs), complete angiographic nidus obliteration was documented in 17 (89.5 %) cases at a mean of 32 months (range; 8-65 months) after SRS *"Fig. 1"*.

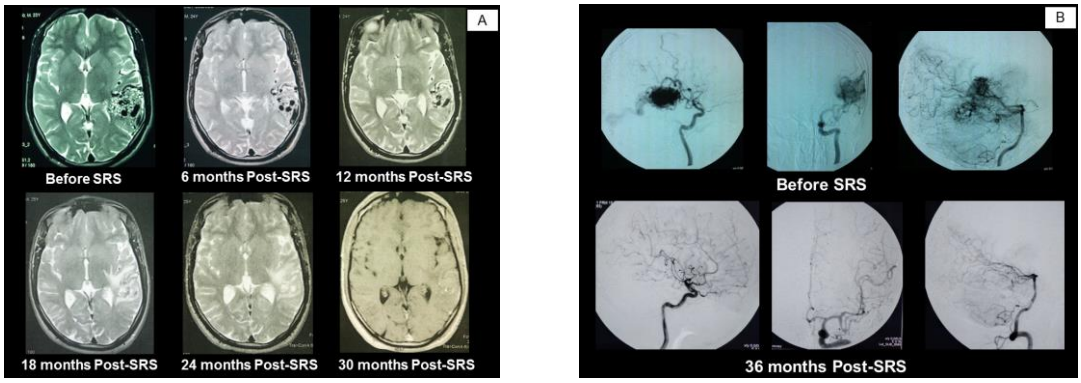

Fig. 1: *(**A**) Axial brain MRI of a patient with left tempro-parietal AVM treated with Linac-based SRS. T2-weighted images showing the appearance of perinidal high T2 signal at 6, 12, 18, and 24 months after SRS, which was associated with progressive reduction in the size of the signal voids of the treated AVM nidus. Gadolinium-enhanced axial T1-weighted MRI, at 30 months post-SRS, showed non-visualization of signal voids and slight contrast enhancement at the gliotic area that was previously occupied by the AVM nidus.* ***(B)*** *Digital subtraction angiograms (DSA) of the same patient confirming the complete obliteration of the AVM nidus at 36 months after radiosurgery.*

In the Gamma knife-SRS series (n = 41 patients/AVMs), complete angiographic nidus obliteration was documented in 13 (81.3 %) cases at a mean of 41 months (range; 20-66 months) after SRS *"Fig. 2"*.

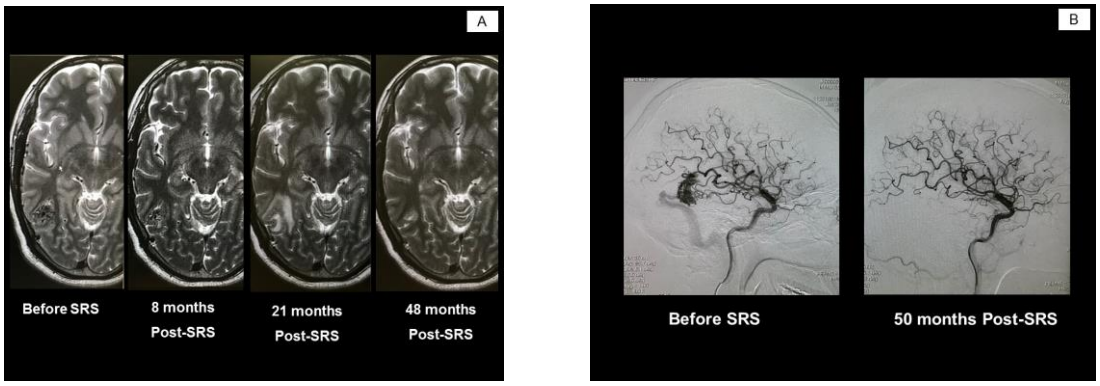

Fig. 2: (A) *Axial brain MRI, T2-weighted images, of a patient with right parietal AVM treated with GK-based SR), showing that the signal voids of the AVM nidus progressively decreased in size at 8 months and 21 months post-SRS and became non-visualized at 48 months post-SRS. Also noted is the appearance of perinidal high T2 signal at 21 months after SRS, which almost completely resolved at 48 months post-SRS.* ***(B)*** *Conventional cerebral angiograms of the same patient at 50 months after radiosurgery documented the complete obliteration of the AVM nidus.*

In the combined-SRS series (n = 62 patients/AVMs), complete angiographic nidus obliteration was documented in 30 (85.7 %) cases at a mean of 36 months (range; 8-66 months) after SRS *"Tab. 3"*.

Tab.3: AVM nidus obliteration following SRS treatment in the studied cases

Study series / ***Parameter***	***Linac-based series***	***GK-based series***	***Combined study series***
No. of reviewed cases	*33*	*60*	*93*
No. of cases with available ≥2 years clinical and MRI follow up	*21*	*41*	*62*
No. of cases with MRI evidence of complete nidus obliteration	*18*	*32*	*50*
MRI obliteration rate	*85.7%*	*78.1%*	*80.6%*
Timing of MRI obliteration (months): • *Mean* • *Range*	*24* *8-39*	*33* *16-66*	*29* *8-66*
No. of cases with available angiographic follow up	*19*	*16*	*35*
No. of cases with angiographically-verified complete nidus obliteration	*17*	*13*	*30*
Angiographic obliteration rate	*89.5%*	*81.3%*	*85.7%*
Timing of angiographic obliteration (months): • *Mean* • *Range*	*32*	*41*	*36*

	8-65	*20-66*	*8-66*

The post-radiosurgery serial follow up MRIs showed the appearance of perinidal high T2 signal in 34 (54.8%) cases. Such T2 hyperintensity was transient and reversible in 13 (20.9%) cases and persistent in 21 (33.9%) cases. The perinidal high T2 signal appeared between 6 and 45 months (mean; 12 months) after radiosurgery and the transient changes resolved within 6-30 months (mean; 17 months). Symptomatic T2 hyperintensity signal, which required steroid treatment, occurred in 8 (12.9%) cases *"Tab. 4"*.

Tab.4: MRI changes after SRS in the combined series of 62 cases with AVMs

MRI finding	***Cases***
Perinidal high T2 signal: • *Reversible* • *Persistent* • *Symptomatic*	*34 (54.8%)* *13 (20.9%)* *21 (33.9%)* *8 (12.9%)*
Timing of appearance of perinidal high T2 signal (months): • *Mean* • *Range*	*12* *6-45*
Duration of reversible perinidal high T2 signal (months) : • *Mean* • *Range*	*17* *6-30*

Of the 30 AVMs with both MRI evidence of non-visualized nidus (i.e., complete nidus obliteration) and angiographic verification of complete nidus obliteration, 20 (66.7 %) AVMs were associated with the prior MRI evidence of appearance of perinidal T2 hyperintensity signal on an average of 12 months (range; 3-45 months) after radiosurgery. Of the 5 AVMs with both MRI evidence of decreased nidus size and angiographic verification of partial nidus obliteration, 4 (80 %) AVMs showed perinidal T2 hyperintensity signal on post-SRS follow up MRIs *"Fig. 3"*.

Lower Spetzler-Martin AVM grade (grades I-III), smaller AVM volume (< 10 cc), and appearance of perinidal T2 hyperintensity signal in post-SRS follow up MRIs were the statistically significant independent predictors of AVM obliteration in Cox proportional hazards regression analysis. The development of perinidal hyperintensity on T2 MRI after SRS was the strongest predictive factor of eventual AVM obliteration in the multivariate analysis (P = 0.007) *"Tab. 5"*.

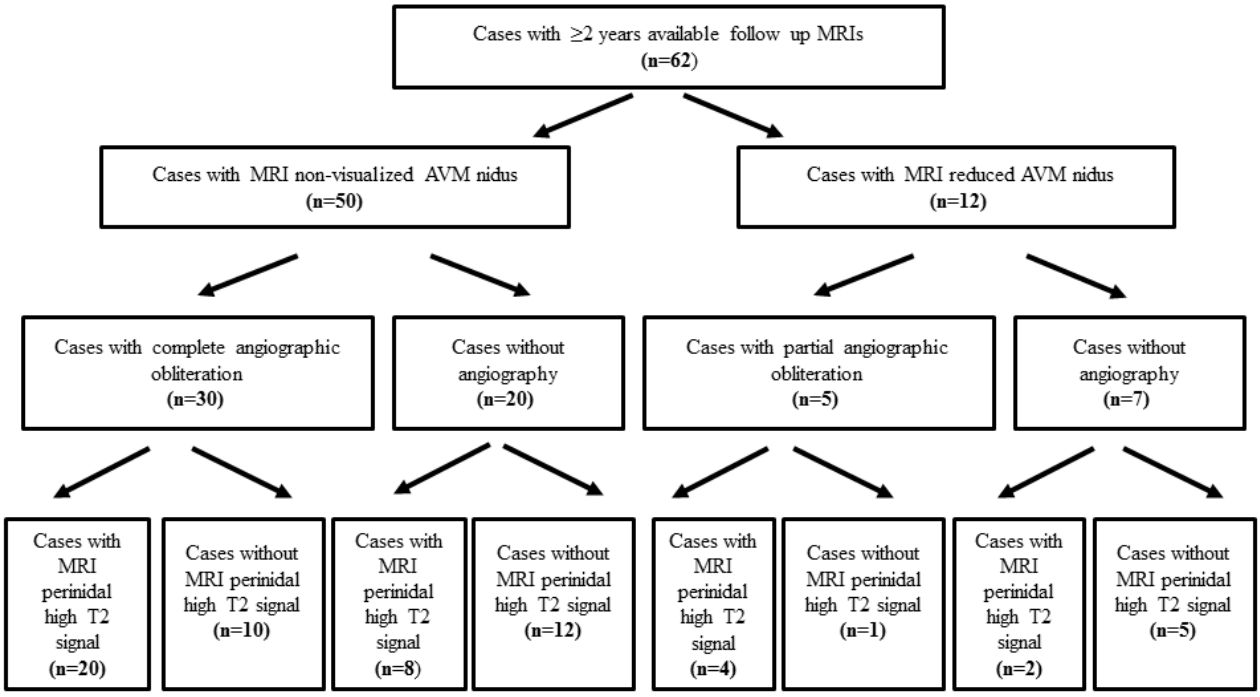

Fig. 3: *A flow chart showing the distribution of appearance of MRI perinidal high T2 signal in the 2 subsets of patients with angiographically-verified, complete or partial obliteration of AVM nidus in response to stereotactic radiosurgery (SRS) treatment.*

Tab.5: Univariate and multivariate Cox proportional hazards regression analysis for predictors of AVM obliteration after SRS

Variables	***Univariate***			***Multivariate*****		
	Hazard ratio (HR)	***95% Confidence interval (CI)***	***P value***	***Hazard ratio (HR)***	***95% Confidence interval (CI)***	***P value***
Patients' age	*0.170*	*0.988-1.068*	*1.027*			
Patients' sex	*0.304*	*0.083-2.170*	*0.425*			
AVM location						
Superficial	*0.388*	*0.076-1.976*	*0.254*			
Deep	*0.637*	*0.116-3.497*	*0.604*			
Cerebellum	*1.184*	*0.201-6.984*	*0.852*			
Brain stem	*4.143*	*0.230-74.699*	*0.335*			
Lower Spetzler-Martin AVM grade	*8.600*	*2.124-34.815*	*0.003**	*11.934*	*1.685-84.548*	*0.013**
Hemorrhagic presentation	*0.544*	*0.131-2.264*	*0.403*			
Previous treatment	*1.062*	*0.278-4.055*	*0.929*			

Smaller AVM volume	*7.333*	*1.778-30.250*	*0.006**	*18.239*	*1.667-199.539*	*0.017**
Higher marginal dose	*1.049*	*0.830-1.327*	*0.688*			
Higher isodose line	*0.984*	*0.938-1.033*	*0.514*			
Higher maximum dose	*1.020*	*0.937-1.110*	*0.643*			
Post-SRS perinidal T2 hyperintensity signal	*8.889*	*1.752-45.110*	*0.008**	*50.531*	*2.914-876.118*	*0.007**
Post-SRS persistent contrast enhancement	*2.415*	*0.276-21.159*	*0.426*			

** Statistically significant at $p < 0.05$*

*** Only variables with $p < 0.05$ were included in the multivariate analysis*

Discussion

The desired radiobiological effects of radiosurgery treatment of AVMs are morphologically, histologically, immunohistochemically, electronmicroscopically and radiologically demonstrated by the hallmarks of both the small vessel wall changes and the proliferative and degenerative changes occurring in the connective tissue stroma of the AVM after stereotactic irradiation. [9,10,19-23]

It has been reported that in ≥30% of patients treated with radiosurgery for AVMs, follow up neuroimaging studies demonstrated transient changes, namely a high-signal region on T_2-weighted spin-echo MRI or a low attenuation area on CT scan in areas surrounding the treatment volume that had previously appeared normal. [6,14,17,24,25] Levegrün et al. [16.26] and Tu et al. [27,28] have attributed these image-defined responses following AVM radiosurgery to either post-radiation changes (i.e., blood-brain barrier injury or interstitial vasogenic edema or both) or to a local biologic effect in the adjacent brain parenchyma (i.e., reactive astrogliosis) in response to AVM obliteration.

Serial brain MRI studies have proved accuracy and safety in analyzing both early and delayed radiation changes following radiosurgery of AVMs. [11-13,15,23] The early radiosurgery effects are thought to contribute to the appearance of the T2 hyperintensity signal in the follow up MRIs. Such radiological finding could be attributed to swelling of the endothelial cells, opening of the intervening tight desmosomal junctions, breakdown of the blood-brain barrier, and hence transudate formation, resulting in vasogenic brain edema. [9,24,26] However, cerebral angiographic studies following radiosurgery of AVMs have demonstrated that progressive decrease in blood flow usually precedes the reduction in the size of the treated AVMs. [29]

The explanation of the radiological appearance of perinidal T2 hyperintensity signal in the post-radiosurgery MRIs, as proposed by the authors of the present study, could be the greater sensitivity of the endothelial tissue of the smaller nidal blood vessels to irradiation than that of the larger perinidal blood vessels. The inhomogeneous radiation dosimetry within the radiosurgery treatment volume will result in differential radiobiological effects, which are maximal closer to the isocenter and minimal closer to the periphery of the target. Accordingly, the smaller nidal vessels will receive much greater radiation dose compared to the larger perinidal vessels. Such proposed explanation is further supported by the findings of other researchers [24,30,31] who reported that, in contrast to the radiation-induced obliteration cascade of the smaller nidal vessels, the radiation-induced damage of the larger perinidal vessels will hinder the vessel wall nourishment and lead to subsequent increased vessel wall permeability.

The increased intraluminal hydrostatic pressure in the perinidal vessels, coupled with the radiation-induced reduction in the sizes of feeding arteries and draining veins, is the driving force for trans-luminal transudation of plasma proteins and fluids through the highly permeable vessel walls and hence the formation of perinidal vasogenic brain edema. [24,29,32] However, the ongoing radiation-induced progressive decrease in the size of the

AVM nidus will result in progressive decrease, and eventually loss, of the differential pressure gradient between the perinidal and intranidal vessels. In turn, the rate of transluminal fluid transduction and the perinidal vasogenic brain edema would gradually subside. Such hemodynamic changes would be seen, in the serial follow up MRIs following AVM radiosurgery, as a gradually successive decrease of the intensity of the prior perinidal high T2 signal. [1,24,29,32]

Radiation-induced changes (RICs), the most common complications of radiosurgery for brain AVMs, are defined as newly developed perinidal T2 hyperintensity on MRI, with or without associated neurological symptoms. These changes are usually observed from 6 to 18 months after radiosurgery and are frequently transient and reversible (i.e., resolving over weeks or few months). [1,2,24,14,15,33-36] Ilyas et al. [35], based on pooled data from 51 studies, reported that approximately 1 in 3 patients with AVMs treated with SRS develops radiologically-evident RIC, and of those, 1 in 4 patients develops neurological symptoms. The present study showed 20.9%, 33.9%, and 12.9% rates of transient, persistent, and symptomatic RICs, respectively. However, Feutren et al. [36] reported a much higher rate of radiologic brain edema (66%) in his series of 48 patients treated with Cyberknife for AVMs. Matsuo et al. [34] reported post-Linac SRS actuarial symptomatic radiation injury rates of 12.3%, 16.8%, and 19.1%, at 5, 10, and 15 years, respectively, and recommended long-term observation after SRS for AVMs. Ding et al. [33] reported that the rates of radiologic, symptomatic, and permanent RICs (35%, 10%, and 4%, respectively) were not significantly different in the 2 cohorts of patients with repeat SRS versus those with initial SRS.

Literature review revealed that the most commonly reported factors associated with favorable outcome of radiosurgery for AVMs were; ruptured AVMs, lower AVM grade, smaller AVM volume, and higher marginal dose. [2,34,37-41] The present study showed that Spetzler-Martin grades I-III, AVM volumes < 10 cc, and more significantly, the appearance of perinidal T2 hyperintensity signal in post-SRS follow up MRIs were independent predictors of AVM obliteration, which is consistent with other AVM radiosurgery series. [2,24,34,37-42]

The importance of MRI appearance of perinidal high T2 signal, after radiosurgery of AVMs, in predicting nidal obliteration has been highlighted by other investigators. [24,37,42] Arrese Regańón et al. [37] reported that the development of hyperintensity on T2 MRI after the treatment was among the strongest predictive factors of achieved nidal obliteration in 77% of their series of 59 radiosurgically treated AVMs. Van den Berg et al.[42], in a series of 30 patients with post-SRS T2 high-signal-intensity changes surrounding brain AVMs, achieved a 88% obliteration rate in 14 (47%) patients with high signal intensity changes beyond the 10-Gy isodose area. Mobin et al. [24] reported, in their series of 50 AVMs treated with Linac radiosurgery, that the appearance of perinidal high T2 signal had 72% sensitivity, 70% specificity, and 71% overall accuracy in predicting nidal obliteration in 13 (72%) patients who had concomitant perinidal high T2 signal in follow up MRI studies. Findings of the current study showed that out of the 34 (54.8%) patients, who showed post-SRS perinidal T2 hyperintensity signal, 24 (70.6%) patients demonstrated eventual angiographically-verified obliteration of their AVM nidi. The relatively lower obliteration rate, in the present study, is attributed to the strict inclusion of only patients with documented angiographic nidus obliteration. None of the patients without available angiographic studies were included in the statistically-tested series, since angiography is the gold standard for adjudicating AVM obliteration.

Conclusions

The current study might further refine the explanatory mechanisms of the radiation-induced tissue changes following AVM radiosurgery. The development of MRI perinidal hyperintensity was the strongest predictive factor (P = 0.007) of eventual angiographic obliteration of the AVM nidus following photon radiosurgery. The appearance of perinidal high T2 signal in the follow up MRIs after radiosurgery would be a valuable prognostic sign of the AVM response to radiosurgery treatment.

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De Novo Aneurysm Formation Following Arteriovenous Malformation Excision: A Case Series

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Abstract

De novo aneurysm formation in general is 0.84% per year (1). Age, female sex, smoking and hypertension and infratentorial location of AVM are risk factors (1,2). Rapid development and rupture within 1 year is known and shortest reported interval within 10 days. De novo formation of an intracranial aneurysm that develops at sites that were previously angiographically normal have been well described, and are either new spontaneous aneurysms at site separate from the inital aneurysm or aneurysm that were not detected by preoperative angiograph. New aneurysm developing following exclusion of arteriovenous malformation from the brain circulation are rarely described in literature, typically occurring after radiosurgery or embolization. Several possible explanations for the de novo formation of aneurysm. A change in the hemodynamic environment caused by major vessel ligation, after stent placement, and after removal of arteriovenous malformation (3) may induce the de novo aneurysm by overloading some vascular territories. Interaction between hemodynamic stress and structural weakness plays a major role in development of the aneurysm, and can typically be seen after therapeutic occlusion of the carotid artery. In patients with brain arteriovenous malformation (AVM), it usually arises on the feeding artery due to abnormal high flow. Abnormal high flow in the vessel results in smooth muscle damage and release of local factors related to aneurysm progression, such as nitric oxide synthase. (4)Furthermore, congenital defect in the tunica media and acquired factors, such as degenerative changes, arterial hypertension, is also involved in the pathogenesis. This flow-related aneurysm often decreased in size after removal of AVM or aberrant hemodynamic stress.(5) Formation of the aneurysm in our patient may have been part of the natural history of the lesion, independent of treatment. It is difficult to know, from a case series what set of factors or circumstances led to aneurysm formation in our patient. We were fortunate in documenting the progression of these events before a new rupture. These are rare cases, first reported in our centre, to our knowledge, de novo aneurysm developed in an artery hemodynamically related to a surgically removed AVM. This complication was probably due to the postoperative hemodynamic changes in the vessels afferent to the AVM, associated with arterial wall dysplasia.

Keywords: De Novo Aneurysm, Arterio-venous malformation excision

Introduction

Aneurysms associated with AVM most commonly develop on newly formed primary collateral routes as a result of increased flow through these collaterals. Development of aneurysms is not commonly seen in vessels whose flow has been directly decreased bytherapeutic or natural occlusion. Typically these aneurysm are classified in terms of flow in relation to the arteriovenous malformation. The pathogenesis of aneurysm formation is primarily attributed to hemodynamic stress leading to degeneration and remodelling of the internal elastic lamina resulting in development of aneurysm De novo formation of an intracranial aneurysm that develops at sites that were previously angiographically normal have been well described, and are either new spontaneous aneurysms at site separate from the initial aneurysm or aneurysm that were not detected by preoperative angiograph. New aneurysm developing following exclusion of arteriovenous malformation from the brain circulation are rarely described in literature, typically occurring after radiosurgery or embolization.

Case Series:

Case Report 1

A 27 years old man presented with severe headache, nausea and vomiting, in the absence of an obvious cause. He had no previous history of trauma. A CT brain revealed a spontaneous left intracranial haemorrhage for which he underwent decompressive craniectomy. Subsequently an MRI/MRV/MRA and cerebral angiogram was done which showed 2.7 x 2.1 x 2.6 cm left frontal insular AVM. He underwent excision of AVM. He subsequently developed subarachnoid haemorrhage 6 months after surgical excision of AVM. Cerebral angiogram confirmed the findings of 2 aneurysms; fusiform ACOM measuring 4.6 x 3.2 mm and Left supra-clinoid aneurysm of 3.7 x 2.5 x 3.2 mm. No residual AVM was noted.

Case Report 2

A 3 years old girl presented with sudden onset of right upper limb weakness. Further investigations showed a left temporal intracranial bleed with AVM. CT angiogram and MRI showed temporal AVM measuring 1.1 x 0.5 x 0.7 cm draining into deep cerebral veins. She underwent embolization of the AVM, with complete excision. Follow up of 6 months revealed 2 distal aneurysms measuring 0.6 x 0.7 x 0.6 cm and 1.3 x 1.0 x 1.3 cm.

Case Report 3

A 55 years old man with underlying hypertension presented with history of throbbing left sided headache, slurred speech associated with right sided body weakness. He was found unconscious and was brought in to Hospital. His workup revealed a left parietal arteriovenous malformation and aneurysm over the left MCA bifurcation. He underwent craniotomy and excision of AVM and clipping of aneurysm. Follow up imaging done at 9 months after AVM removal, revealed new ACOM aneurysm measuring 2.5 x 2 x 2.4cm.

Case Report 4

A 38 years old lady with underlying hypertension, presented in March 2012 with right sided hemiparesis,slurred speech with reduced level of consciousness. Cerebral angiogram revealed a left frontal parietal AVM measuring 2.2 x 2.0 x 2.5 cm with right supraclinoid aneurysm measuring 2.2 x 2.5 x 1 draining tosuperior sagittal sinus. (Spetzler Martin II). She underwent craniotomy and excision of AVM. Intraoperatively, AVM was successfully excised. However, at 6 weeks post excision, patient presented with spontaneous IVH, angiogram done showed a Right supraclinoid aneurysm, measuring 2.2x1.8.2.7 cm, and a newly developed ACOM aneurysm measuring 1.1 x 1.8x.1.3cm. No residual AVM was noted on the angiogram.

Figure 1:

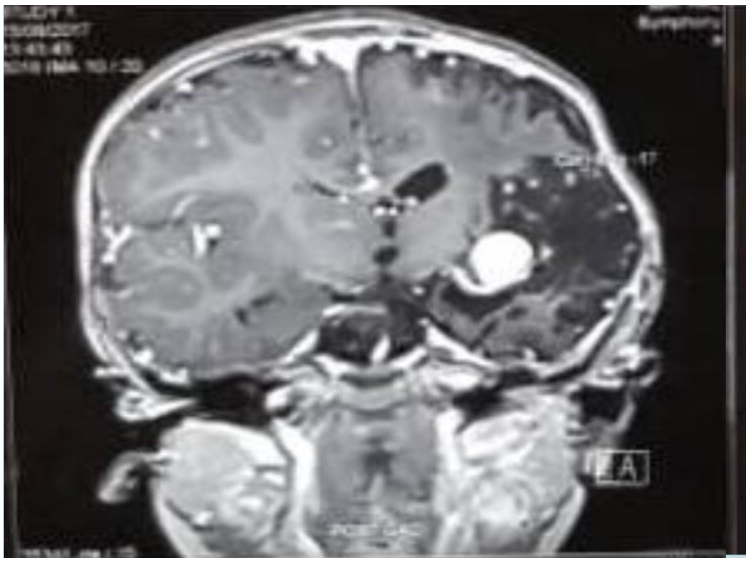

Figure 2

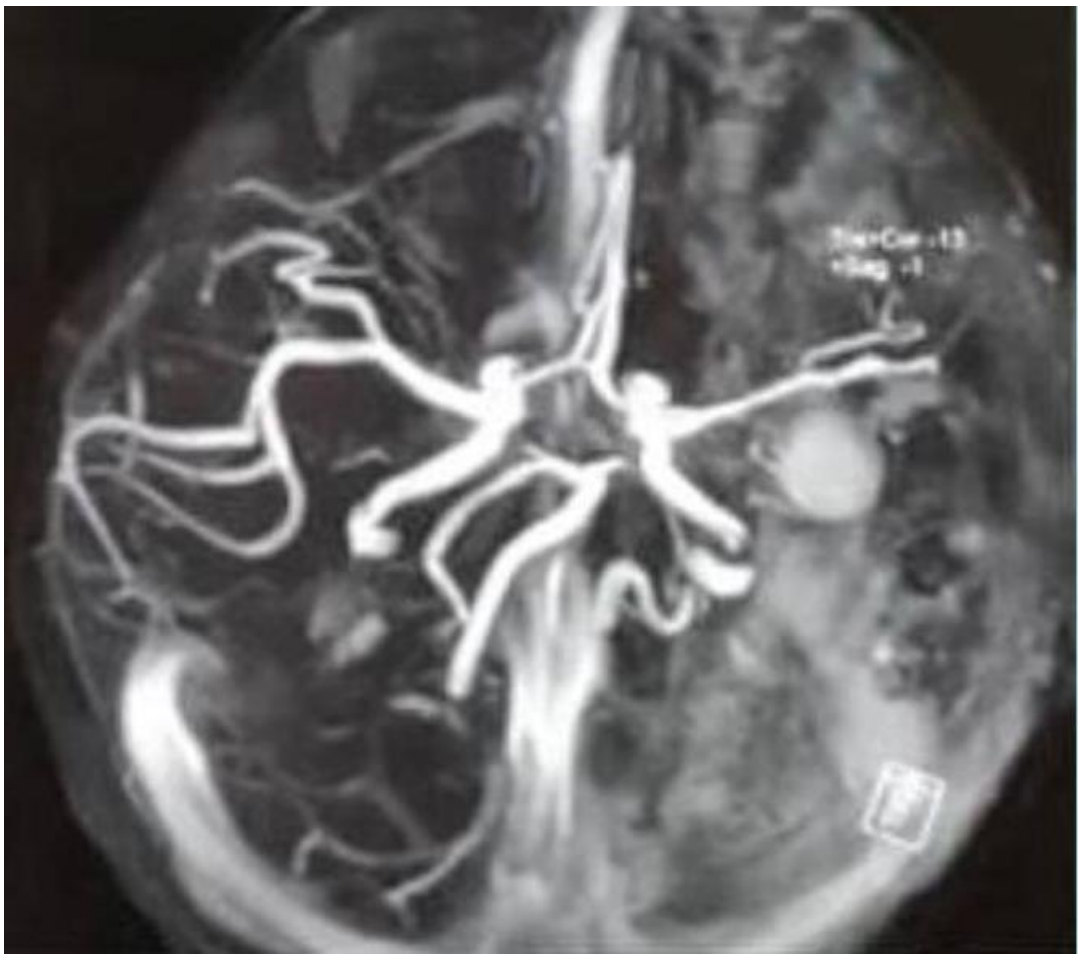

Figure 1 and & 2 : MRI & CT Angio showed Left temporal AVM measuring 1.1 x 0.5 x 0.7 cm draining into deep cerebral veins.

Figure 3:

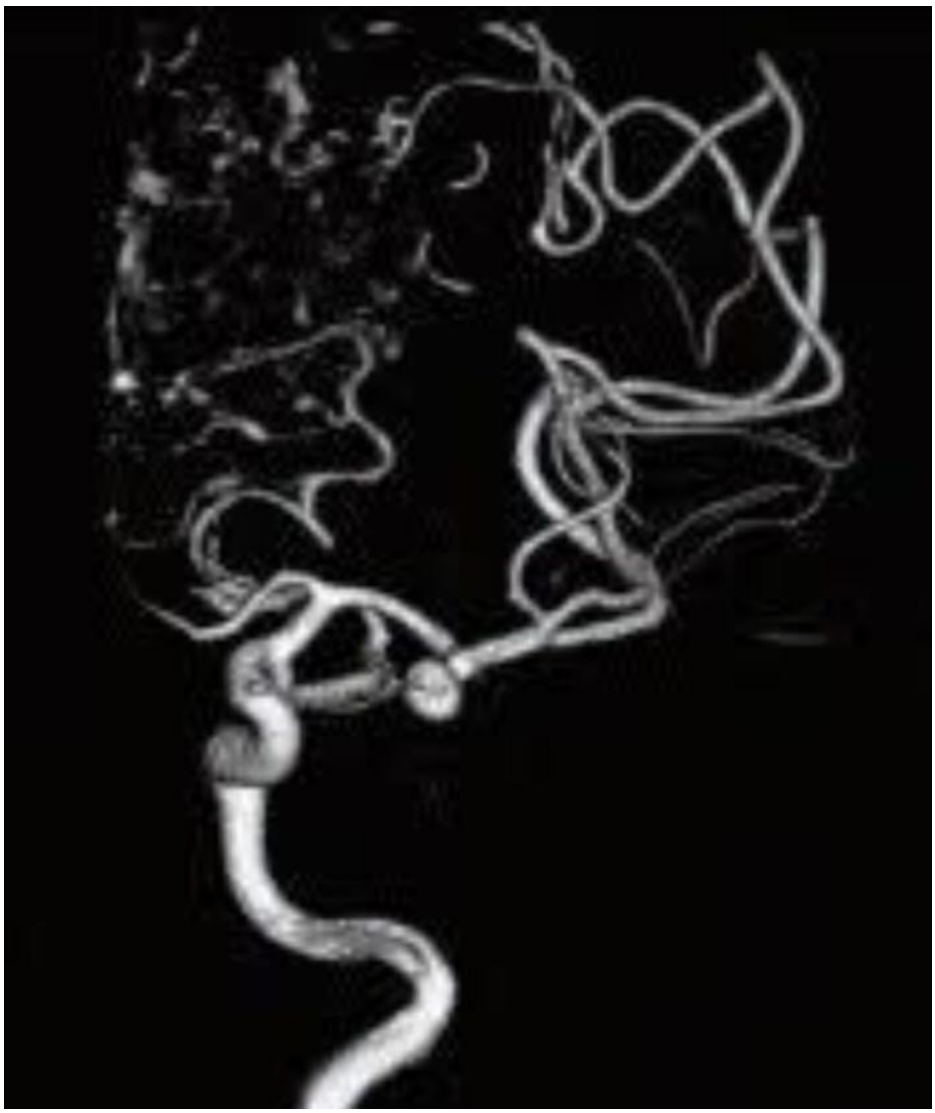

Figure 3: Cerebral angiogram showed left parietal AVM and aneurysm over the left MCA bifurcation.

Figure 4:

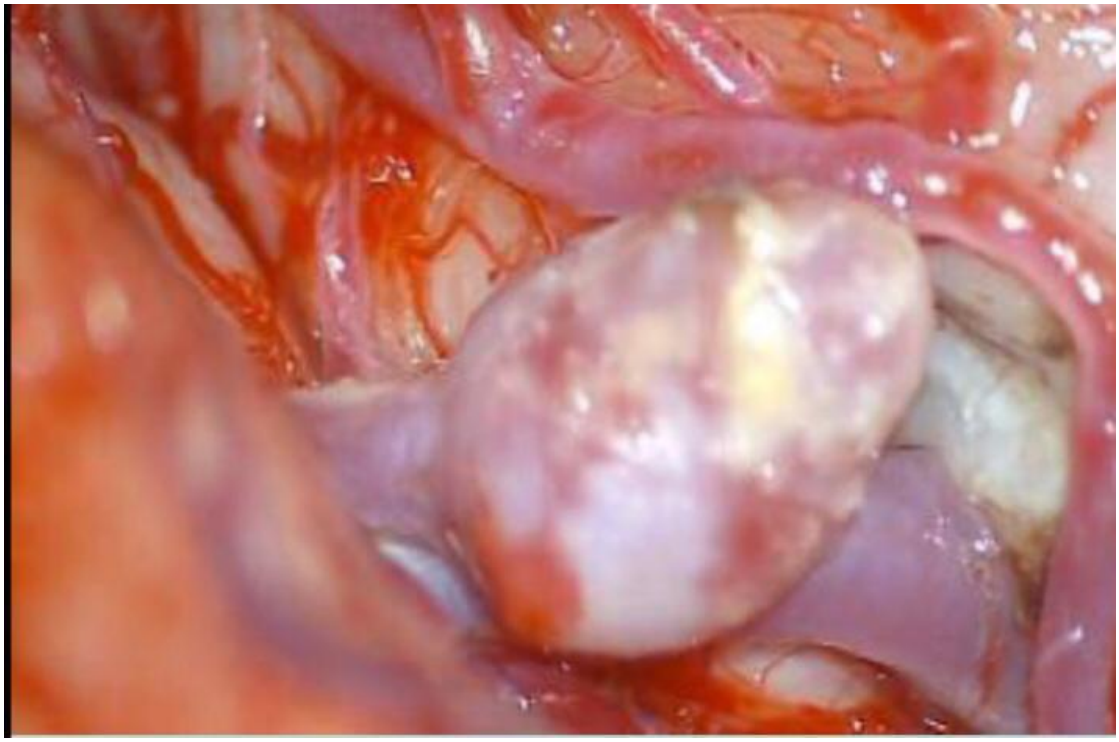

Figure 4: Intraoperative findings of Left MCA bifurcation which was clipped successfully.

Figure 5:

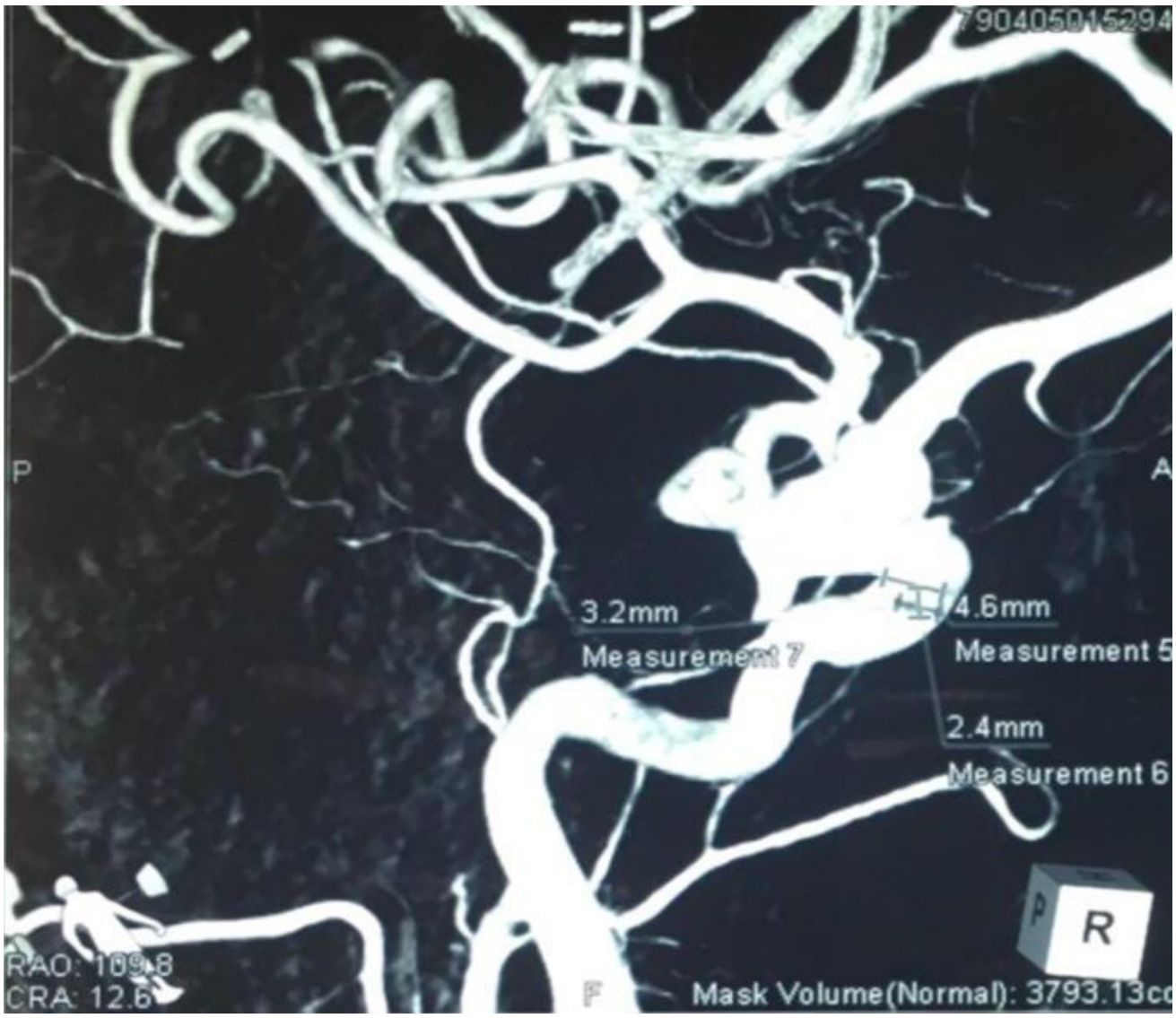

Figure 5: Cerebral angiogram showed right supraclinoid anuerysm and newly developed Acom aneurysm post excision of AVM.

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Early Prognostication Tool For Patients At Risk Of Cerebral Infarction After Anterior Circulation Aneurysm Rupture

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Abstract

Purpose

Cerebral infarction(CI) causes poor outcome after aneurysmal subarachnoid haemorrhage(SAH) and is secondary to multiple factors. This necessitates a simple prediction model for establishing high risk group patients for early preventive treatment of CI.

Methods

All anterior circulation aneurysm rupture patients with SAH who were surgically clipped in Queen Elizabeth 2 Hospital from 1st July,2014 to 31st January,2018 were retrospectively analysed. Significant predictors for CI after multivariate analysis were used to develop the VINODH score which is named after the author and was also internally validated. Patient risk groups for developing CI were derived from this validation and was correlated with mRS score at the time of discharge.

Results

200 patients were included after applying strict exclusion criteria and also excluding missing data. Median age of patients were 51 years with 59.5% female. Multivariate analysis proved only four out of the nine predictors were significant for developing CI when other factors were adjusted which are female gender, hydrocephalus requiring CSF diversion, poor Fischer score and poor WFNS score. These were used for the development of VINODH score. This highly predictive score was internally validated as the sole predictor of CI after aneurysmal SAH and associated mRS score at discharge which showed high significance with a p-value of <0.0001.

Conclusion

Higher VINODH score is directly associated with higher risk of CI and poorer mRS score at discharge. It is a simple and reliable tool which is accurate for early identification of patients at risk of CI after aneurysmal SAH.

Keywords: subarachnoid hemorrhage, cerebral vasospasm, aneurysm rupture, cerebral infarct, prediction model.

Introduction

Intracranial aneurysms are not a rare diagnosis anymore due to diagnostic breakthroughs. It mainly occurs in the anterior circulation of about more than 80%. Site of origin is usually at the diversion of blood flow from the main arterial vessel causing some flow to continue to hit at the original trajectory instead of the diversion.

Mortality of aneurysm rupture patients who usually die before reaching the hospital is about ten percent. Despite survival, morbidity is high as they suffer from vasospasm and cerebral infarction (CI)[1].

Aneurysm ruptures are regarded as emergency condition because re-rupture can happen and carries a mortality risk of about 70%. Risk of re-rupture is about 3 to 4 % within 24 hours and 1 to 2 % each day within 30 days. Prevention of re-rupture can only be achieved by either surgical clipping or interventional radiological approach. Commonest cause of CI is either due to surgery or vasospasm but vasospasm can be prevented and needs early identification for medical intervention[2].

The brain aneurysm foundation quotes that in every 18 minutes; one brain aneurysm ruptures and up to one third of the survivors have cerebral vasospasm. Vasospasm causes hypo-perfusion which leads to CI if left untreated. Besides that, subarachnoid hemorrhage (SAH) also attenuates effect of vasospasm. Early recognition is crucial for prevention[3].

A study which used the data from the Prospective Registry of Subarachnoid Aneurysms Treatment (PRESAT) cohort; identifies predictors for CI after aneurysmal SAH. It proves that multiple factor including vasospasm causes CI and reflects poor outcome among patients. Symptomatic vasospasm was proven medically treatable; thus warranting prompt recognition and prevention[4].

Prevention of CI is currently the mainstay of treatment strategy. These factors necessitate a new and simple prediction model which can be implemented in most centres. Thus, we decided to develop a score which will predict CI in all anterior circulation aneurysmal rupture patients with our own set of locally available parameters using non-invasive methods and if this score is reliable; it will probably lead to the testing of this score also in the posterior circulation aneurysm rupture patients with SAH. This score is named VINODH score after the name of the main author.

Methodology

This prognostic study was done in a retrospective manner after obtaining approval from the Medical Research & Ethics Committee of Ministry of Health Malaysia and registered in the national register for clinical trials (NMRR-17-647-34496). All anterior circulation aneurysm rupture patients aged 18 and above with SAH who were admitted within 72 hours from onset of rupture and were surgically treated by clipping and at risk of developing cerebral infarction at the Queen Elizabeth 2 Hospital in the state of Sabah in Malaysia were included. Data was collected from 1st July 2014 to 31st January 2018. The general objective of the study is to analyze significant predictors and develop a score to predict CI among aneurysmal SAH patients. This score was also tested to analyze the association with patient outcome at discharge. The endpoint of this study is to identify high risk target group patients for prevention management of CI.

Data Management

Parameters included were age, gender, World Federation of Neurosurgical Societies (WFNS) score, Fischer grade, presence of acute hydrocephalus requiring drainage after aneurysmal SAH, presence of intracerebral hemorrhage, presence of intraventricular hemorrhage, Glasgow Coma Scale (GCS) score and time of aneurysm rupture. All parameters used in the score are reported by two clinicians with relevant experience of more than 3 years to avoid inter-observer bias. Definition of CI is taken as an area of new hypo density seen in the CT scan within 21 days after aneurysm rupture. The location of the infarct must not correlate with preexisting neurology or not part of a documented surgical complication. If the cause of hypo density is doubtful with reference to the above mentioned two conditions, the case will be excluded. All patients will get at least one routine CT scan

after surgical clipping of ruptured aneurysm within 24 hours and additional CT is repeated selectively in cases with new neurologic deficits or a prolonged state of impaired consciousness.

Patients with undetermined cause of SAH, posterior circulation aneurysm, multiple intracranial aneurysms and unknown pre-existing neurological deficit before the aneurysm rupture were excluded from the study.

ANEURYSM RUPTURE PATIENT MANAGEMENT

In our center, all patients with confirmed SAH on plain computed tomography (CT) after aneurysm rupture will get an immediate CT angiography. The CTA is only delayed if the patient has a life threatening hydrocephalus which requires CSF diversion first or in cases with deranged renal profile whereby prophylactic renal protective measures will be taken prior to CTA. Patients are then admitted to neurosurgical high dependency unit (HDU). Nimodipine of 40mg for 6 times daily and prophylactic levetiracetam of 500mg for twice daily are given orally or via a nasogastric tube. Nimodopine is continued for 21 days from the onset of ictus while levetiracetam is given for one week if there wasn't evidence of seizure or continued for one month if patient fitted. All patients without severe life threatening cardiac or renal cases will get a maintenance of normal saline 0.9% intravenous fluid of 3-4mils/kg/day. Hydrocephalus is treated with external ventricular or lumbar drain. All patients will be subjected to surgical clipping within 24 hours from admission. Direct intraoperative papaverine of 60mg is given. Once clipped, hypertension is preferred aiming at MAP of 80-90mmHg but if vasospasm is suspected intraoperative or any time after clipping; desired MAP is aimed at 100-120 mm Hg. Hematocrit and $PaCO_2$ is maintained at 30-35% and 35-40mmHg respectively. We subject all our patients to surgical clipping but complex inoperable patients or patients who do not want to go for surgery; will be referred for interventional endovascular procedure to the National Neurosurgical Centre in Hospital Kuala Lumpur.

STATISTICAL ANALYSIS

Univariable analysis of the association between each predictor and cerebral infarct was done using Fisher's exact test. Multivariable binary logistic regression model was employed to build the prediction model for cerebral infarct. Backward selection with *p*-value for removal of 0.05 was used to select the predictors into the main effects model. Interactions among the selected predictors were checked by adding one interaction term at a time to main effects model and Wald test was used to determine the significance at 0.05 level. The overall fit of the resulting preliminary final model was assessed using Hosmer-Lemeshow goodness of fit ($\hat{C}$), Pearson chi-square (χ^2) and deviance (D) statistics. The abilities of the model to predict and discriminate between the presence and absence of cerebral infarct were assessed using classification table with probability cut point 0.5 and plot of area under receiver operating characteristic (ROC) curve respectively. Influential outliers were identified by plotting Pregibon Delta-Beta influence statistic (Cook's distance) against predicted probability. Covariate pattern with Cook's distance greater than 1.0 was considered influential outlier. The decision to keep or delete influential outliers was based on the change in the signs of the coefficients as well as the magnitude of change. In our case, the signs did not change, and the largest change was less than 20% so all observations were kept in the model. The resulting model after the last step was called final model.

VINODH score which is named after the author was derived from the odds ratios (OR) in the final model. The utility of the score to predict CI was assessed by regressing using binary logistic regression method. The model's fit and diagnostics were checked. In addition, the observed and predicted probabilities were plotted together against the score to visualize the fit. The score's utility to predict poor mRS Score at discharge was assessed in a similar manner.

Results

A total of 237 patients' medical records were analyzed and only 200 were included which comprised of 100 events and 100 non-events. Event in this case refers to aneurysm rupture patients with SAH who developed CI. Out of the 37 excluded cases, 13 were due to strict exclusion criteria while another 24 more were due to missing data in their medical records. There were more females with 59.5% if compared to males. Majority patients presented with a good WFNS score and a poor Fisher score. Detailed demographic data is given in Table 1. The median age of patients analyzed was 51.

Variable	***n* (%)**
Age (years)	
Less than 51	97 (48.5)
51 or more	103 (51.5)
Gender	
Male	81 (40.5)
Female	119 (59.5)
Hydrocephalus requiring CSF diversion	
Yes	101 (50.5)
No	99 (49.5)
WFNS score	
Good: 1 – 3	114 (57.0)
Poor: 4 – 5	86 (43.0)
Fisher score	
Good: 1 – 2	64 (32.0)
Poor: 3 – 4	136 (68.0)
GCS score	
Good: 9 – 15	161 (80.5)
Poor: 8 or less	39 (19.5)
ICH	
No	141 (70.5)
Yes	59 (29.5)
IVH	
No	132 (66.0)
Yes	68 (34.0)
Aneurysm rupture time	
Day: 06:00 – 17:59	106 (53.0)
Night: 18:00 – 05:59	94 (47.0)
mRS score at discharge	
Good: 0 – 3	104 (52.0)
Poor: 4 – 6	96 (48.0)

Table 1: Demographic and clinical characteristics of subjects (n = 200)

IDENTIFYING SIGNIFICANT PREDICTORS & DEVELOPING VINODH SCORE

We analyzed a total of 200 patients of which 100 patients were with CI and 100 patients without CI. This data which contained 100 cases and 100 controls was judged as enough to fit a model with up to 9 predictors if the rule of 10 is followed. The rule stated that at minimum, 10 events of the least frequent outcome should be observed per parameter.

All the 9 predictors were then applied into multivariable binary logistic regression model and backward selection with *p*-value for removal of 0.05 was used to select the predictors for inclusion in the main effects model. As seen in Table 2; out of the 9 analyzed predictors; female gender, CSF diversion for hydrocephalus, poor Fischer score, and poor WFNS score proved significant for developing CI and were used for the development of VINODH score.

Predictor	***OR***	**95% Confidence interval for *OR***	***p*-value[a]**	**VINODH score**
Fisher Grade				
[b]Poor: 3 – 4	11.0	3.9, 30.9	<0.001	3
[c]Good: 1 – 2	1.0			0
Gender			0.004	
[b]Female	3.5	1.5, 8.4		1
[c]Male	1.0			0
Hydrocephalus requiring CSF diversion			<0.001	
[b]Yes	6.2	2.7, 14.0		2
[c]No	1.0			0
WFNS score			<0.001	
[b]Poor: 4 – 5	12.3	5.2, 29.5		4
[c]Good: 1 – 3	1.0			0

a Wald test; b Indicator; c Reference; *OR* odds ratio

Table 2: Final multivariable binary logistic regression model (n = 200)

For indicator, VINODH score was calculated by dividing its *OR* by the smallest *OR*, rounded to the nearest integer. For reference, the score was zero. Finally VINODH Score was developed with a minimum score of 0 and maximum score of 10. The score is shown in Table 3.

Predictors	Score
FEMALE GENDER	1
CSF DIVERSION FOR HYDROCEPHALUS	2
FISHER GRADES 3 & 4	3
WFNS GRADES 4 & 5	4
Total Score	**10**

Table 3: Final model of VINODH Score

This score was then applied as the sole predictor of CI and showed high significance with a *p*-value of <0.01. The observed probabilities for developing CI by VINODH score is shown in Table 4.

VINODH score	Observed CI	95% Confidence interval for predicted CI
0	0.000	0.000 - 0.044
1	0.000	0.006 - 0.079
2	0.333	0.027 - 0.139
3	0.263	0.078 - 0.234
4	0.318	0.180 - 0.367
5	0.400	0.335 - 0.533
6	0.550	0.511 - 0.708
7	0.571	0.670 - 0.852
8	1.000	0.793 - 0.939
9	0.905	0.878 - 0.981
10	1.000	0.931 - 0.997

Table 4: Observed probabilities of CI for VINODH score

The area under receiver operating characteristic curve (ROC) was 0.90 which indicates outstanding discrimination and using probability cut off point of 0.5, the model's sensitivity and specificity were 79.0 % and 83.0 % respectively. Plot of predicted and observed probabilities of CI against VINODH score is shown in Figure 1.

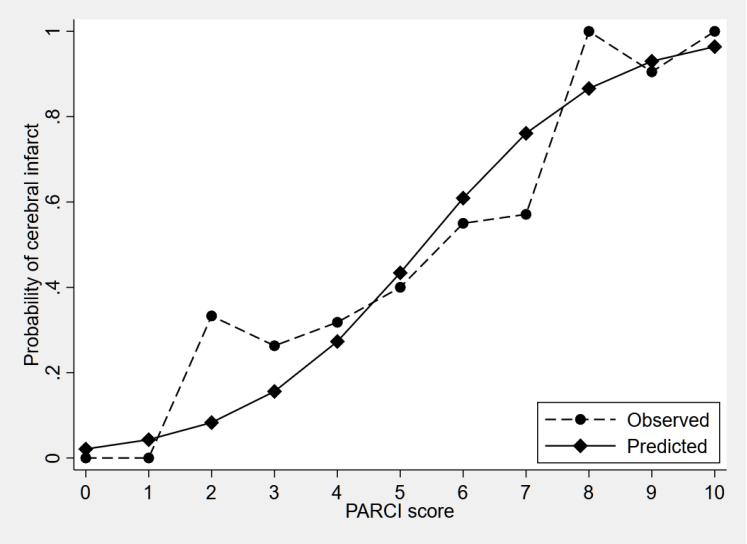

Figure 1: Plot of predicted and observed probabilities of cerebral infarct against VINODH score

Patients were then stratified into risk groups of very low, low, moderate and high risk for developing CI based on VINODH score's occurrence of CI as seen in Table 5 which showed high accuracy for very low risk and high risk group.

RISK GROUP	VINODH SCORE	CI ABSENT - n (%)	CI PRESENT - n (%)
Very Low	0-1	**40 (100)**	0 (0)
Low	2-4	31 (70.5)	13 (29.5)
Moderate	5-7	27 (50)	27 (50)
High	8-10	2 (3.2)	**60 (96.8)**

Table 5: Patients observed risk for developing CI based on VINODH score

As for the analysis of the secondary outcome to correlate the mRS score at discharge and VINODH score, this study showed high significance of *p*-value <0.0001. The area under receiver operating characteristic curve (ROC) was 0.89 which again indicates outstanding discrimination.

Discussion

There are many available scores for prediction of CI after aneurysmal SAH. Even though poor Hunt & Hess and Fischer score are associated with poor outcome; CI after SAH often occurs as a result of multifactorial cascade. There are many independent predictors to be analysed. One of such score developed was BEHAVIOR score which showed high diagnostic accuracy in identifying patients at risk for developing CI after aneurysmal SAH[17]. However, we were not able to apply this score to our daily neurosurgical practice due to the fact that not all neurosurgical centers use Hunt & Hess score in assessing patients as it can be very subjective to the clinician and not all centres have a routine digital subtraction angiography facility or adequate intracranial pressure (ICP) probe monitoring devices due to financial constraints.

We realized the need for a new scoring system which will have the same outcome but only by making it simpler and using non-invasive parameters. Neurosurgery is a rapidly growing field in most of the developing countries especially where most of the funding is siphoned to core neurosurgical procedures. In our centre, diagnosis of ruptured aneurysm is confirmed by performing a CTA. We do not have the facility of DSA. Furthermore, we have limited ICP probe monitoring devices which are mainly reserved for brain trauma cases.

Out of the nine analysed parameters, three were excluded due to insignificance which are gender, presence of intracerebral hemorrhage (ICH) and time of aneurysm rupture. Aneurysm is a commoner disease among females but in this study seems to be a predictor in causing CI after rupture if compared to males. Aneurysm ruptures rarely cause large ICH and if present it is associated with higher mortality but in our study we found that ICH is not a significant predictor of CI after SAH. The same goes with presence of IVH as it is not a significant predictor. We wanted to also analyze if time of aneurysm rupture actually predicts occurrence of CI as for the common belief of delay of presentation to the hospital if the rupture occurs at night and thus prolonging time from rupture to treatment but this also proved insignificant between day and night rupture.

Identification of high risk group patients for developing CI after aneurysmal SAH will require an early intervention aimed at prevention measures. “Triple-H” therapy which comprises of hypertension, hypervolemia and hemodilution is of standard practice in most centers for vasospasm with clinical improvement noted. This therapy is considered safe after aneurysm rupture is secured[5].

Crystalloids are commonly used such as normal saline 0.9% intravenous fluid of 4-5mils/kg/day to maintain hypervolemia state despite no good data to support hypervolemia over euvolemia. As for hypertension, vasopressors such are phenylephrine and noradrenaline are used with MAP aimed at about 100-120mmHg[24]. Hemodilution also has no good data to support the usage but the proposed mechanism is that a decreased hematocrit improves blood rheology and increases flow through the vasospastic vessel. Common agents used are intravenous albumin and fresh frozen plasma. Hemodilution with these agents are usually avoided at initial stages as hypervolemia itself causes dilution and these agents are associated with hypersensitivity reactions[6].

The advantage of magnesium in SAH stems from its biochemical properties as a potent antagonist of calcium, cost effective and generally safe with minimal side effects. Serum Magnesium is maintained at 1mmol/l values of for the first seven days after aneurysm rupture as there is higher risk of infarct during this period of time. A small study showed a trend towards lesser symptomatic vasospasm with magnesium but a large controlled trial of continuous magnesium infusion did not find conclusive effects on CI. Magnesium also has no benefit for prophylaxis of CI in SAH patients[7].

The limitations faced in this study were mainly the design of retrospective data collection which would not represent a prospective cohort in improving the accuracy of the created score. There were numerous missing data which lead to exclusion of those patients which would have resulted in a bias. The current VINODH score has only gone through internal validation with the pre-existing sample population and a future multicentre external validation is required.

Conclusion

A high VINODH score is directly related to higher incidence of CI and poorer mRS score at the time of discharge. VINODH score is a simple and reliable tool which is accurate for early identification of patients at risk of CI after aneurysmal SAH and thus can be used in establishing high risk target group patients for early preventive treatment of CI.

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Efficacy Of Intraoperative Cone Beam CT In Spinal Surgery

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Abstract

Utilization of intraoperative cone beam computed tomography (CBCT) in spinal surgery is useful in many points such as precise screw placement. We are using portable CBCT (O-ARM, Medtornic) from 2014 and Robotic digital subtraction angiography (DSA) system (Artis zeego, Siemens AG) from 2016 as surgical support. In this study, we examine its usefulness and problems. In recent 3 years, 21 patients out of 178 cases with spine disorders underwent surgeries using intraoperative CBCT. The time required for imaging, and the accuracy of screw placement in fusion surgery cases were examined. In cases with ligament ossification or foraminal stenosis, the influence of intraoperative CT imaging on surgical procedures was examined. CBCT was used in the following cases: lumbar fusion (9), cervical fusion (2), cervical foraminotomy (3), decompression for ligament ossification (4), percutaneous endoscopic lumbar discectomy (2), and removal of schwannoma (1). CBCT was performed 1 to 3 times, and the interruption time by imaging was 11.6 minutes by O-ARM and 9.8 minutes by Artis zeego respectively. In 11 fusion surgery, 55 screws placed with real-time navigation and there was no screw perforation. In 6 cases, additional procedures such as removal of residual lesion and replacement of screws after imaging. The convenience of the robotic DSA was superior to the O-ARM in surgical procedures in which intraoperative lateral fluoroscopy is important such as anterior foraminotomy or percutaneous endoscopic lumber discectomy (PELD). Intraoperative use of CBCT in spinal surgery is useful technique for improving safety and reliability of surgical procedures.

Keywords: intraoperative CT, navigation, spinal surgery

Introduction

In recent years, the importance of intraoperative image-guided neurosurgery has been increasing. Many studies have proven the safety and efficacy of computer-assisted spinal neurosurgery. In O-ARM-assisted spinal navigation (Medtronic), high-resolution 3-dimentional (3D) data is obtained intraoperatively, fully automatic registration becomes possible, and it contributes greatly to improving the safety of the screw installation technique[1]. Furthermore, recently developed robotic digital subtraction angiography (DSA) system (Artis zeego, Siemens AG) is able to obtain cone beam computed tomography (CBCT) by rotating C-ARM in a short time and is useful for not only cerebrovascular hybrid surgery but also spinal surgery[2]. On the other hand, these intraoperative image guide systems have disadvantages such as the time required for the setting and imaging. We have been using portable CBCT (O-ARM, Medtornic) from 2014 and Robotic DSA system (Artis zeego, Siemens AG) from 2016 as surgical support. In this study, we investigated the usefulness and suitability of each device for spinal surgery based on our experience.

Material and Methods

From 2014 to 2017, among 178 cases of spinal surgery, we examined 21cases using intraoperative CBCT. Depending on the surgical procedure, the device selected one of three methods of O-ARM alone, O-ARM combined with navigation, and Artis zeego. Artis zeego is able to obtain CBCT by rotating C-ARM in a short time. We examined the following points: the time required for device setting and imaging, and the accuracy of screw placement in fusion surgery cases. We also examined the contents and results of additional procedures after CBCT.

Results

Sugical procedures assisted by intraoperative CT

CBCT was used for nine lumbar fusion, two cervical fusion, three cervical foraminotomy, four

decompression for ligament ossification, two percutaneous endoscopic lumbar discectomy (PELD), and one removal of schwannoma. Fusion surgery requiring screws placement was the most frequent in eleven cases, and subsequently, foraminotmy or decompression of ossified lesions were common.

Device selection for each surgical procedure

All eleven cases requiring screw placement were assisted by O-ARM with navigation system. O-ARM alone was used in 3 simple decompression cases: posterior decompression for ossification of ligamentum flavum (2), posterior cervical foraminotomy (1). Artis zeego used in the cases which lateral fluoroscopy is important during the procedure: anterior decompression and fusion for OPLL (2), anterior cervical foraminotomy (1), percutaneous endoscopic lumbar discectomy (2).

Time required for setting and imaging

The time for initial setting of each device was 12.7 minutes by O-ARM and 8.3 minutes by Artis Zeego. The time required for intraoperative imaging was 11.6 minutes and 9.8 minutes, respectively. Although there is no significant difference, Artis zeego was shorter in less than 10 minutes in comparison with O-ARM (Table 1).

Device	Setting (min)	Imaging (min)
O-ARM (n=16)	12.7±2.8	11.6±1.6
Artis zeego (n=5)	8.3±1.9	9.8±2.1

Table 1 Time required for setting and imaging

Accuracy of screw placement (O-ARM with navigation system)

Total 55 screws were installed in 11 fusion surgery cases. Two screws misplacement were confirmed during lumbar fusion surgery by CBCT (3.6%), but finally misplacement could be avoided by intraoperative re-placement (Table 2).

Method	Cases	Screws	Intraoperative screw misplacement	Postoperative screw misplacement
Cervical LMS	1	7	0	0
C1 LMS, C2 PS (Goel-Harms)	1	4	0	0
Lumbar PS (TLIF)	9	44	2	0
Summary	11	55	2	0

Table 2 Results of accuracy of screw placement. LMS: lateral mass screw, PS: pedicle screw, TLIF: transforaminal lumbar interbody fusion

Additional procedures after intraoperative CBCT imaging

In Six cases (28%) , additional procedures such as screw replacement (3) and bone removal (3) were required after CBCT. These cases finally achieved appropriate screw placement or sufficient decompression by adding procedures (Table 3).

Method	Cases	Procedures	Final result
Lumbar PS (TLIF)	3	Screw replacement	Appropriate screw position
Posterior decompression for OLF	2	Additional removal	Sufficient decompression
Anterior decompression for OPLL	1	Additional removal	Sufficient decompression

Table 3 Results of additional procedures after intraoperative CT imaging

TLIF: transforaminal lumbar body fusion, OLF: ossification of ligamentum flavum,

OPLL: ossification of the posterior longitudinal ligament

Illustrative case 1

78 year-old male, a case of ossification of ligamentum flavum. We selected O-ARM alone for intraoperative image assisted device. After performing the posterior decompression, we performed CBCT and confirmed residual bone lesions. By adding bone removal, finally sufficient decompression was achieved (Fig.1).

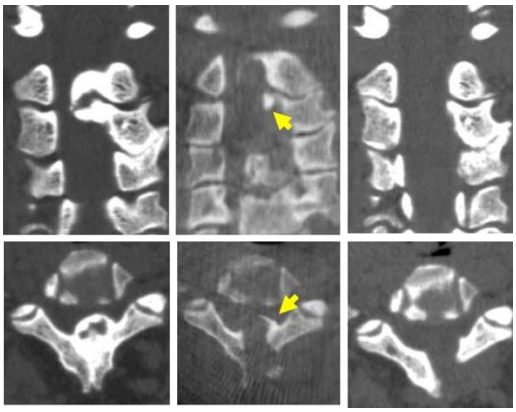

Fig.1 Pre, intra and post operative images of a case of ossification of ligamentum flavum.

Illustrative case 2

76 year-old female, a case of lumbar spondylolisthesis. We performed TLIF under assistance of O-ARM with navigation. With the O-ARM navigation system, automatic registration is possible in a short time, and screw insertion is carried out while confirming the 3D image. In the initial imaging after the screw placement, lateral deviation of the right L5 pedicle screw was confirmed, so the screw was replaced and the appropriate placement was confirmed in the second imaging (Fig.2).

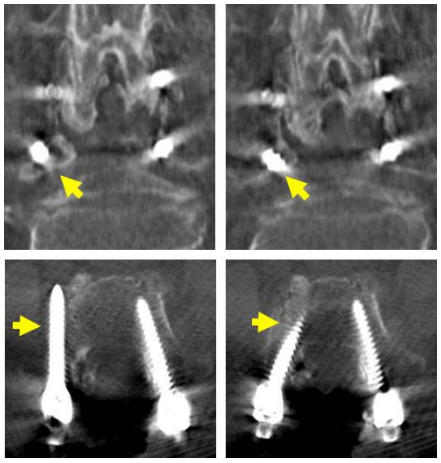

Fig.2 Intraoperative O-ARM images during screw installation procedure in lumbar spinal fusion.

Illustrative case 3

48 year-old male, a case of cervical spondylotic radiculopathy. we selected transvertebral anterior foraminotomy, a minimally invasive procedure to decompress the intervertebral foramen without resecting the intervertebral disc[3]. In this procedure, it is important to confirm lateral fluoroscopic images during surgery. Artis zeego has high convenience in that fluoroscopic images can be obtained quickly while securing the working space of the operator (Fig.3). Since the bone removal status can be understood accurately with a 3D image, inadequate decompression can be avoided (Fig.4).

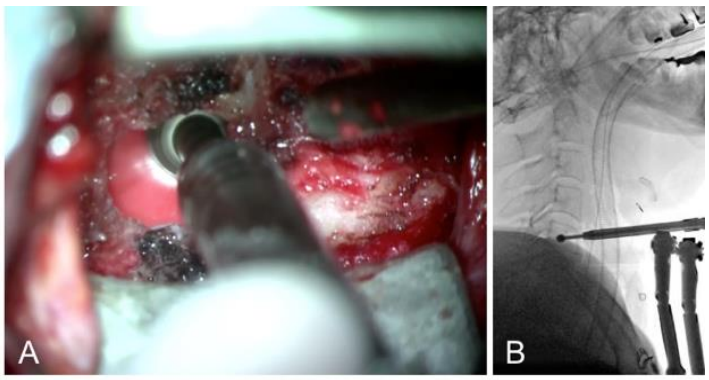

Fig.3 Intraoperative images of transvertebral anterior foraminotmy.

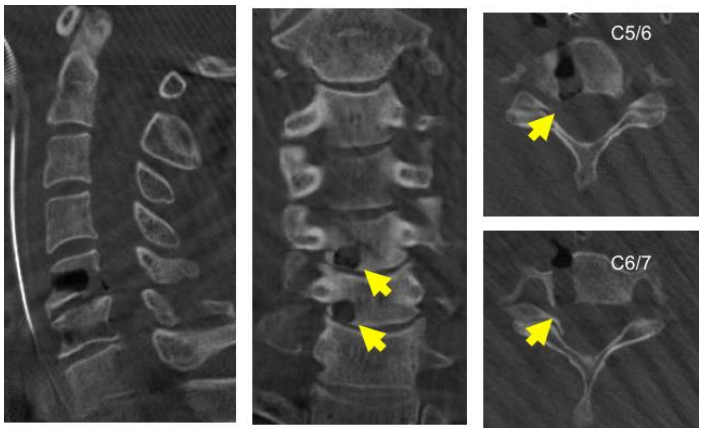

Fig.4 Intraoperative CBCT images by Artis zeego during transvertebral anterior foraminotomy

Discussion

Intraoperative computer-assisted spinal surgery is becoming more common. The greatest advantage is that surgeons can easily understand the status of bone removal or device instrumentation during surgery[4]. On the other hand, disadvantages may include taking time for setting and imaging, or increasing radiation exposure. In our study, it took about 10 minutes to set up and imaging, but it was a useful surgical assistance method considering the benefits of enhancing the safety and durability of spinal surgery.

O-ARM navigation system provides high accuracy compared with traditional methods. However, even in previous study using O-ARM, it has been reported that pedicle perforation is recorded in 3.2% and there is an error of screw insertion angle between virtual and actual screw[1]. In this study, intraoperative screw misplacement was recorded in 3.6%, and in 29% of our cases, the screw misplacement or insufficient decompression could be avoided by confirming intraoperative CBCT. From these results, O-ARM navigation is a useful device to support accurate screw installation, but careful confirmation is important as it does not guarantee perfect safety.

Because O-ARM has a tubular shape, so it is difficult to obtain lateral fluoroscopy during the procedure. On the other hand, Artis zeego can get intraoperative image while securing the working space of the operator. Based on the suitability of each device, we believe that O-ARM is suitable for lumbar fusion surgery and Artis zeego is high convenient in cervical anterior decompression and PELD.

Conclusion

Utilization of intraoperative CBCT contributes to improvement of the safety and durability of spine surgery, although it has the possibility of extending the operation time. Intraoperative CBCT with navigation system enhances the accuracy of screw placement in spine fusion surgery under the consideration of the navigation and human errors.

Legend

Figure 1. Pre, intra, and postoperative images of a case of ossification of ligamentum flavum. *Left column:* Preoperative images indicated ossified lesion localizing at C2-C3 level. *Center column*: Intraoperative O-ARM images revealed residual ossified lesion. *Right column*: Complete removal of ossified lesions was revealed in postoperative images.

Figure 2. Intraoperative O-ARM images during screw installation procedure in lumbar spinal fusion. *Left column:* Imaging just after screw placement indicated lateral deviation of right L5 pedicle screw (arrow). *Right column:* Final imaging after screw replacement revealed appropriate placement of L5 pedicle screw (arrow).

Figure 3. Intraoperative images of transvertebral anterior foraminotomy. A: Intraoperative microscopic view shows drilling into the vertebral body with a diameter of 7mm. B: Intraoperative fluoroscopic image by Artis zeego can clearly confirm the drilling direction and depth of the tip.

Figure 4. Intraoperative cone beam CT images by Artis zeego during anterior foraminotomy. The bone removal status can be understood accurately with a three-dimensional images. The arrow shows a foraminotomy of a vertebral body with a diameter of 7 mm.

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Efficacy Of Neuroendoscopy Versus Open Craniotomy In The Management Of Spontaneous Intracerebral Haemorrhage (SICH): A Systematic Of Randomized Trials

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Abstract

Spontaneous intracerebral hemorrhage (SICH) is an emergency case related to high morbidity, high mortality and high disability which need prompt neurosurgical intervention. Accounting more than 20 per 100,000 incidences of all stroke patients end up with death with more than 80% associate with disability-adjusted life-years (DALYs) lost. Neuroendoscopy is one of several methods in neurosurgery field which recently emerge as a promising method. Compared from conventional craniotomy method, neuroendoscopy offers several advantages in certain conditions. We performed this review based on the Preferred Reporting Items for Systematic review and Meta-Analysis. We searched on PubMed, EMBASE, and Cochrane Central Register of Controlled Trials to identify relevant studies. The subgroup analyses were stratified by clinical outcomes, evacuation rates, complications, operation time, and length of hospital stay for patients who underwent neuroendoscopic surgery (NE group) or craniotomy (craniotomy group). More than 800 abstracts of articles were reviewed after the topic search ("Endoscopic surgery OR neuroendoscopic surgery" and "Intracerebral hemorrhage OR intracranial hemorrhage OR intracerebral hematoma OR intracranial hematoma"), also adding similar article or related articles, and manual search of cross references from full text article). A total of 4 RCT articles were included in this study after detailed study of 32 relevant articles. From this study, we conclude that the neuroendoscopy is a safe technique which provide better outcome, better evacuation rate, faster in operating time, fewer blood lost and shorter hospital stay than conventional craniotomy technique. However, further evidences are warranted to confirm our findings.

Keywords: Neuroendoscopy, craniotomy, intracerebral hemorrhage

Introduction

1.1. Background

Spontaneous intracerebral haemorrhage (SICH) is an emergency case related to high morbidity, high mortality and high disability which needs prompt neurosurgical intervention. SICH has an incidence of around 20 per 100,000.[1] SICH itself contributes to massive health problems ranging from disability to death. The use of anticoagulants such as heparin, chronic hypertension, and aneurysms is also related to the incidence of SICH.[1] SICH itself is associated with many risk factors such as obesity, alcohol consumption, diabetes mellitus, smoking and hypertension. More than 80%, SICH patients have disability-adjusted life-years (DALYs) lost.[2] A third of SICH patients will have hematoma growth so that clinical presentation will worsen after 3-6 hours of onset.[3] SICH has become a global health problem and is increasingly important, with two-thirds of strokes now occurring in developing countries.[2] Based on data from the Indonesian Ministry of Health, the prevalence of SICH patients in Indonesia is 7 per 1000.[4] Continuous medical rehabilitation is also needed to prevent further disability. So, it is concluded that SICH has the potential to become a major health problem. One of the principles of handling SICH is bleeding evacuation to prevent the process of increasing intracranial pressure. Neuroendoscopy (NE) is a surgical procedure or technique that uses a camera and special lighting to access structures through a small incision. NE is a novel minimally invasive surgery used in the last few decades. NE is widely used in some cases such as obstructive hydrocephalus, various intraventricular lesions, tumours and SICH.[5] But at present, there have not been many studies comparing outcomes between NE and other conventional surgical technique such as craniotomy. Further studies are needed to evaluate outcomes such as mean operative time, hematoma evacuation rate, mortality, GCS score, functional outcome and postoperative complications such as rebleeding, rate of infection and ICU length of stay.

Method

2.1. Information Sources and Search Strategy

This study was conducted based on the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol) guideline.[6] Authors collected studies from several databases such as PubMed, EMBASE, and Cochrane Central Register of Controlled Trials to identify relevant studies in July 2018. Selected studies is a study written in Language and English. Authors used the following keywords to collect studies: "Endoscopic surgery OR neuroendoscopic surgery" and "Intracerebral hemorrhage OR intracranial hemorrhage OR intracerebral hematoma OR intracranial hematoma". The study in the form of unpublished articles and abstracts will be excluded. The study characteristics were presented as PICO (Tab. 1). The quality of each study was assessed using the risk-of-bias assessment tool based on the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0).[7]

2.2. Study selection and data collection

The study selection and data collection was carried out by all the authors with the same portion. Discrepancies between the two authors were resolved by discussion until decisions were made. Every article obtained is selected based on the inclusions and exclusion criteria. Articles that use the population not in accordance with the PICO will be excluded. The selected study was analysed in full text. Authors used the Cochrane Review Manager 5 application for statistical analysis.

2.3. Assessment of bias and statistical methods

The quality of studies is assessed based on bias which includes sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance and detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other sources of bias. Risk Ratio (RR) is calculated for non-continuous variables. Homogeneity is assessed using Random Effect Model (REM) and Fixed Effect Model (FEM). REM is used if I2> 75%. Otherwise, the Fixed Effect Model (FEM) was used. $P \leq .05$ (2-sided) was statistically significant.

2.4. Outcomes

The outcomes analysed were mean operative time, hematoma evacuation rate, mortality, GCS score, functional outcome and postoperative complications such as rebleeding, rate of infection and ICU length of stay. The diagnostic criteria for SICH in each study was used as the basis for the analysis because the criteria may differ in each study.

Table 1. PICO

Patient	Patients with age range 30-100 years old, CT confirmed intra-cerebral sub-cortical, supra tentorial hemorrhage, hematoma volume ≥25ml, surgery to be instituted within 72 hours of the onset of clinical symptoms.
Intervention	Neuroendoscopy
Comparison/ Control	Open craniotomy
Outcome	Clinical outcome, evacuation rates, complications, operative time, and length of stay

Table 2. Study characteristics

Study, Publication Year	Country	Study Design	Study Population	Other Demographic Data Included
Cho D. et al [8], 2006	China	Randomized clinical trial	90 patients	Age, hematoma volume, GCS, operative time
Feng Y. et al [9], 2015	China	Randomized clinical trial	184 patients	Gender, age, diabetes mellitus, aspirin, GCS, operative time
Ibrahim A.[10], 2016	Indonesia	Randomized clinical trial	43 patients	Gender, age, hematoma volume, GCS, operative time, GOS
Zhang H. et al [11], 2014	China	Randomized clinical trial	51 patients	Gender, age, hematoma volume, GCS, hypertension

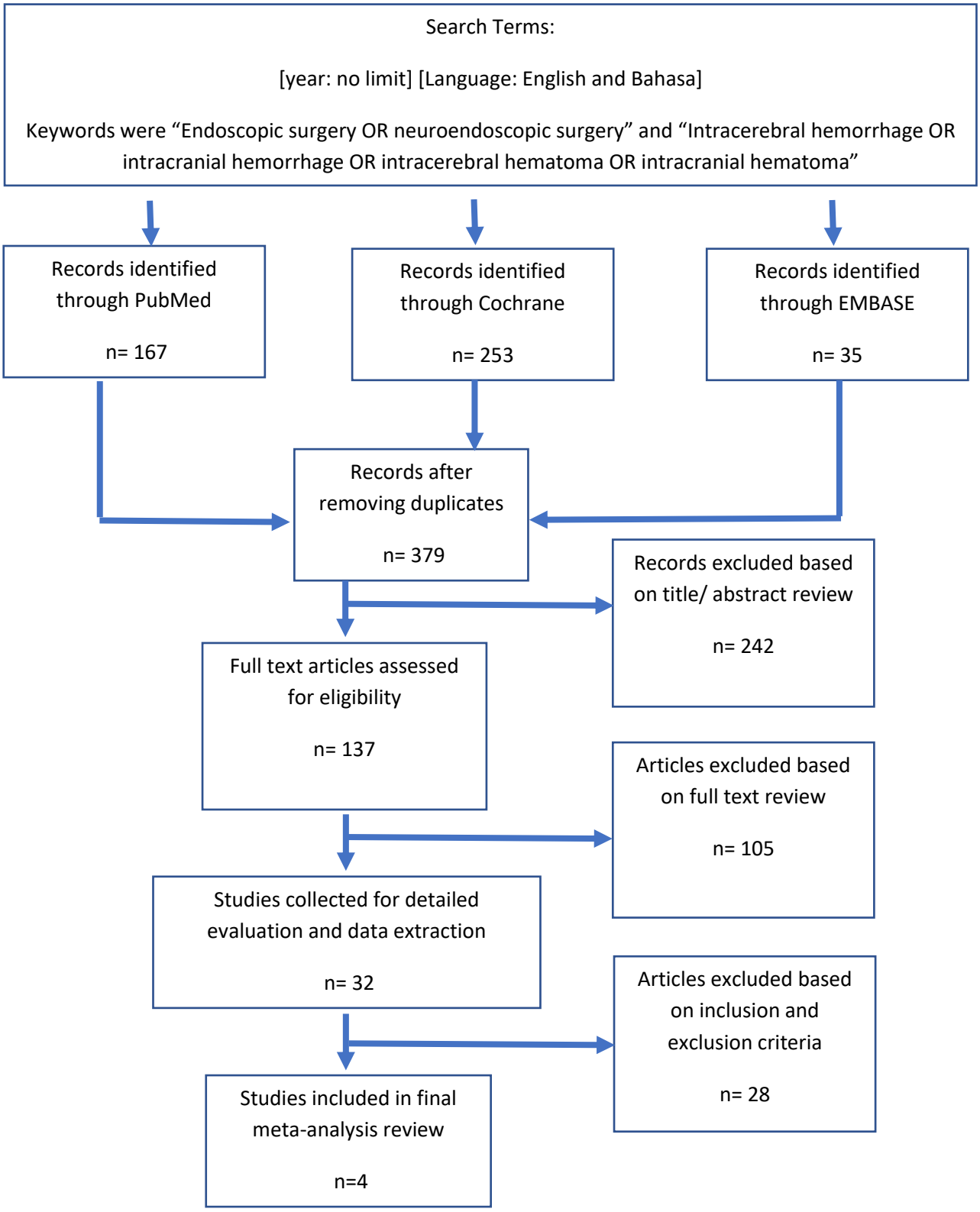

Figure 1. Study flow chart

Result

3.1. Study selection and bias

A flow diagram of study selection is shown in Figure 1. 379 abstracts of articles were reviewed after the topic search ("Endoscopic surgery OR neuroendoscopic surgery" and "Intracerebral hemorrhage OR intracranial hemorrhage OR intracerebral hematoma OR intracranial hematoma"), also adding similar article or related articles, and manual search of cross references from full text article). A total of 4 RCT articles were included in this study after detailed study of 32 relevant articles (Table 2). Each study has a good random sequence generation and allocation conceived but is assessed as good attrition and reporting bias. (Table 3).

3.2. Study results

Studies results stated evacuated hematoma 7.09% more effective than craniotomy (mean difference 7.09) (Figure 2). Mortality less appeared in Neuroendoscopy (RR 0.44) than in craniotomy (Figure 3). Neuroendoscopy took operative time shorter 104.10 minute (mean difference -104.10) than craniotomy (Figure 4). Both patients treated with NE and craniotomy had insignificant difference in GCS at discharge (MD 0.51) (Figure 5).

Patients treated with NE had better functional outcome 1.78 times than those treated with craniotomy (Figure 6). Patients treated with NE tended to have lower rebleeding rate (RR 0.4) (Figure 7) and lower infection rate (RR 0.25) (Figure 8).

Table 3. Bias assessment

	Cho D. et al [8], 2006	Feng Y. et al [9], 2015	Ibrahim A.[10], 2016	Zhang H. et al [11], 2014
Random Sequence Generation?	No	No	No	No
Allocation concealment?	No	No	No	No
Incomplete outcome data (attrition bias)?	Yes	Yes	Yes	Yes
Selective reporting (reporting bias)?	Yes	Yes	Yes	Yes

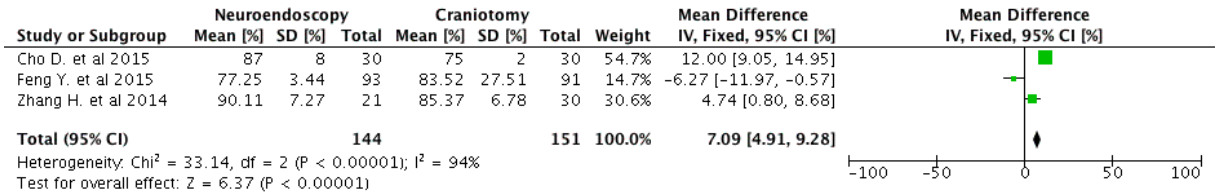

Figure 2. Hematoma evacuation rate

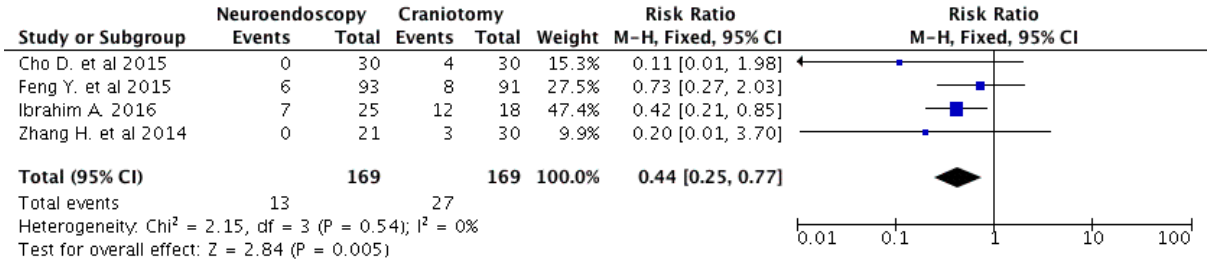

Figure 3. Mortality rate

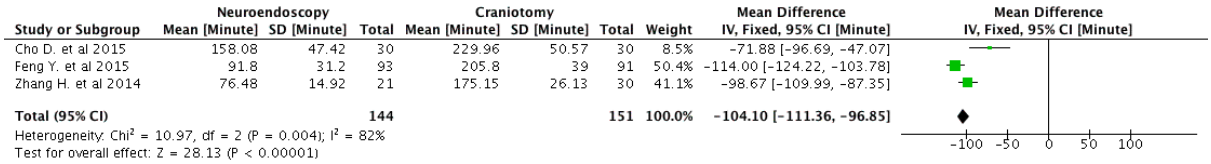

Figure 4. Mean operative time

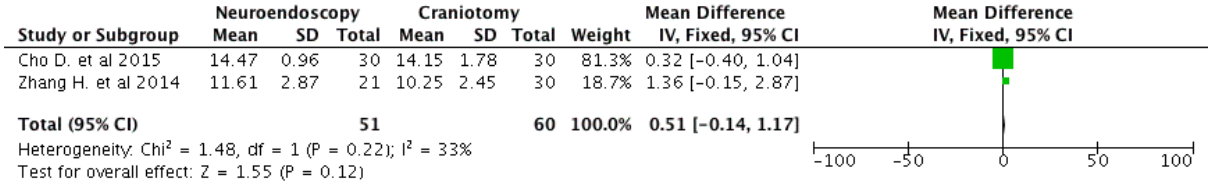

Figure 5. GCS at discharge

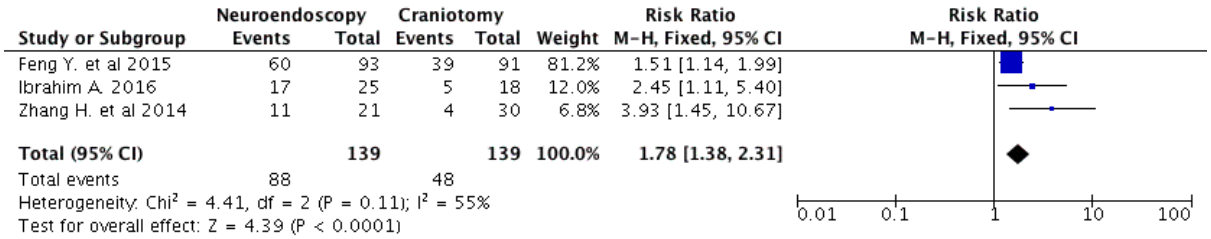

Figure 6. Functional outcome

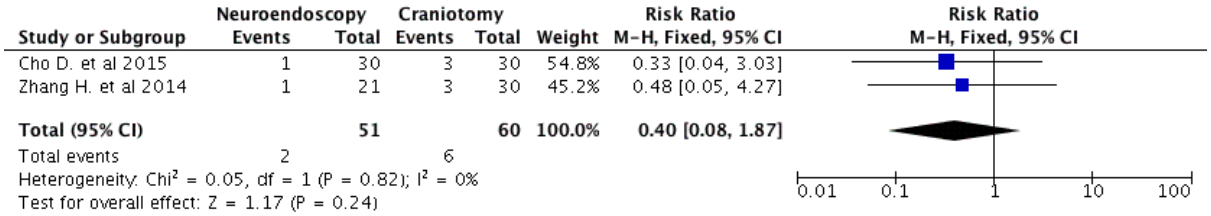

Figure 7. Rebleeding

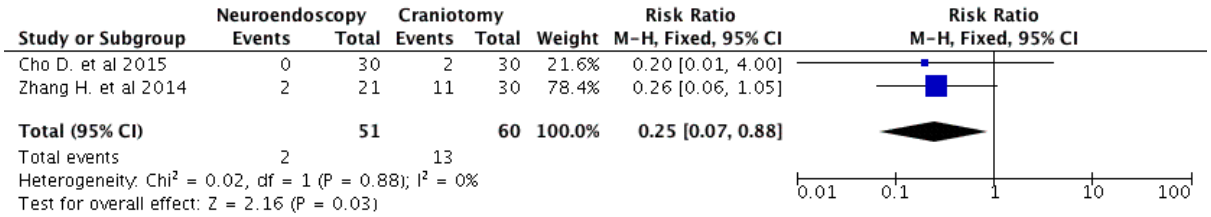

Figure 8. Infection

Discussion

NE tends to provide a good outcome when compared to craniotomy. NE provides a better evacuation rate hematoma. Cho et al[8] and Zhang et al[11] in their study obtained a higher evacuation rate hematoma in the NE compared to craniotomy (79.07% vs 68.02). Eerly evacuation of hematoma allows the perfusion of brain tissue to be maintained and avoiding a mass effect that is susceptible to causing brain herniation. This is associated with direct vision, where the operator has a wide visual operative field when performing procedures.[12] In contrast, Feng et al[9] in their study concluded that craniotomy has a better evacuation rate. Feng et al[9] stated the reason why NE and craniotomy did not produce significant results was when the keyhole technique was selected, neurosurgeons could have difficulties in finding the most appropriate cortical cutting site so that the

evacuation is not much different. But NE has advantages in terms of lighting intensity, flexibility and multi-angle observation.[9] Mortality is lower in all studies in patients treated with NE. Mortality is associated with the end result of ICP decline, of cerebral edema, and improvement in local blood circulation from a better evacuation rate.[8-11] Ibrahim[10] also found mortality was greater in hemiplegic patients than hemiparesis patients. Functional outcome assessment used was defined as a patient being able to care for him/herself, corresponding to a modified Rankin Scale (mRS) of 0, 1, 2, or 3, a Glasgow Outcome Scale (GOS) of 4 or 5, or activities of daily living (ADL) score of 1, 2, or 3. Patients treated with NE had better functional outcome 1.78 times than those treated with craniotomy.

Mean operative time was shorter in NE. NE allows neurosurgeons to more quickly access the location of hematoma and the important blood vessels as well as functional areas so as to accelerate the evacuation hematoma, this made the NE could be done faster than the craniotomy.[12] The shorter the operating time, the shorter the anesthesia time, this will minimize the effects of anesthesia exposure. NE is a minimally invasive procedure with a narrower incision area which allows a lower amount of bleeding and lower rates of complication of rebleeding and infection. The above analysis yield the RR of 0.4 and 0.25 for rebleeding and infection, respectively. This finding illustrates that NE is superior to open craniotomy based on complications point of view. Patients treated with NE had better functional outcome and postoperative GCS because the NE had a more minimal intervention in normal brain tissues compared to craniotomy.[12] The NE of SICH procedure is preceded within the cavity thereby minimizing the damage. Patients treated with NE have been treated with craniotomy. But this result is not significant due to several factors such as complications related to ventilator use, rehabilitation, and family care ability. But overall, the handling of NE is more cost effective when compared to craniotomy during hospital treatment.[8]

Yao et al[13], in a systematic review comparing NE and other treatment modalities (craniotomy, conservation, and stereotactic aspiration), also found that NE reduced mortality rate, poor outcomes, rebleeding, and pneumonia. This systematic review included 18 studies with average hematoma volume of 56 ml. All patients in the included studies were treated within the first 48 hours of onset. However, this study reported that six of the included studies had high risk of bias. A study by Xu et al[14] also revealed that NE is more beneficial than craniotomy in terms of evacuation, operation time, and functional outcome in patients with hypertensive intracerebral hemorrhage. This retrospective study compared 82 patients in NE group with 69 patients in craniotomy group. Patients in both group were reported to have similar baseline characteristic. In the NE group, operation in average lasted for only 1.6 ± 0.7 hours, while the craniotomy group lasted for around three times as long (5.2 ± 1.8 hours). Evacuation rate reached 90.5±6.5% in NE group, while in craniotomy group 82.3±8.6%. This study also reported that, in average, intraoperative blood loss in craniotomy group is six times as much as that in the NE group (605.6±602.3 ml and 91.4±93.1, respectively).

Although this systematic review and some other studies showed that NE seems to be superior, a larger systematic review is strongly recommended in order to provide better evidence. Another limitation of this study is that one of the included studies did not include the standard deviation of their data.

Conclusion

Neuroendoscopy technique has better hematoma evacuation rate, less mortality rate, less operative time, less length of stay, better GCS and functional outcome, and less complication rate (rebleeding and infection). However, further evidences are warranted to confirm our findings. It still needs more long term period researches in the future to get better understanding for other aspects of evaluation like preparation time, cost effectiveness.

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Conflict of interest

None declared.

Ethical approval

Not required.

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Endoscopic Endonasal Approach For Posterior Fossa Tumors: Pushing The Edge Of The Envelope

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Abstract

One of frontiers of the endoscopic endonasal approach is the management of posterior fossa tumors. Differently from other lesions resectable from such ventral route, they are challenging for their deep location, which could involve the cranio-vertebral junction, for their possible paramedian extension to highly complex skull base regions, or for their intradural extension with close relationship with the delicate neural and/or vascular structures of posterior cranial fossa. The main advantage of this approach is the possibility to expose these tumors frontally and with a complete extracranial route tailored on their extension, reducing the risk of nervous or vascular complications related to the approach, although the risk of CSF leak is higher than for other transcranial approaches. Initially, the endoscopic endonasal approach was reserved to mainly extradural forms, such as clivus chordomas or chondrosarcomas, but recently it has expanded its indications, including intradural lesions, as meningiomas, or intraxial ones, as brainstem cavernomas. However, despite any advantage given by this route, surgery of these lesions remains complex and at high risk for possible damages of functional structures of the posterior fossa or of their vascularization. The key of success of this approach is based on strict case selection and accurate pre-operative surgical planning. Moreover, this ventral route, which is, usually, technically demanding, requires a careful post-operative management of patients, to avoid possible dramatic consequences.
The aim of this study is to review our surgical experience, including pre- and post-operative patients management also in case of complications, to underline advantages of this route for posterior fossa lesions but also presenting its limitations and potential risks.

Keywords: endoscopic endonasal approach, posterior fossa, chordomas, meningiomas, complications, radiation therapy

Introduction

Tumors in the posterior fossa are a real challenge not only for the surgeon but also for the whole multidisiplinary team, involved in their management (i.e. radiation and medical oncologists, neuroradiologists, neurologists and neuro-ophthalmologists) for their deep location and complex relationship with surrounding vital structures such as brainstem, cerebellum, cranial nerves from III to XII, vertebro-basilar system and its branches. Many surgical approaches have been proposed for these lesions, including postero-lateral approaches (i.e. retrosigmoid, lateral suboccipital and far lateral), lateral approaches (i.e. transpetrosal and its variants or middle fossa approach such as Kawase approach) (1-4). The ventral route was suggested, initially, extending the microsurgical transsphenoidal approach to the clivus for extradural eroding tumors spreading out into the sphenoid sinus, with bioptic or debulking aim and only rarely with respective goal (5-9). Due to the relevant limitations in the caudal extension and the lack of versatility of the microscopic approach, only after the advent of the endoscopic technique this corridor has became popular (5-9)

Also, the endoscopic endonasal approach was, initially, considered indicated for midline extradural tumors, eroding the spheno-occipital bone in the clivus region, like some chordomas and chondrosarcomas, or other more uncommon histotypes such as osteomas, osteosarcomas, haemangiomas, isolated fibrous tumors, plasmocytomas and bone metastases (10,11). The improvement of the anatomical knowledge of area, as well as the development of new surgical technologies, such neuronavigation, intra-operative eco-doppler, modern HD

or 3D visualization systems, have allowed to extend the indications for this approach, including also tumors with paramedian extension, such as to the cavernous sinus, spheno-petrous syncondrosis, jugular foramen or occipital condyles, and involving the entire clivus from dorsum sellae to foramen magnum and the cranio-vertebral junction (12-19). Moreover, the aim of surgery has modified, moving from a bioptic/subtotal resection purpose to a total resection goal when possibile (12-19). Furthermore, even intradural midline tumors have been, progressively, considered suitable for this ventral approach in the more advanced endoscopic centers (12-23). Indeed, few papers have, recently, reported the endoscopic endonasal experiences for petro-clival or foramen magnum meningiomas, for lesions of the ventral brainstem, such as pons cavernomas, or for posterior arterial circulation, such PICA or vertebral artery aneurysms (12-23).

Indeed, this route has the advantages to be direct and straightforward, giving a frontal exposure of the tumor, following its own growth pattern, passing throughout the nasal and paranasal sinuses, with consequently minor risk of damage of neural or vascular structures, despite the increased risk of CSF leak (5-9).

Although the brilliant results reported in these papers, we would like to consider that this approach is usually complex and technical demanding, and it presents some surgical pitfalls, with potentially heavy risk for patients. Peculiar attention should be paid not only to more technical aspects of such approach, which should be reserved to highly trained surgeons in endoscopic endonasal route, but also to patients selection and pre/post-operative management, especially in routine clinical setting. Thus, we would like to review our surgical experience to underline advantages of this route but also presenting its limitations and potential risks.

1.1. Anatomy of Posterior Fossa

The posterior fossa extends from the tentorial incisura, throughout it communicates to the supratentorial spaces, to the foramen magnum, a narrow space which delimitates the lower limit of the cranial cavity. The ventral border of the posterior fossa is represented by the clivus, which is formed by sphenoid bone from the dorsum sellae to the spheno-occipital syncondrosis and by occipital bone inferiorly. The lateral borders of the posterior fossa are formed by petrous portion of temporal bones and mastoids with the contribution of the occipital and of a minimal portion of parietal bones above and behind the mastoid angles. Posteriorly, the squamous part of the occipital bone closes the fossa. For its location, it is the deepest of the three cranial fossae, and the largest, representing one height of the entire cranial space (1). Within this space, many vital neural structures, regulating the consciousness, the autonomic, sensorial and motor activity of all the body and the balance and gait, such as cerebellum and brainstem, are contained. Ten of the twelve cranial nerves (from III to XII) run in the posterior cranial fossa, where they take relevant relationships to the vertebro-basilar arterial system, which provides the vascular supply to all the parenchymal structures of the region by means of tiny and delicate perforating arteries. From a surgical point of view, three major neurovascular complexes can be identifies: the upper composed by III, IV, V CN and superior cerebral artery (SCA), the middle composed by VI, VII, VIII CN and anterior inferior cerebellar artery (AICA) and the lower composed by IX, X, XI, XII CN and posterior inferior cerebellar artery (PICA) (10). The SCA derives from the basilar trunk in front of the mesencephalon, passes below the III and IV and above the V CN toward the superior cerebellar pedicle, to terminate supplying the tentorial surface of cerebellum. The AICA arises from basilar trunk at pontine level, it courses in strict relationship with VI and acustic-facial nerves to reach the middle cerebellar pedicles and terminate to supply the petrosal surface of cerebellum. Finally the PICA arises, usually, by the vertebral artery in front of the medulla, which encircles at the level of inferior cerebellar pedicle, in close relationship with the IX, X, XI and XII CN.

The ventral surface of the posterior fossa is characterized by the presence of multiple foramina, throughout the nervous, venous and arterial structures can penetrate in the intracranial space. The jugular foramen is formed by the petrosal part of temporal bone and condylar part of occipital bone. It can be dived in three compartments, two venous and one neural. The venous compartments consist in a larger postero-lateral venous channel, named sigmoid, which receives blood from the sigmoid sinus and in a smaller antero-medial one, the petrosal, where the inferior petrosal sinus drains. The neural part is located between the petrosal and sigmoid venous channel and it allows the IX, X and XI CN to exit the cranial cavity. The jugular tubercle is a prominence located at the junction of the basal and condylar parts of the occipital bone, medial to the jugular foramen. Finally, the hypoglossal canal is located in the middle third of condyles and it present an inclination of 45° anteriorly and laterally. It contains the hypoglossal nerve, followed by a meningeal branch of ascending pharyngeal artery and venous connection between basilar venous plexus and plexi surrounding the foramen magnum.

1.2. Anatomical Landmarks for endoscopic endonasal approach

The main gate to approach the posterior fossa through an endoscopic endonasal route is represented by the clivus. For surgical aims, it can be schematically divided in three portions: upper, middle and lower, corresponding to different ventral corridors and to the three neurovascular complexes of poster fossa (10).

Indeed, the upper third of clivus is usually approached throughout the sphenoid sinus (16). The main landmarks of this corridor are the same routinely adopted for a mid-line endoscopic transsphenoidal approach, i.e. the tail of superior turbinate to identify the spheno-ethmoidal recess and the opening of the sphenoid sinus, the sellar bulge and the two optic-carotid recesses, to localize course of the carotid artery and the location of the pituitary gland. Intradurally, the upper third of the clivus corresponds to the interpeduncolar cistern, occupied by the tip of basilar artery, posterior communicating artery, SCA and the III CN in its cysternal portion.

To expose the middle clivus is necessary to extend caudally the previous route, drilling off the floor of the sphenoid sinus (16). The main risk of this maneuver is represented by the risk of ICA injury. An useful landmark to localize the course of this vessel in this region is represented by the vidian nerve, which points out the genu between the petrosal and paraclival artery and then allows to identify a safe area for drilling comprised by the two vidian nerves. Intradurally the middle clivus corresponds to the pons, to the basilar trunk and AICAs and to the cysternal portion of VI CN.

Finally, the inferior third of clivus can be identify, detaching the rhynopharyngeal muscles (longus capitis and rectus capitis anterior) and mucosa, below the floor of the sphenoidal sinus (Fig. 3a). This route gives access to the lower part of the clivus and to the craniovertebral junction (the lower point that could be reach can be approximated by a line passing through the anterior border of nasal bone and inferior border of hard palate) (16,24). The surgical landmarks of this corridor are represented by the inferior turbinate and by the choana, while the Eustachian tube is of crucial relevance, to point out the parapharyngeal tract of carotid artery. Thus, the detachment of the rhynopharyngeal mucosa and of parapharyngeal muscles should be performed medially to the tube to avoid injuries to this vessel. This approach gives access to a trapezoid space, wider superiorly and limited by the condyles inferiorly. The main anatomical structure of the condylar area is represented by the hypoglossal canal, which divides the infero-lateral portion of clivus in two segments, a superior or tubercular, representing the ventral portion of jugular tuberculum and an inferior or condylar, which is part of the occipital condyle. Intradurally, this segment of the clivus corresponds to the tracts of IX, X, XI CN toward the jugular foramen and to the vertebral artery. The condylar compartment is inferiorly limited by the articular surface, and laterally by the XII CN. Intradurally, it corresponds to first segment after the piercing of the dura of the vertebral artery which is crossed anteriorly by the cysternal segment of the hypoglossal nerve.

Pre-operative assessment

Pre-surgical planning for an endoscopic endonasal approach to a posterior fossa tumor requires multiple informations, coming from both neuroradiological and clinical evaluation of the patient. These features should be combined to evaluate different aspects of surgery case by case:

- presence of anatomical or clinical contraindications;
- planning of the surgical trajectory, tailored on tumor extension;
- defining the aim of the surgery (i.e. gross tumor removal; debulking to decompress the neural structure and favoring adjuvant therapies; biopsy);
- considering what technique of plastic repair is more appropriate in case of foreseeable CSF leak.

2.1. Indications and contraindications

MRI with gadolinium is the golden standard to analyze the tumor location, its relationship to the surrounding anatomical structures and to suspect its histological nature. Among the others, this examination is useful to analyze if the tumor is suitable for an endoscopic endonasal approach. As, up to time the intra-dural location is not considered an absolute contraindication, it is should be remarked that surgery for tumors with this extension (i.e. chordomas or meningiomas) are at higher risk of complications or unfavorable results and should be reserved to dedicated advances endoscopic skull base centers (5-9). A further relevant parameter is represented by the location of the tumor in relationship to vascular and neural structure. Indeed, tumors should be placed ventrally to cranial nerves to be considered suitable for the endoscopic endonasal approach. Lateral extension beyond these structures constitutes an absolute contraindication for this route, following the golden rule of never crossing any nerve (5-19). Moreover, vascular encasement represents a further contraindication to this approach, because of the risk of direct injuries (5-19). The histological nature of the tumor is an additional element, that can be suggested by MRI. Richly vascularized lesions or tumors with malignant features, infiltrating the parenchymal and vasculo-nervous structures can represent relative contraindication to this approach, which can be limited to biopsy (5-19).

General contraindications, common to other transcranial approaches, are represented by the general Karnofsky grade of the patients and by the presence of heavy comorbities, which could increase the complications risk of the patients. It is not unusual that patients with posterior fossa may present with poor clinical conditions, such as tetraparesis, swallowing impairment or recurrent inhalation pneumonia. In these

cases, the surgical indication should be evaluated case by case in a multidisciplinary team, often requiring pre-operative tracheostomy or the a long post-operative rehabilitation time.

Before starting any surgery through this ventral approach the risk of CSF leak and how to manage its closure should be peculiarly assessed (5-19). Particularly, the viability and anatomical integrity of nasal structures, such as middle turbinate or septal mucosa, to perform flaps or grafts, the effects of previous surgeries or of radiotherapies, as well as the availability of other structure for closure such as temporo-parietal flap, fascia lata or others, should be carefully considered. Indeed, the risk of persistent CSF leak for the impossibility to achieve a satisfactory plastic repair represents a contraindications for this approach.

2.2. Surgical Planning

In order to define the more appropriate surgical trajectory for each case, the informations given by MRI may not always be sufficient. Indeed, an accurate evaluation on the nasal and paranasal anatomy is relevant to tailor the approach on the tumor extension. These features can be assessed by a CT-scan with tiny slices. Moreover, this examination may be associated to a CT-angiogram (CTA) to precisely evaluate the corse of major vessels, such as ICA and basilar trunk. These evaluations are always relevant, but they may have a crucial role in case of incomplete pneumatization of the paranasal sinuses, namely the sphenoid one, or in case of second surgery, in which the normal anatomy is commonly distorted by presence of scars, fibrous tissue or clousure material. We prefer to use in the neuronavigation system the CTA merged with pre-operative T1WI with gadolinium slice, to combine both the informations related to bony and vascular anatomy and the location and extension of the tumor (16).

In case of tumors involving the cranio-vertebral junction, X-ray of the cervical spine with dynamic projections could be useful for the suspect of instability. This is usually due to a massive bilateral erosion of the condyles and or the other fixation elements, because it could require a posterior fixation during or after the respective surgery (16).

Further pre-operative examinations necessary to an adequate pre-operative planning are the motor and somatosensorial evoked potentials (MEPs and SEPs) in case of brainstem compression and the electromyography (EMG) for the cranial nerves involved by the tumor. This examinations gives a precise knowledge even of subclinical neurological deficits (16). Moreover, they can be adopted intraoperatively to monitor these functions with the aim to reduce the risk of permanent damages.

2.3. Aim of surgery

Although it is accepted that the aim of surgery is the tumor resection wider than possible with minimal risk of post-operative complications, all these clinical and radiological features should be kept under consideration to evaluate for what case radical removal is a desirable goal or when resection should be arrested. The tumor extension is a crucial element, indeed lesions extending to many portions of posterior cranial fossa, such as petroclival meningiomas, or invasive chordomas, can be resected subtotally from the ventral approach, requiring combined surgery or complementary treatments. As general rule, the extradural portion of these tumors is more prone to be resected radically, with some possible exceptions for lateral extension in tumors of the lower third of clivus or for tumors, such as chondrosarcoma, extending laterally or posteriorly to paraclival carotid artery.

Moreover, in case of suspect of malignancy at pre-operative assessment, such as plasmocytomas, metastases or rhynopahrynx carcinomas extended to posterior fossa, a simple biopsy can be an acceptable goal, leaving the treatment of the tumor to radiation or medical therapies (2-19).

Surgical Technique

3.1. Patient preparation and position

Surgery is performed under hypotensive general anesthesia with oro-tracheal intubation and laryngopharynx is packed with gauzes to avoid blood and fluid leakage. Routine prophylactic antibiotic is administered intravenously 30 to 60 minutes before surgery and a further dose is administered if the procedure lasts more than 6 hours, as we have already reported (25).Neuromuscular blockade must be avoided during the procedure when intraoperative neurophysiologic monitoring are performed.

The patient is placed semisitting position, with the thorax slightly elevated on the operating table. To gain access to posterior cranial fossa, we prefer to keep the head more flexed than routinely, about 30°-40° on the thorax. Routinely, we adopted a neuronavigation system (StealthStation S7 MEDTRONIC, Louisville, CO. USA), processed through StealthMerge Software (MEDTRONIC, Louisville, CO. USA).

3.2. Choice of the surgical corridor

The main factor in the selection of the surgical corridor is represented by the location of the tumor along the clivus. Different routes are performed depending on the tumor localization in the upper, middle or lower clivus or in case of its lateral extension. Anatomical variants or incomplete pneumatization of the paranasal sinuses may have a role in the selection of the more appropriate surgical corridor.

3.3. Nasal phase

For tumors located in the upper clivus, we started displacing laterally the middle and inferior turbinates. When necessary, the tail of the latter can be resected to widen the surgical corridor. Surgery was performed through both nostrils and with four hands technique, after the detaching of the vomer from its insertion and resection of the posterior part of the septum. Afterward, an anterior sphenoidectomy was completed. In case of adeguate pneumatization of sphenoidal sinus, the clivus can be identified as a midline indentation below the sella and between the course of the two carotid arteries. The dorsum sellae lies behind the pituitary gland, thus it is been described that a pituitary gland transposition is required to access to this region (26). However, it is debatable if this maneuver is necessary for tumors, such as chordomas, requiring a post-operative radiation therapy, which would lead to endocrinological deficits. Chordomas can be, usually, identified after drilling as much as necessary the upper clivus, and eventually the dorsum sellae, while intradural tumors require the opening of the dura wall. For upper clivus extradural lesions the lateral limit of this approach is represented by the paraclival carotid artery, while for intradural tumors this limit is given by the III CNs, which can not be trespassed to avoid injury. This midline approach can be combined with an ethmoido-pterygo-sphenoidal route, consisting in an ethmoidectomy, followed by medial maxillectomy and drilling of top of the vertical process of the palatine bone and of upper part of the medial pterygoid process. This extension allows to gain access to the cavernous sinus, particularly to its lateral compartments lateral and permits to move the surgical trajectory lateral to the carotid artery, partially overwhelming this anatomical limitation (17,27).

To expose the middle clivus, we perform an inferior extension of the previous approach drilling the sphenoidal floor between the paraclival carotid. As we have already showed, the vidian nerve represents the main anatomical landmarks to the petrosal-paraclival genu of carotid artery. Therefore, drilling medially to these structures allows to expose middle clival tumors in a relative safety. However, the course of the ICA must be confirmed by neuronavigation system and Doppler (20 MHz Surgical Doppler System, Mizuho America, Inc. Union City, CA, USA). For intradural tumors, the opening of the dura should be performed carefully to avoid injuries to the VI CN. Indeed, this nerve pierces the dura medially to the carotid artery above the level of the vertebro-basilar junction. Many techniques have been proposed to avoid to damages this nerve, including intraoperative elettrophysiological stimulation of the dura to recognize the location of the VI CN, and ecodoppler and/or neuronavigation to localize the vertebro-basilar artery and thus start opening the dura inferiorly (10). For extradural lesions the main limitation of this approach is given by the paraclival caratid artery, while for intradural tumors the cisternal portion of the VI CN represents its lateral limit. Not infrequently tumors of the middle clivus can spread to surrounding regions, such as pterygopalatine of infratemporal fossa. To follow the tumors extending to these areas, a transmaxillo-pterygoid approach could be useful. It requires a medial maxillectomy (or an anterior and medial maxillectomy according to Denkel for tumors located more laterally), followed by the opening of the posterior wall of maxillary sinus and drilling of vertical process of the palatine bone and of the medial pterygoid process. During this approach particular care should be paid to the management of the internal maxillary artery, which usually requires a clipping to avoid intra or post-operative bleeding. The posterior limit of this approach is given by V3, which is the landmark for the petrosal portion of the carotid artery, running behind the nerve.

A further inferior extension of the this approach allow to expose the inferior third of the clivus and the cranio-vertebral junction. For lesions in this latter region, we prefer at the beginning of the surgery to retract the soft palate through two thin rubber nasogastric probes inserted through the nose and extracted through the mouth. Many technique to skeletonizing the rinopharynx mucosa and dissecting the muscular planes have been proposed, we preferred to perform an inverted U-shaped flap from one Rosenmuller fossa to the other. Before surgery, it should be considered mandatory to perform a CTA to study the location of the parapharyngeal carotid artery. Indeed, it is not uncommon to observe mid-line loop of the vessel, which could represents a major caveat for this surgery. As in the other segments of the clivus the carotid artery in its para-pharyngeal tract represents the main lateral extradural limit of this approach, while for intradural lesions this limit is represented by XII CN. To expand laterally this access, some Authors proposed a transcondylar and/or transjugular tuberculum approach (so called “far medial”) (12). It consists in the removal of respectively condylar and tubercular regions. The trancondylar approach allows to maximize the exposure of the foramen magnum area, while the transjugular tuberculum approach permits to obtain an exposure of the medial border of the jugular foramen.

3.3. Tumor removal

Tumor removal is performed through the usual microsurgical technique: the lesion is dissected bimanually by the surrounding anatomical planes (we prefer to fix the endoscope on the holder to allow both surgeons to operated with four hands), avoiding tractions it is progressively debulked and finally resected. When it present a soft consistency, the tumor removal can be performed throughout the suction, conversely for harder consistency curettes and dissectors can be adopted and for calcified tumors a drill could be necessary. Debrider could be an useful tool to reduce the tumor mass, but it should be adopted carefully, after localization of the vessels and nerves, and it should it avoided intradurally. In this space the CUSA (Integra LifeSciences, Plainsboro NJ, USA) or Nico (Myriad Corporation, Indianapolis, IN, USA) can be adopted to debulk the neoplastic mass. The first one is limited by its axial work channel, which avoids to resect lateral portion of the tumors. The relationship of the tumor with the dura is of crucial importance for the surgical strategy. When there is no invasion, the tumor should be dissected by this layer and then resected. In case of dura infiltration, without trespassing in the intradural space, it is not possible to perform this dissection, and the radical removal is often impossible. When the dura is trespassed by the tumor, it is possible to follow its extension, entering in the posterior fossa. If the dural dimple is of small dimension, a bigger opening can be performed to visualize all the tumor extension. Furthermore, the tumor should be careful dissected by nearby vascular, nervous and axial structures.

Moreover, for intradural tumors, such as meningiomas, this approach allows to achieve an early devascularization, coagulating the dural implant of the tumor and drilling its eventual associated hyperostosis. Afterwards, the dura can be cut and the tumor removed with the standard microsurgical technique.

3.4. Closure phase

In case of CSF leak a plastic repair is mandatory. We usually adopt a multiplayer technique, requiring at least three layers of mucoperiostium and fascia lata. The first layer is composed by fascia lata or other heterologue material, such as Biodesign (Cook Medical, Bloomington, IN, USA) and it is placed intracranially intradurally. It should be larger than 20-30% than the dural defect to cover it completely. A further external layer of fascia lata or heterologous material is placed intracranially extradurally, than a rigid scaffold with bone or cartilage may be put in place to sustain the closure. This plastic is finally covered by mucoperioustium graft or nasoseptal flap. In case of approaches to lower clivus, the U-inverted muscular and mucosal flap can be re-positioned with some stitches to repair the CSF leak. Nasal cavity is filled with gelfoam and usually merocel is kept in place for the first 2 days.

Post-operative and complications management

4.1. Post-operative clinical and radiological monitoring

Although surgery represents the more challenging time dealing with posterior fossa tumors, a post-operative optimal clinical and assistential management has an equal or superior role to determine the final outcome. We prefer to extubate and awake all patients at the end of the surgical procedure, unless a suspect of post-operative dysphagia is present, such as after manipulation of IX, X or XI CNs. Afterwards, the patient remains for 24-28 hours in Intensive Care Unit for clinical monitoring. Whether an intra-operative CSF leak has been observed the patient remains in supine position for 72 hours, otherwise he can stand up and mobilize the same day of surgery. Oral feeding is started the same day of surgery as well, unless for suspect of dysphagia, which requires an oro-gastric tube. Nasal packing is kept in place for 48 hours. No special medications are prescribed in post-operative time and low-molecular weight heparin at prophylactic doses can be started at the first day after surgery to reduce the risk of deep vein thrombosis and pulmonary embolism.

A CT scan is performed 6-8 hours after surgery to exclude early hematomas or other complications. Afterwards, an MRI is performed within the first 72 hours to have an early assessment of the surgical results, which need to be confirmed at late follow-up. If necessary, rehabilitation is started 2-3 days after surgery and it lasts as long as patient has recovered a sufficient autonomy in daily activities. Patients are discharged from hospital in a mean of 5-7 days after surgery.

Post-operative follow-up includes an MRI 3 months after surgery and then after 6-12 months. At the same times, all pre-operative clinical tests were repeated to asses the patient outcome and his/her quality of life.

4.2. Complications

Each phase of surgery, from positioning to closure, may lead to potentially relevant complications and special care should be provided to avoid them. The adoption of the neurosurgical technical principles and the selection only of an approach for which the surgeon is highly trained, preferable in a multidisciplinary team, are

the basic rules to reduce the risk of complications. Complications of posterior fossa surgery may be classified as vascular, neurologic, and infective.

4.3. Vascular Complications

Vascular complications may be related to the approach phase and/or to vascular dissection during tumor resection; these may be categorized into arterial or venous hemorrhages.

• Vascular Complications in the Approach Phase. The most frequent arterial hemorrhage during endoscopic skull base surgery occurs as a result of bleeding from branches of the external carotid artery, namely the sphenopalatine artery (28-30). In a midline transsphenoidal approach, the septal branch may accidentally be lacerated during the enlargement of the sphenoid ostium inferiorly, and the external nasal branch may be interrupted at the posterior end of the middle turbinate when performing a middle turbinectomy. Bleeding of the main trunk or of the branches of the sphenopalatine artery requires the meticulous coagulation of the vessel, not only to stop the blood loss but also to prevent possible delayed epistaxis. Particular care to the management and preservation of spheno-palatine artery should be paid for surgeries requiring large osteo-dural defects with relevant CSF leak intra-operatively. Indeed, the branches to the septum from this artery are the main feeders for the naso-septal flap. Thus, their injury can lead to impossibility to adopt the standard nato-septal flap for the skull base closure. Bleeding from the internal carotid artery is very rare and it has been estimated in 1% of the procedures, however when occurs it may be dramatic with estimated morbidity of 24% and a mortality of 14% (28-30). Favoring factors potentially leading to ICA injury if not properly considered are: 1. bulging of the ICA within the sphenoidal sinus; 2. sphenoidal septa inserting on the prominence of the ICA; 3. reduced intercarotid space; 4. the persistence of the trigeminal artery or the presence of vascular malformations, such as an aneurysm. Moreover, also the malignant nature of tumors or the presence of scar tissue derived from previous surgical procedures or from radiotherapy may increase the risk of ICA injury. The first trick to avoid any damages is to assess and re-assess many times the course of ICA during surgery by means of anatomical landmarks and neuronavigation and Doppler confirmations. Although all these devices, if an injury occurs it is necessary to stop the bleeding by compression the vessels. Some Authors propose to cauterize the bleeding site with bipolar, nevertheless this may lead to an increasing bleeding for retraction of the arterial wall. During this compression, it is crucial that the blood pressure and vascular volume would be kept hight enough to give an adequate cerebral perfusion and the head should be lowered to level of the heart. After control of the bleeding, it is necessary an angiography to assess the presence of a pseudoaneurysm, the site of the vascular injury and the effectiveness of the collateral circulation. Afterwards the vessel could be repaired through a placement of a stent, occluding the tear in the vessel wall and maintaining blood flow, or with endovascular permanent occlusion of the ICA. If no adequate contralateral collateral circulation exists, this last option is not advisable and a bypass should be performed. There is still disagreement regarding the value of routinely performing a preoperative balloon occlusion test (28-30). Due to the potential procedure complications, a balloon occlusion test is advisable only in selected cases where the risk of carotid injury is greater than that of the test.

Venous hemorrhages during the approach phase are mainly due to the cavernous and intercavernous sinus or to the basilar plexus. Bipolar coagulation is generally effective, particularly after the dura opening. Otherwise, several hemostatic materials may contribute to controlling venous bleeding (e.g., FloSeal, Avitene, Gelfoam).

• Vascular Complications in the Dissecting Phase. The management of extradural arterial or venous bleeding is identical in the approach phase. The hemostatic techniques are the simple packing and irrigation with warm water (effective for venous oozing); the use of hemostatic agents (effective for venous bleeding and also for mild arterial bleeding); and the use of bipolar cauterization (especially necessary for arterial bleeding). The experience of the surgeon guides the choice of the technique because each one has both some advantages and disadvantages (28-30). Although any meticulous hemostatic technique, some limited postoperative bleeding are often unavoidable. Asymptomatic hematomas in the surgical field, incidentally discovered at routine postoperative neuroradiologic controls, are not infrequent and do not require treatment, but they are to be monitored until their disappearance. Conversely, symptomatic hematomas need a prompt treatment; an endonasal reintervention may be sufficient, but sometimes a craniotomy procedure is necessary, particularly when the surgeon suspects that the bleeding source is a major arterial vessel.

4.4. Neurological Complications

Neurologic complications may be the consequence of vascular damage or may be due to direct injury of the nervous tissue and nerves. It is generally assumed that endoscopic skull base surgery has a reduced neural morbidity. Indeed, transcranial approaches to the ventral skull base often require some degrees of brain manipulation. Furthermore, they follow a lateral-to-medial direction, and access to midline lesions requires the

dissection of the neurovascular structures displaced at the periphery of the expanding mass. Conversely, endoscopic skull base approaches allow an extracerebral direct access to the ventral skull base, avoiding brain manipulation and neurovascular dissection. It allows to follow the tumor extension, tailoring the approach on the tumor, reducing the risk of damaging of the neural structures. However, injuries to these structures are always possibile. Intra-operative monitoring may be useful to localize the neural structures and to avoid dangerous maneuvers.

4.5. Infections

Two main types of infections may occur: systemic infections (urogenital, pulmonary, and cardiac infections) and local infections. The former depends on the operative time, and bed rest, and on factors related to the general health conditions of the patient. Conversely, local infections at the surgical site (sinusitis, meningitis) are related to the surgical procedure. Factors influencing the reduction of infections of the surgical field include antibiotic prophylaxis, sealed closure of the dural defect, prompt management of the postoperative CSF leak and intra/postoperative management of the sinonasal cavity. Antibiotic prophylaxis helps to prevent infection by reducing the "infectious load" in the presence of the clean contaminated surgery such as in endoscopic endonasal surgery. A standardized regimen of antibiotic prophylaxis maintains a low incidence of postoperative infection, particularly from resistant organisms, allergic reactions and side effects, and antibiotic-related complications such as *Clostridium difficile* enterocolitis and thrombophlebitis from intravenous lines. We prefer an ultra-short profilaxis, as reported by Milanese et al. In case of CSF leak, its prompt management remains the key to reduce the risk of meningitis (25).

Moreover, to prevent acute or chronic alterations of the sinuses and nasal cavity functioning and/or infection and/or postsurgical mucocele, it is important to avoid unnecessary stripping of mucosa, to preserve sinus patency, and to correct any tendency toward lateralization of the middle turbinate. In the postoperative period, we suggest frequent nasal cleaning with saline solution and a transnasal endoscopic examination 3 to 4 weeks after the surgical procedure or earlier in the case of disturbing sinus symptoms, such as rhinorrhea, a foul smell, and/or nasal obstruction.

4.6. CSF leak

CSF leak from the subarachnoid space into the paranasal sinuses and, finally, into the nasal cavities may produce disastrous intracranial complications such as meningitis and pneumocephalus. Its incidence for posterior fossa surgery is higher than for standard procedure and this risk may always been considered in the post-operative rime. The features favoring such a complication are mostly uncontrollable expiratory reflexes, such as sneezing, coughing, or vomiting. A smooth emergence from anesthesia as well as preoperative instructions regarding activity restrictions are useful expedients in preventing such events.

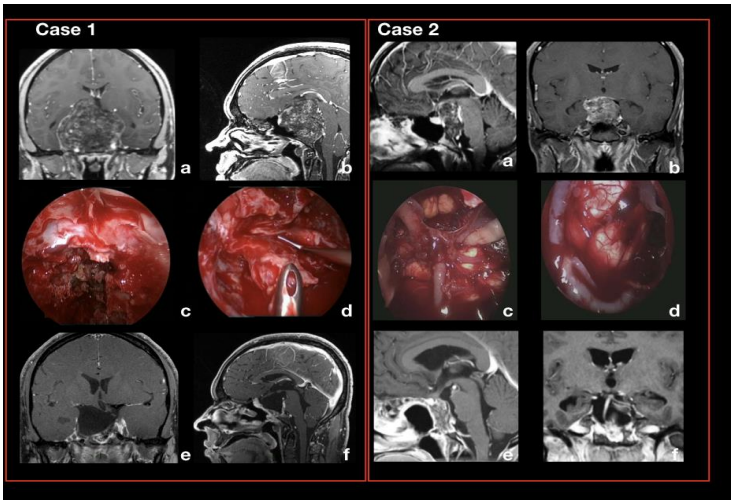
Before any treatment, postoperative CSF leak should be confirmed with clinical, radiological and laboratory tests. The suspicion that clear fluid leaking from the nose is CSF may be increased significantly using the tilt test (head flexed). However, the certainty that the fluid is CSF may be reached only by the beta-2-transferrin test or the beta-trace protein test. High-resolution CT, combining fine slices in two planes, is the primary and often the only imaging modality for the localization of defect. It may show the osteodural lack and the opacification of contiguous sinuses or air cells, and it gives indirect sign of CSF leak such the appearance or the increasing in the pneumocephalus. For very doubtful case, intrathecal fluorescein may prove the presence of the CSF leak or to confirm the effectiveness of the repair (30-31).

If the CSF leak is confirmed, a prompt revision surgery is necessary to avoid worst complications.The material available for the repair may be heterologous or autologous, depending on surgeons preference. The adoption of lumbar drainage is still debated. We advise to adopt in only two circumstances: (1) recurrent small leakage after a previous tissue repair; and (2) the presence of CSF hypertension suggesting the use of lumbar drainage to support a tissue repair because it reduces the pressure on the graft. However, it should be considered that that lumbar drainage may precipitate a rare and severe complication of CSF leak: tension pneumocephalus. Typically, pneumocephalus is asymptomatic, but if it evolves in a tensive forms, it could lead to a quick neurological deterioration of the patient. In this rare condition, it is mandatory to remove the lumbar drainage, evacuate the air, and repair the leak directly at the site of origin (30-31).

Conclusion

Endoscopic endonasal approach for posterior fossa tumor is a complex surgery, which should be reserved to experienced surgeon, skilled in endoscopic technique. It requires a good knowledge of the ventral anatomy of this region, which is usually not familiar for the most of surgeons, to avoid dramatic mistakes, as well as peculiar skills for plastic repair to limit the risk of the more common complication, consisting in the post-post-operative CSF leak. The coordinated team working between ENT and neurosurgeon is a the more

practical and effective tool to maximize the advantages of this approach, keeping its risks at an adeguate rate. In our experience, the more crucial phase is represented by the case selection. Among the others, the main limitation is given by the mid-line tumors of these lesions with a limited lateral extension. Indeed, extradurally the main lateral anatomical limit of this approach is given by the course of the carotid artery. This limits can be



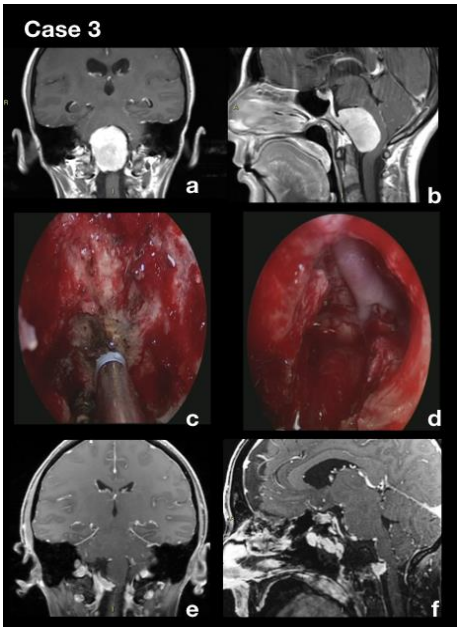
partially overwhelmed, adopting some paramedian endoscopic endonasal corridors, such at the transpterygoid or the transmaxillary ones, to gain access also to portion of the tumor lateral to this vessel (Fig. 1, 2). Conversely, although selected mid-line intradural tumors are suitable for this approach, in case of lateral extension, beyond the cranial nerves, the endoscopic endonasal route should be combined to others to complete the surgical removal, avoiding an unjustified morbidity rate.

Considering the possibile complications related to this surgery, it is mandatory to achieve a complete pre-operative evaluation of each single patient, including neuroradiological and clinical assessment. Post-operative care should be careful, keeping these patients under careful clinical monitoring.

The management of posterior fossa tumors through this ventral approach represents a current evolution of this technique and its correct indications are still debated. We believe that this corridor is highly promising for many tumors, such as chordomas, chondrosarcomas, meningiomas and others, but for each case the balance between the possible advantages and disadvantages given to the patients should be carefully considered.

Fig. 1. Two different cases of clivus chordomas are presented. Case 1. The first case is an extradural chordoma extended for the whole extension of the clivus and invading both cavernous sinuses. A and B. Pre-operative MRI, T1 WI with gadolinium in coronal and sagittal slice. C and D. Intra-operative image. 0° degree scope. The tumor is debulked and than cleaved from the dural plane. E and F. Post-operative MRI, T1 WI with gadolium, sagittal and coronal slice. The radical resection of the tumor is demonstrated. Case 2. The second case is an intradural chordoma. A and B. Pre-operative MRI, T1 WI with gadolinium in coronal and sagittal slice. C and D. Intra-operative image. 0° and 30° degree scope. The tumor is resected and the vascolo-nervous structure of the posterior fossa are visible (C: basil apex with its branches and CN III, D vertebro-basilar junction). E and F. Post-operative MRI, T1 WI with gadolium, sagittal and coronal slice. The gross tumor removal was achieved.

Fig. 2. A case of posterior fossa meningioma is presented. A and B. Pre-operative MRI, T1 WI with gadolinium in coronal and sagittal slice. C and D. Intra-operative image. 0° degree scope. The dura is extensively coagulated to reduce as first step of tumor removal. Afterwards, it could be resected, cleaving the lesion from the surrounding structures.E and F. Post-operative MRI, T1 WI with gadolium, sagittal and coronal slice. The subtotal resection of the tumor is demonstrated, with small remnant which has required a proton bean therapy for a tumor progression at follow-up.



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Factors Predicting Rupture Of Intracranial Aneurysms In Patients With Multiple Intracranial Aneurysms

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Abstract

Aim: To evaluate the various morphological and flow-related factors that may predict rupture of an intracranial aneurysm

Materials and Methods: 10 patients with multiple intracranial aneurysms (IA) were selected. Morphological factors, wall motion analysis (WMA), and "eddy currents" in parent vessel and aneurysm were analysed.

Results: Daughter sacs, aspect ratio and size ratio are important indicators of site of rupture. All 10 patients showed eddy currents along ruptured aneurysms as against none along un-ruptured aneurysms.

Conclusions: "Eddy Current" generation is the single most important factor in determination of rupture of an intracranial aneurysm compared to other morphological or flow-related factors.

Keywords: Multiple intracranial aneurysms, eddy currents

Introduction

How do you determine which aneurysm has ruptured in a patient with diffuse subarachnoid haemorrhage (SAH) and multiple aneurysms on the angiogram? What are the factors that led to rupture of one aneurysm but spare the others? Which aneurysm will you treat first? These are practical questions that we encounter on a regular basis in our clinical practice.

A lot of research has gone in determining factors that may affect the progression of an intracranial aneurysm ultimately leading to its rupture. However, there is lack of consensus on the ability of these factors to predict a rupture. There is a new factor which gets analysed in every new publication and purported as the best indicator for rupture risk of an aneurysm. However on practical application to our patients we found that they are not reliable as they seemed to be. Hence, an additional study was designed to try and validate existing factors and study an additional factor as discussed below and their ability to predict a rupture.

Materials and Methods

10 patients with multiple intracranial aneurysms one of which had ruptured were selected for the study. The study was conducted over a 2 year period from January 2016 to December 2017. All patients with SAH and multiple aneurysms on digital subtraction angiography (DSA) were included. Site of rupture was determined with CT (site of maximal hematoma), DSA (daughter sacs) and per-operative findings. All patients underwent surgical clipping of the ruptured aneurysm and followed up later for optimum management of other un-ruptured aneurysms.

Morphological and hemodynamic factors were studied with an eye for practical application in clinical practice. Morphological factors that were studied are location, shape, size, presence of daughter sacs, depth: width ratio, size ratio, bottleneck factor, flow angle and parent vessel diameter. Wall motion analysis (WMA) was done by using 3D rotational angiography. An additional novel factor, "eddy current" generation within the aneurysm and in the parent vessel was studied in detail for its role in propagation of aneurysm.

Results

The morphological factors as discussed above are listed below in Tab. 1.

Tab.1: Comparison of the morphological factors between ruptured and un-ruptured aneurysms

Factors	Ruptured	Un-ruptured	P value
Bifurcation	0.6	0.60	
Shape	0.7	1.00	
Daughter Sacs	0.9	0.00	0.001
Maximum Size	6.22	4.99	0.19
Depth	5.27	3.61	0.1
Width	4.03	3.67	0.34
Neck	2.33	2.52	0.37
AR	2.393	1.56	0.04
D:W	1.3165	1.00	0.055
Bottleneck Factor	1.809	1.56	0.1
Flow Angle	130.57	118.62	0.19
Parent Vessel Diameter	2.75	3.32	0.14
Size Ratio	1.986	1.17	0.03

Legend: AR – aspect ratio, D – depth, W – width.

The results of WMA on 3D rotational angiography are listed below in Tab. 2.

Tab.2: Results of Wall Motion Analysis (WMA)

Wall Motion Analysis	Ruptured	Un-ruptured
Present	6	4
Absent	4	6

Eddy current generation was observed by development of segmental layering effect with actual observation of turbulence with naked eye as the injected dye passes the involved region. All 10 patients showed similar phenomenon around the neck of the ruptured aneurysm which was not visualized across the neck of un-ruptured aneurysms.

Discussion

As we set out to answer the questions asked in the introduction we came across in the literature a multitude of factors, both morphological and hemodynamic, that were studied in detail and thought to influence

the formation and progression of an aneurysm ultimately to its rupture. The premise of the study is that not all aneurysms rupture. It was not always possible to correlate these factors with the site of rupture generating the need to study in detail the existing and additional factors which by itself or in combination help us in predicting which aneurysm has ruptured or more importantly which will rupture.

We chose multiple intracranial aneurysms, as patient related biases and such contributing factors like patient's age, sex, co-morbidities, and recreational habits, hemodynamic status etc. remains constant and does not have an effect on the structural and hemodynamic factors under study. Aneurysms can be looked at as herniation of the lumen of the vessel or herniation of the vessel wall. These are divergent views but in actuality interplay in between the both may contribute to the formation and propagation of an aneurysm as evidenced by our experience that not one single factor by itself could reliably predict the site of rupture.

We already know that vascular remodeling is activated by shear stress on the vessel wall. There is failure of remodeling over a period of time due to persistence of abnormal triggering factors (as discussed above) that leads to formation of an aneurysm and subsequently to its growth. The morphological factors Aspect Ratio (AR; aneurysm depth to aneurysm neck) and Size Ratio (SR; aneurysm depth to parent vessel diameter) were statistically significant (P values 0.04 and 0.03 respectively). However the most important single factor corresponding to ruptured aneurysm was presence of daughter sacs (P value 0.0001). Other individual factors did not seem to play a significant role. Similarly, we found WMA ineffective in identifying the ruptured aneurysm.

During DSA, we observed there are segmental areas of the cerebral vasculature where laminar flow is lost. These areas are in the vicinity of the aneurysm and can be divided into pre-aneurysmal, aneurysmal and post aneurysmal segments. This loss of laminar flow leads to turbulence within the vessel wall which forms pressure currents or "Eddy Currents" which act on vulnerable segments resulting in progression of these aneurysms. This phenomenon was seen along all the ruptured aneurysms in our study and was absent along the un-ruptured aneurysms. (Fig 1 and 2)

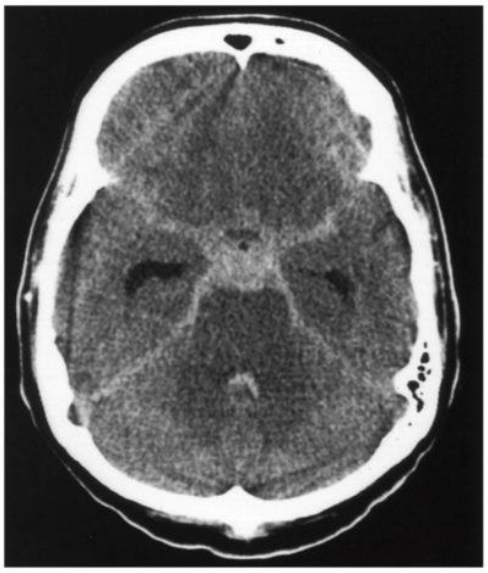

Fig. 1: Diffuse SAH in a 33 year old female patient.

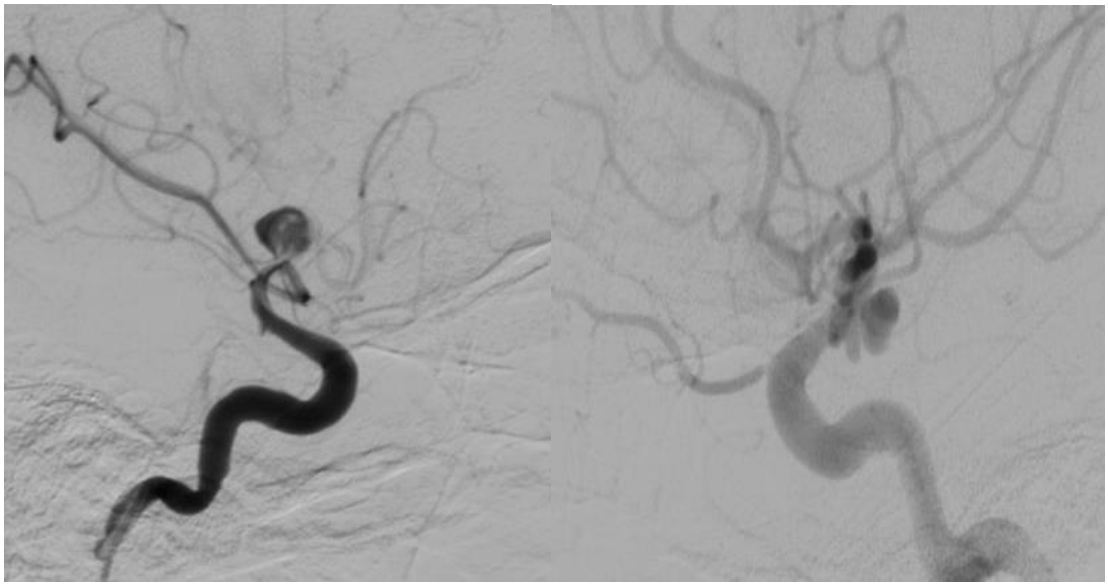

Fig. 2: Same patient had a ruptured right MCA aneurysm and an un-ruptured left communicating segment ICA aneurysm. The right MCA aneurysm showed a layering effect within the aneurysm and the parent vessel, at and proximal to the neck of the aneurysm demonstrating the eddy currents. Similar phenomenon was not seen on the contralateral side harboring the un-ruptured aneurysm.

Legend: MCA – middle cerebral artery, ICA – internal cerebral artery

To our knowledge, this phenomenon has not been reported in literature world over. It's a novel factor hitherto unstudied and requires more analysis to assess its possible role in the formation and progression of the aneurysms. The persistent presence of this phenomenon in the parent vessel along the ruptured aneurysm is worth noting. New software is being created to qualify and quantify the presence of the eddy currents and additional results supporting the preliminary data would be available soon.

Conclusions

Generation of eddy currents due to segmental loss of laminar flow which act on vulnerable segments and impair the vascular remodeling process ultimately leading to formation and rupture of the aneurysm as an additional factor should be studied in detail. AR and SR, presence of daughter sacs are more reliable morphological factor over others like WMA in determining the site of rupture.

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Factors Predicting Outcomes In Pediatric Traumatic Brain Injury

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Abstract

Introduction: Traumatic brain injury (TBI) is a common presentation to the pediatric emergency department. Understanding factors that predict outcomes will be useful in clinical decision making and prognostication. The objective of this study was to identify important clinical parameters predictive of outcomes in pediatric TBI patients who underwent surgery.

Methods: This retrospective study included 43 pediatric TBI patients who underwent surgery from January 2011 to January 2017. Clinical parameters including presenting signs and symptoms, intracranial pressure, need for inotropes and CT findings were collected. Outcomes were assessed using the Glasgow outcome scale (GOS) based on the latest follow up. Outcomes were divided into favorable (GOS 4-5) and unfavorable (GOS 1-3).

Results: Surgery was performed in 43 patients. The mean age was 9.6±4.9. The mean follow-up period was 31 weeks. 30 (70%) patients had favorable outcome and 13 (30%) had unfavorable outcome. On univariate analysis, vomiting, GCS score, pupil size and reactivity, hypotension, cerebral edema on CT, inotropic use, need for blood transfusion and raised ICP (all $p<0.005$) were significantly associated with outcomes. On stepwise logistic regression, only raised ICP (OR=35.6, p=0.008) and hypotension (OR=26.1, p=0.01) were found to be statistically significant.

Conclusion: Our study suggests that surgical intervention for the majority of pediatric TBI patients have favorable outcomes. Closer attention should be paid to raised ICP and hypotension as they were strong predictors of unfavorable outcomes. These findings also help manage expectations of patients' family and clinicians.

Keywords: Traumatic brain injury; outcomes; pediatric population; head injury

Introduction

Traumatic brain injury (TBI) is a significant cause of mortality and disability worldwide[1]. In the United States, approximately 600 000 pediatric patients are admitted to the Emergency Department due to TBI[2]. In Singapore, TBI is the leading cause of trauma among pediatric patients[3]. Pediatric TBI is a crippling condition which extends not just to oneself but the society. However, significant variations of clinical data and management strategies exist in the literature[2].

Adult and pediatric TBI have different pathophysiology and outcomes[4, 5]. An infant skull being less rigid with higher plasticity allows more movement in response to mechanical stress. In neonates, the cerebral white matter contains less myelin. These factors result in different absorption of forces in the adults and pediatric patients[4]. Furthermore, neonates having a larger head to body ratio are more susceptible to head injury. This corroborates with many studies that reported worse outcomes following TBI in infants[6-8]. Moreover, Bruce et al found cerebral edema twice more common in pediatric patients after TBI due to cerebral hyperemia[5, 9].

A review of literature revealed multiple factors which were associated with poor outcomes in pediatric TBI. Age, Glasgow Coma Scale (GCS) scores, clinical features (vomiting, pupil size etc) and injury mechanisms have been reported in various studies[5, 10-12]. Radiological studies also attempted to examine the relationship between computer tomography (CT) findings and outcomes. Presence of subarachnoid hemorrhage(SAH), diffuse axonal injury, brain swelling have been reported to predict poor outcomes in pediatric TBI[13]. However, the few studies that investigated predictive factors of TBI outcomes have revealed variable results. For instance, pupil size was only a significant predictor only in certain studies[13]. Post-

resuscitation GCS score was a significant predictor[14] in some studies but not in others[15]. The same issue applies for age, duration of loss of consciousness, presence of hypothermia and presence of injury severity scores[2, 5, 10]. Much debate exists between clinicians regarding the priority of management of clinical parameters upon presentation of a pediatric TBI.

Surgery for pediatric patients with TBI remain a controversial topic of discussion. Commonly practiced procedures such as intracranial pressure (ICP) monitoring have conflicting evidence of utility[16]. Although many clinicians still edge on the conservative side of management, there is growing evidence that decompressive surgery could improve outcomes of pediatric TBI patients[5, 17]. Minimal data exists in the literature that identifies risk factors which predict outcomes in pediatric TBI patients who underwent surgery.

The objective of our study was to identify pertinent clinical parameters and radiological factors that could predict outcomes in pediatric TBI patients who underwent surgery.

Materials and methods

This institutional review board approved study was conducted in the National University Hospital of Singapore. Pediatric patients aged 18 and under were retrospectively collected from June 2011 to January 2017. Inclusion criteria were any pediatric patient who suffered a TBI and was referred to the neurosurgical unit for any form of neurosurgical procedure including decompressive craniectomy, craniotomy and external ventricular drain insertion. Pediatric TBI patients who did not undergo surgery, patients with preinjury neurological or psychiatric conditions, patients who had no follow up after initial hospitalization and patients who did not survive before any surgery performed were excluded.

Demographic data collected include age, gender, mechanism of injury and type of hemorrhage. Patients were grouped into 3 groups based on their age; 0-6 years, 7-12 years and 13-18 years. Predictor variables collected for analysis include: GCS score, presence of loss of consciousness, vomiting, palpable skull fracture, signs of basilar skull fracture, presence of a non-frontal scalp hematoma, pupil size and reactivity, CT findings of type of hemorrhage, CT findings of severity of injury (midline shift, edema, mass effect), presence of hypotension (age adjusted), ICP, need for blood transfusion and use of inotrope prior or during surgery. Hypotension was defined as systolic blood pressure (SBP) less than 90mmHg for patients over 10 years, SBP less than 70 + (2 x age in years)mmHg for patients aged 1 to 10 years old and SBP less than 70mmHg for infants (1 month to 12 months). Table 2 summarizes all the predictor variables included for analysis. The verbal and motor component of the GCS scale was modified for pediatric patients below the age of 2 according to local institution guidelines. For the verbal component, 5 describes an infant that coos and babbles. 4 corresponds to an infant who is irritable and crying, 3 describes crying in response to pain, 2 moaning in response to pain and 1 has no response. For the motor component: 6 describes an infant moving spontaneously and purposely, 5 corresponds to withdrawing in response to touch, 4 for withdrawing in response to pain, 3 for abnormal flexion, 2 for abnormal extension and 1 for no response. Severity of TBI was categorized into mild (GCS 13-15), moderate (GCS 9-12) and severe (GCS≤8). Raised ICP was defined as ICP>20mmHg. At our center, The CODMAN ICP intraoperative monitor was used to measure ICP intraoperatively at the parenchymal level. The highest reading intraoperatively was chosen. All data were extracted from electronic medical records.

Outcomes were measured using the Glasgow outcome score (GOS). The GOS scale was modified for it to be applicable to pediatric patients based on Prasad's et al report[5]. Good recovery (GOS 5) referred to patients who returned to age appropriate levels of functioning or returned to normal classes without special assistance. Moderate disability (GOS 4) referred to patients with reduced cognitive function from premorbid levels, neurological deficits affecting daily activities or patients who were enrolled in classes with special needs. Severe disability (GOS 3) referred to patients who were deficient in cognitive function or patients who were unable to carry out age appropriate motor tasks. Vegetative state (GOS 2) referred to patients who required full dependence on daily activities. GOS 1 represented death of the patient. Patients were divided into 2 groups based on their GOS scores. Patients with a GOS score of 1-3 represented the unfavorable outcome group while patients with a GOS score of 4-5 represented the favorable outcome group. Outcomes of the patients were taken at their latest follow up appointment. The mean follow-up period was 31 weeks post discharge. Neurological, psychological and social assessments were reviewed by study investigators before awarding a GOS score to the patient.

Statistical analysis was carried out using IBM SPSS 20.0. Continuous variables were represented as mean ± standard deviation if normally distributed. For skewed distribution, data was presented as median and interquartile ranges. Chi square, Fisher's exact and paired T test were used for univariate analysis. Binary logistic regression was used to examine variables that were significant on univariate analysis. A p value of <0.05 was taken to be significant.

Results

A total of 43 pediatric patients were included into this study. 33 were males and 10 were females. The mean age was 9.6±4.9 years. 14 (33%) patients were aged 0-6 years, 15 (35%) patients were 7-12 years old and 14 (32%) patients were 13-18 years old. Mean GCS score was 10.3±4.3. Majority of the patients (17, 39.5%) presented with a mild GCS score of 13-15. The most common type of injury was an extradural hemorrhage (EDH) (19, 44%), followed by a sub-dural hemorrhage (SDH) (10, 23%), sub-arachnoid hemorrhage (7, 16%) and intraparenchymal hemorrhage (4, 8%). 30 (70%) patients had favorable outcomes while 13 (30%) patients had unfavorable outcomes. The basic characteristics of the patients were summarized in Table 1.

Table 2 summarizes the factors that were analyzed for univariate analysis. On univariate analysis, the following factors were found to be significantly associated with outcomes following pediatric TBI: GCS scores ($p=0.001$), presence of vomiting ($p=0.004$), pupil size>3mm ($p=0.001$), bilaterally non-reactive pupils ($p<0.001$), edema on CT scan ($p=0.023$), use of inotropes ($p<0.001$), presence of hypotension ($p<0.001$), raised ICP ($p<0.001$)and blood transfusion required during operation ($p=0.007$).. For severity of TBI based on GCS scores, 15 patients had severe, 11 patents had moderate and 17 patients had mild TBI. Among the 15 patients with severe TBI, 9 (60%) had unfavorable outcomes. Among the 11 patients with moderate TBI, 4 (36.4%) had unfavorable outcomes. None of the 17 patients with mild TBI had unfavorable outcomes. Vomiting was seen in 13 patients. None of the patients who vomited had unfavorable outcomes. 9 patients had pupils>3mm. Of these 9 patients, 7 (77.8%) had unfavorable outcomes. 2 patients had unilaterally non-reactive pupils of which 1 had an unfavorable outcome. 9 patients had bilaterally non-reactive pupils. 7 of these 9 patients had unfavorable outcomes. Edema on the CT scan was seen in 3 patients. All 3 had unfavorable outcomes. Inotropes were used in 8 patients. 7 (87.5%) patients had unfavorable outcomes. Hypotension was recorded in 12 patients. 10 (83.3%) patients had unfavorable outcomes. ICP was raised intraoperatively in 17 patients. 12 (70.6%) had unfavorable outcomes. 6 patients required blood transfusion intra-operatively. 5 (83.3%) patients had unfavorable outcomes.

Factors that were statistically significant on univariate analysis were examined using a backward stepwise binary logistic regression. On multivariate analysis, only patients who had raised ICP (OR=35.6, $p=0.008$, 95% CI 2.6-493.5) and hypotension (OR=26.1, $p=0.010$, 95% CI 2.2-311.8) emerged to be statistically significant.

Discussion

This study examined the relationship between different clinical parameters and the outcomes of pediatric TBI patients who required surgery. In our cohort of 43 patients who underwent surgery, it was found that raised ICP and hypotension were significant independent predictors of unfavorable outcomes. Although multiple predictor variables have been reported in the literature, there is no agreement as to which variable is most predictive of outcome. The aim of this study was to find out pertinent clinical parameters that would predict outcomes after TBI in a defined group of pediatric patients. Ultimately, this would improve the focus of management in pediatric TBI patients undergoing surgery.

Despite TBI being a common cause of mortality and morbidity, clinical management of pediatric patients are not as well established as adults. Many authors have reported different results over the past 20 years. An important point of discussion would be the use of GCS scores in predicting outcomes due to its extensive use in daily clinical practice. Initially, GCS was thought to be a significant predictor of outcome in pediatric TBI patients[18]. Subsequently, there have been two sides to the story regarding the value of GCS scores in predicting severity[14, 15, 19]. We believe this is due to a few reasons. Firstly, different authors reported GCS scores at different stages of clinical assessment. Ducrocq et al reported that initial GCS score at presentation was a significant predictor of unfavorable outcome[20]. However, Massagli et al reported that GCS recorded only at 24 and 72 hours were significant predictors of outcome[18]. Furthermore, the sample population in different studies varied in terms of sample size, age and patient characteristics. Some studies included patients with only moderate to severe GCS scores[18, 21] while others included all patients regardless of their GCS score[5]. The different range of GCS scores coupled with the different target age groups and sample size could have well affected statistical significance. In this study, different pediatric age groups were well represented as each age category had approximately one-third the sample population. Furthermore, our sample population was specific to those who underwent surgery following TBI. Our results showed that GCS scores were significantly associated with outcomes only on univariate analysis ($p=0.001$). This is in line with authors who reported the limited use of GCS scores to predict outcomes of pediatric TBI patients[19].

The same problem with GCS scores is encountered for other factors that have been reported in literature. A review of literature showed that common predictor variables investigated include: age, injury severity scores, mechanism of injury, pupil size, vomiting, loss of consciousness, base of skull fracture, CT findings, blood

pressure, intracranial pressure[5, 11, 21, 22]. Prasad et al and Wells et al reported that age at injury was not a good predictor of outcome in pediatric TBI patients[5, 23]. However, Prigatano et al found that age was the strongest predictor of post traumatic brain injury performance in neuropsychological tests in school going children[24]. Similarly, pupil size was only found to be a significant predictor in certain studies[5, 25]. Kamal et al reported that GCS score, brain CT findings and hypotension were significant predictors of outcome on univariate analysis in a pediatric population younger than 12 years old[26]. In a French trauma center with 585 patients of mean age 7 years, Ducrocq et al reported that initial hypotension, GCS and injury severity score were significant predictor variables on multivariate analysis[20]. Results from this study on univariate analysis were not entirely different from those published. We found that only bilaterally non-reactive pupils were significantly associated with unfavorable outcomes. Presence of unilaterally non-reactive pupils was not a significant factor. Furthermore, use of inotrope and patients requiring blood transfusion are variables that have not been reported before. It is to the best of our knowledge that the present study included the most number of predictor variables for analysis. Essentially, in the few studies that investigated predictor variables of outcome in pediatric TBI, no consensus has been reached by authors. This presents as a clinical problem as doctors are unaware of important clinical parameters to pay close attention to when managing pediatric TBI patients. Although all clinical parameters should be monitored, there are some that requires closer attention.

Perhaps another reason for the dissimilarity in predictor variables is the measure of outcome in pediatric patients post TBI. Authors reported different follow up periods as well as different outcome measures. Anderson et al utilized intellectual measures such as verbal and non-verbal skills, attention and processing speed to examine outcome 5 years post injury in preschool pediatric TBI patients[27]. Prigatano et al measured outcome based on performance cerebral functioning tests[24]. A recent study by Hale et al measured outcome by the presence of post discharge seizures[28]. The GOS scale is the most commonly used measure of outcome in the literature[20, 21]. However, it has been reported that the GOS scale underestimates the impact of brain injury in young children[5] as it was developed for use in adults[29]. In 1981, the GOS scale was modified to the GOS-Extended (GOS-E)[30] and a pediatric revision, GOS-E Peds was created and validated by Beers et al[31]. However, to the best of our knowledge, very few studies reported the use of GOS-E Peds to measure outcomes[32]. The GOS-E Peds has a maximum score of 8 which is more time consuming to conduct than the original GOS scale. In our study, we used a GOS scale modified by Prasad et al for pediatric patients[5]. Although further validation is required, the modifications appeared to have increased the sensitivity of GOS in pediatric TBI outcomes[5]. Our study shows that majority of the patients had favorable outcomes (70%) after undergoing a neurosurgical procedure. This result is similar to most of the data published in the literature[5, 13, 20, 33].

Several authors have used stepwise logistic regression to identify variables most predictive of outcome[5, 18, 20, 21]. We adopted the same method for our study. The results from this present study found that raised ICP and hypotension were variables most predictive of outcomes. This is similar to the findings of a French trauma center reported by Ducrocq et al on a multivariate analysis[20]. White et al also reported that supra-normal blood pressures and mannitol administration were associated with improved outcomes on multivariate analysis[21]. However, both studies only focused on pediatric patients with GCS≤8. This present study included all patients regardless of GCS scores that underwent any form of neurosurgical procedure. A reduced blood pressure would result in a decrease in cerebral perfusion leading to ischemic brain damage. This increases secondary brain damage which worsens outcome. Furthermore, raised ICP would cause a decrease in cerebral perfusion pressure which have been reported by Carter et al[34] to be an accurate cause of unfavorable outcome in pediatric TBI patients. Our results show that priority must be given to manage these 2 clinical parameters in a pediatric TBI patient. Further work needs to be done to accurately identify blood pressure and intracranial pressure targets which are more precise in preventing unfavorable outcomes.

There were several limitations in this study. Being a retrospective review in a single-center neurosurgical unit, the sample size was smaller compared to multi-center studies. Larger sample size and multi-center studies should be undertaken to validate the current findings. However, our targeted sample population is the first of its kind which will be beneficial to neurosurgeons. Since our study only included patients who underwent surgery, the results might not apply to pediatric TBI patients managed conservatively. Thirdly, it is also important to recognize that the GOS scale measures neurological and psychiatric disorders[35]. Other outcome measures such as quality of life, education level, social function were not clearly defined in the GOS scale.

In conclusion, this study is the first of its kind to quantify that raised ICP and hypotension were variables most predictive of unfavorable outcomes in a targeted population of pediatric TBI patients who underwent neurosurgery. Our results also suggest that surgical intervention for the majority of pediatric TBI patients have favorable outcomes. Neurosurgeons should play closer attention to ICP and blood pressure when managing pediatric TBI patients.

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Tables

Table 1. Patient demographics

Parameter	Value
Gender	
Male	33 (77%)
Female	10 (23%)
Average age, years	9.6 +/- 4.9
Age categories	
0-6 years	14 (32%)
7-12 years	15 (35%)
13-18 years	14 (32%)
GCS scores	
13-15	17 (39.5%)
9-12	11 (25.6%)
3-8	15 (34.9%)
Type of injury	
Extradural hemorrhage	19 (44.2%)

Subdural hemorrhage	10 (23.3%)
Subarachnoid hemorrhage	7 (16.3%)
GOS scores	
Favorable (GOS 4-5)	30 (70%)
Unfavorable (GOS 1-3)	13 (30%)

Table 2. Factors analyzed on univariate analysis

Variables		Favorable (GOS 4-5)	Unfavorable (GOS 1-3)	*P* value
GCS categories	Mild	17	0	0.001
	Moderate	7	4	
	Severe	6	9	
Vomiting	No	17	13	0.004
	Yes	13	0	
Pupil size	<3mm	28	6	0.001
	>3mm	2	7	
Bilaterally non-reactive to light	Yes	1	8	<0.001
	No	29	5	
Hypotension	No	28	3	<0.001
	Yes	2	10	
Raised ICP	No	25	1	<0.001
	Yes	5	12	
Inotrope use	No	29	6	<0.001
	Yes	1	7	
Presence of polytrauma	No	24	1	<0.001
	Yes	6	12	
CT edema	No	30	10	0.023
	Yes	0	3	
Blood transfusion required	No	29	8	0.007

	Yes	1	5	
Age	0-6	8	6	0.455
	7-12	9	3	
	13-18	13	4	
Unilaterally non-reactive to light	Yes	1	1	0.518
	No	29	12	
Loss of consciousness	Yes	5	6	0.061
	No	25	7	
Altered level of consciousness	Yes	8	5	0.485
	No	22	8	
Palpable skull fracture	Yes	3	2	0.630
	No	27	11	
Signs of base of skull fracture	Yes	2	0	1.000
	No	28	13	
Non-frontal scalp hematoma	Yes	8	3	1.000
	No	22	10	
CT IPH	Yes	1	3	0.075
	No	29	10	
CT EDH	Yes	16	3	0.098
	No	14	10	
CT SDH	Yes	6	4	0.458
	No	24	9	
CT SAH	Yes	3	4	0.172
	No	27	9	
CT mass effect	Yes	11	2	0.279
	No	19	11	
Midline shift >5mm	Yes	25	12	0.649
	No	5	1	

CT fracture	Yes	17	9	0.513
	No	13	4	

Table 3. Factors significant on multivariate analysis

						95% C.I. for EXP(B)	
Variables	B	SE	df	Sig	Exp(B)	Lower	Upper
Hypotension	3.262	1.265	1	.010	26.108	2.186	311.769
Raised ICP	3.572	1.342	1	.008	35.588	2.567	493.452

High Mobility Group Box 1: A Potential Biomarker For Post-Subarachnoid Hemorrhage Complications In Aneurysmal Subarachnoid Hemorrhage

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Abstract

Aneurysmal subarachnoid hemorrhage (SAH) is associated with the highest morbidity and mortality among all stroke subtypes. Endovascular coiling and neurosurgical clipping can successfully obliterate bleeding aneurysms from the circulation in almost all cases. Despite successful obliteration of the bleeding aneurysm, the clinical outcome in these patients is still poor. In a significant proportion of patients, the main reasons for poor outcome are occurrence of life-threatening complications including cerebral vasospasm (CVS), delayed cerebral ischemia (DCI), and systemic infections. Biomarkers in the systemic circulation or cerebrospinal fluid (CSF) may be useful to predict the occurrence of these complications and to provide timely treatment. Well-established and validated biomarkers for the diagnosis and prognosis of post-SAH inflammation in different complications and clinical outcomes in SAH are scarce and unspecific. Molecules released early in the pathophysiology of SAH might be of greater significance. High mobility group box-1 (HMGB1), a prototypical damage-associated molecular pattern molecule (DAMP), is released early after SAH and is known to upregulate inflammation after its extracellular release from damaged, stressed, and necrotic cells. We have identified HMGB1 as a specific and potential biomarker for CVS. This mini-review explores the biomarker potential of HMGB1 in the context of post-SAH complications and clinical outcome.

Keywords: SAH, complications, Damage-associated molecular pattern molecules (DAMPs), HMGB1, clinical outcome, inflammation

Introduction

Aneurysmal subarachnoid hemorrhage (SAH) accounts for only 5% of all strokes, but is associated with very high morbidity and mortality 24. The fatality rate of the disease is nearly 50% within 24 hours; more than 15% die before arrival in the hospital emergency department. Due to ensuing life-threatening complications, nearly half of the survivors die within a month even after successful obliteration of the bleeding aneurysm by neurosurgical clipping or endovascular coiling. Post-SAH complications primarily include cerebral vasospasm (CVS), seizures, ventriculo-peritoneal (VP) shunt-dependent chronic hydrocephalus, delayed ischemic neurological deficits (DINDs), delayed cerebral ischemia (DCI), and systemic or local infections 11,13,21. Aneurysms are weak bulging or ballooning lesions or abnormal dilatations in the arterial walls and often occur at arterial bifurcations due to chronic shear stress resulting from chronic hypertension 8. In more than 85% of the cases, rupture of the intracranial aneurysm injects arterial blood into the subarachnoid space and sometimes also involves deeper brain parenchyma and ventricles 13. The extravasated blood impairs cerebral blood flow due to increased intracranial pressure and reduced perfusion pressure, thus leading to transient global cerebral ischemia 13. The toxic effects of blood and its derivatives also exacerbate the condition. All these events lead to early brain injury (EBI), which occurs within 72 hours of the ictus and includes several phenomena such as apoptosis, necrosis, microthrombosis, and inflammation 3,4,15. The failure of endothelin antagonists to improve clinical outcome despite relieving vasospasm led to a reassessment of the role of inflammation after SAH. Inflammation occurring in the CNS and at the systemic level has become an area of intensive research in SAH 14,15.

Tissue injury unmasks endogenous substances that are normally hidden or sequestered to prevent interaction with immune cells. However, once released, these substances signify danger by interacting with pattern recognition receptors (PRRs) on immune cells that subsequently mount an inflammatory response. Such substances or molecules have been referred to as damage-associated molecular patterns (DAMPs) 23. Several endogenous molecules have been assigned a DAMP role, such as high mobility group box-1 (HMGB1), ATP, uric acid crystals, S100 proteins, hemoglobin and its derivatives, extracellular matrix proteins, heat shock proteins, and interleukins (IL-1α and IL-33) 6. HMGB1, a prototypical protein DAMP, has been well characterized in a number of neuroinflammatory diseases 18. Recently, HMGB1 has been identified as a predictive biomarker to detect post-SAH complications. Here, we briefly review the biomarker potential of this inflammatory protein in SAH and post-SAH sequelae.

1.1. High mobility group box-1 and SAH

HMGB1 is ubiquitously expressed in the nucleus of all eukaryotic cells. It acts as a non-histone DNA-binding transcription factor and also plays critical roles in chromatin maintenance or stabilization 12. The HMGB1 molecule is comprised of two DNA binding domains (box A and box B) and an acidic tail 12. However, extracellular translocation of HMGB1 due to cellular injury enables it to bind several PRRs, such as Toll-like receptor (TLR)-2, 4, and 9 and receptor for advanced glycation end products (RAGE; also known as AGER) 6. In ruptured intracranial aneurysms, upregulation of HMGB1 expression has been observed along with other proinflammatory markers 26. HMGB1 is released passively from necrotic cells and damaged neurons, which begin to die within short time of SAH 22. However, HMGB1 is also actively secreted by monocytes/macrophages acting as a cytokine 12. Both actively and passively released HMGB1 has the potential to upregulate inflammation. The presence of HMGB1 in the CSF and peripheral circulation highlights the release of HMGB1 both in the CNS and systemically. Since inflammation is present during early and delayed brain injury, inflammation potentially contributes to the development of different complications and worsening of the clinical outcome. Therefore, HMGB1 occupies a central place in post-SAH inflammation.

1.2 HMGB1 CSF levels and post-SAH complications

HMGB1 levels are robustly upregulated after SAH in CSF 17. Interestingly, HMGB1 levels measured in CSF are associated with different pro-inflammatory cytokines (such as TNF-α, IL-6, and IL-8), thus highlighting the role of HMGB1 in CNS inflammation 17. CSF HMGB1 levels are associated with SAH clinical severity as assessed by different scores such as the Hunt and Hess grade (HH grade), the World Federation of Neurological Surgeons (WFNS) scores, and the Glasgow coma scale 10,20. HMGB1 levels in CSF are also associated with different post-SAH complications, such as acute hydrocephalus and DCI 2,20. A single-nucleotide polymorphism (SNP) in HMGB1 can lead to enhanced HMGB1 levels leading to DCI 9. Elevated CSF HMGB1 levels correlate with increased intensive care unit stay, disability and dependence, and poor clinical outcome assessed at different times after SAH 10,17,20,25. The compromised blood brain barrier may allow peripheral access to the HMGB1 released in CSF 16. Interestingly, CSF HMGB1 levels follow a declining trend with a rise in plasma HMGB1 levels 2. These lines of evidence suggest that HMGB1 is upregulated in CSF after SAH-initiated inflammation and could potentially contribute to the development of complications and poor clinical outcome.

1.3 Systemic HMGB1 levels and post SAH complications

Determination of HMGB1 in peripheral blood is less invasive and is thus more relevant for clinical translation. Elevated plasma HMGB1 levels have been observed after SAH compared to healthy controls. Interestingly, plasma HMGB1 levels are associated with the development of CVS, poor clinical outcome after 1 year, and mortality rate 27. Recently, Chaudhry, et al. 5 have shown increased serum HMGB1 levels in SAH patients compared to controls over a period of 2 weeks. The serum HMGB1 levels were not affected by clinical severity (H&H grades), treatment modality, patient's sex, location of the aneurysm, and concurrent intraventricular hemorrhage or intracerebral bleeding. Furthermore, during extensive analysis for different complications such as seizures, infections, chronic hydrocephalus, DCI (cerebral infarction), and clinical assessment (GOS and mRS) at discharge, no significant impact on serum HMGB1 levels was found. However, serum HMGB1 levels were significantly elevated in SAH patients who developed CVS compared to non-CVS patients over the entire period of assessment. CVS affects nearly 70% of SAH patients, with an onset from 3 days post-SAH until day 14 1,13. Receiver operating curve analysis for the prediction of CVS at day 1 after SAH showed a cutoff value of serum HMGB1 to be 5.6, with an area under the curve of 0.704 and an approximate 60% sensitivity and 82%

specificity 5. Interestingly, a correlation between serum IL-6 and HMGB1 was also shown, which suggests an upregulated systemic inflammatory response. Similarly, a correlation among peripheral leukocytes and serum HMGB1 indicates that blood leukocytes may be the possible source of HMGB1 5. These findings highlight an important biomarker and prognostic potential of peripherally measured HMGB1.

Discussion

The onset of SAH triggers a complex process of inflammation both at the local and peripheral level 7. Renewed interest in the role of inflammation mediating post-SAH brain damage has identified distinct phases over which brain injury occurs 7. Early brain injury is the term given to deteriorating and innocuous events occurring within 72 hours after SAH; delayed brain injury occurs later during 3 to 14 days after SAH 4,13. In a significant proportion of initial survivors, even successful treatment of the bleeding aneurysms does not prevent morbidity and death due to severe complications that develop after SAH 11,13,21. Therefore, it is critical to understand the pathophysiological events initiated by this sentinel bleed. Sterile inflammation at both the CNS and peripheral levels play an important role during the post-SAH complications 6. DAMPs are critical in initiating an inflammatory response; HMGB1 is well known not only for its role as a DAMP, but also as an inflammatory cytokine 18,19.

Several studies have shown elevated HMGB1 levels after SAH at the CNS and systemic levels 5,10,17,27. Accumulating evidence as discussed above shows HMGB1 to be associated with the development of different complications post-SAH and even the clinical outcome after one year. These findings highlight the potential of HMGB1 to be a candidate biomarker of post-SAH complications. Systemic HMGB1 levels can successfully predict the development of CVS, poor clinical outcome, and mortality 5,27. Therefore, further multicenter validation studies investigating the biomarker and prognostic potential of HMGB1 in post-SAH complications are warranted. Systemically measured prognostic and diagnostic markers in SAH are scarce. There is an urgent need for new systemically validated diagnostic and prognostic markers that may be helpful in identifying the patients at risk of developing complications (such as CVS) or poor clinical outcome and in facilitating aggressive treatment and management measures for these patients.

Conclusion

HMGB1 is a potentially novel biomarker to detect post-SAH complications and clinical outcome after SAH.

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Conflicts of interest

The authors declare no conflicts of interest.

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How Can We Reduce The Risks Of STA-MCA Bypasses?

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Abstract

Purpose:

Direct STA-MCA bypass, first described by Yasargil, is rarely performed. We aim to identify the risk factors associated with post-bypass stroke risk, to stratify patients' surgical morbidity.

Methods:

We studied a large STA-MCA bypass database (769 patients, 1250 bypasses, 1991-2014), and analysed the 30-days stroke risks using univariate/multivariate logistic regression analyses.

Scores assigned.

Suzuki stage as proposed.

DSA score (1.Steno-occlusion; 2.ICIC collateralization; 3.ECIC collateralization)

mMRI brain score (1.Ischemia/hemorrhage/atrophy; 2.DWI+ve infarct)

Haemodynamic reserve(HDR) score (1.Impaired augmentation with acetazolamide; 2.Steal phenomenon)

Results:

The 30-days ischaemic stroke risk is 7.8% (60/769) and 6.2% (29/467) after the first and second bypasses respectively. With 1250 bypasses, 92 strokes (ischaemic and haemorrhagic) were recorded, leading to a 7.3% per procedure stroke risk.

Younger age groups are associated with lower postop stroke risk (5.4% (11/205) in paediatric cohort; 12.9% (73/564) in adults). Furthermore, the older the age category, the higher the postop stroke risk, 9.3% in 19-39years, 16.5% in 40-59years, and 20% in >60years (p=0.001). Other statistically significant factors associated with higher postop stroke risks include ischemic presentation, diabetic, hyperlipidemic, higher Suzuki stage, DSA score, mMRI score, HDR score, types of bypass surgery.

To address the issue of confounding factors, logistic regression analysis was performed, and only older age, DSA score, mMRI score, HDR score, are clearly associated with higher postop stroke risks.

Conclusion:

With the standard direct STA-MCA bypass technique as shown, 4 factors are highly correlated with postbypass morbidity (age, DSA score, mMRI score, HDR score). We will develop a post bypass stroke risk predictive modelling for patient care to reduce surgical morbidity.

Keywords: STA-MCA bypass, stroke risks, regression analysis, predictive modelling

Introduction

Direct STA-MCA bypass was first described by Yasargil in 1970 (Yasargil et al., 1970) for atherosclerotic stroke, however with the advancement of medical and endovascular stroke therapy, direct bypass is rarely required (The EC/IC Bypass Study Group, 1985, Powers et al., 2011, Berkhemer et al., 2015, Campbell et al., 2015, Goyal et al., 2015, Goyal et al., 2016). In modern neurosurgical practice, direct STA-MCA bypass is rarely performed as the indications are very limited. There are 2 broad categories where direct bypasses are employed to prevent ischemia. One setting is to replace native cerebral blood flow, such as when an intracranial vessel sacrifice is necessary as in the setting of complex or giant ICA or proximal MCA aneurysms. The second is to supplement cerebral blood flow in the setting of ongoing poor cerebral perfusion secondary to intracranial vasculopathy like moyamoya diseae (MMD). At Stanford University Medical Centre, due to the large volume of MMD referrals, direct STA-MCA bypass is performed regularly.

1.1. Direct STA-MCA bypass – operative nuances

During surgery under general anesthesia and mild hypothermia to about 33°C, the patient is positioned supine with the head turned lateral and fixed in a Mayfield clamp (so the operative field is parallel to the floor). The most suitable STA branch (frontal vs. parietal branch) is chosen as the donor based on the preoperative angiogram. In most cases the parietal branch is selected as it is behind the hairline, has a straighter course, and there is less risk of damage to the frontalis nerve branches during dissection (Figure 1). Using a handheld Doppler probe, 9 cm of the donor STA branch is transduced above the zygoma and harvested along its course under microscopic magnification. The frontal branch of STA is generally preserved for a potential subsequent revascularization procedure; small distal branches are coagulated and divided to mobilize the STA trunk. Papaverine is intermittently applied to the dissected STA to alleviate spasm, and a Doppler probe used to ensure the patency during STA dissection.

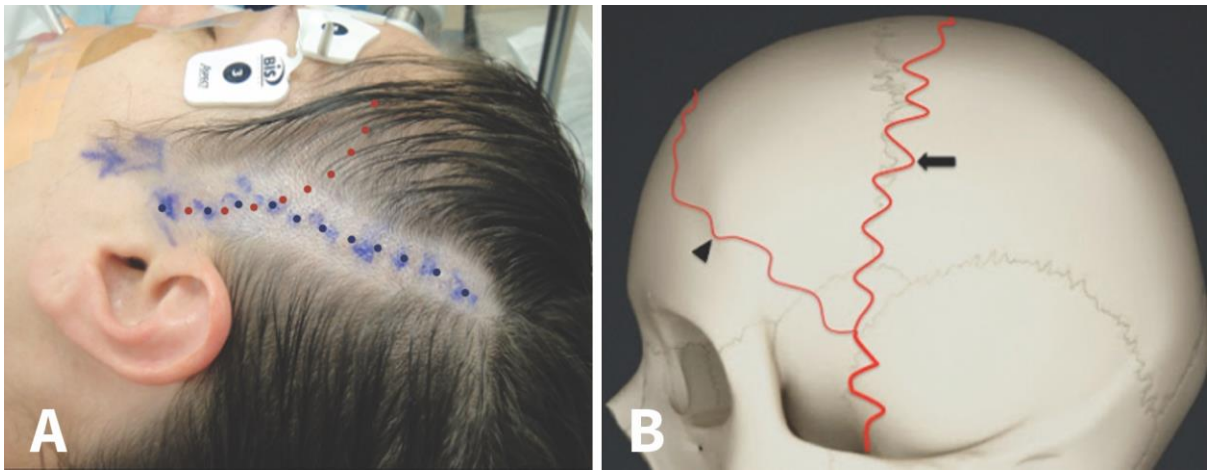

Figure 1. *(A) Patient positioned supine with the operative field parallel to the floor. The STA branches are marked (parietal branch in blue, frontal branch in red). (B) The configuration of the frontal (arrowhead) and parietal (arrow) STA branch on the skull model. Adopted from Teo MK, Johnson JN, Steinberg GK. "Direct Superficial Temporal Artery to Middle Cerebral Artery Bypass" In: Operative Cranial Neurosurgical Anatomy, F Gagliardi, P Mortini, C Gragnaniello, A Caputy Eds. Thieme 2017. (Teo et al., 2017)*

After harvesting the STA vessel off the temporalis fascia, the temporalis muscle is cut and retracted and a craniotomy approximately 6 cm in diameter is performed. Under maximal magnification, 1-2 cm of the distal STA is dissected free of the surrounding tissue and skeletonized using fine micro scissors. Similarly, a short length of the proximal STA is dissected from its surrounding soft tissue cuff to create a site for placement of a proximal temporary clip. The ideal site for temporary clipping is distal to the take-off of the unused frontal branch of the STA; this allows continued flow through the STA into the unoccluded branch, reducing stagnant flow and the risk of thrombosis proximal to the temporary clip.

The dura is then opened in a stellate fashion, and the microscope is used to find a suitable recipient cortical MCA branch. The most important considerations are size of the donor and recipient vessels (0.9 mm or greater is optimal), location of the recipient M4 branch of the MCA (away from the craniotomy edges is preferred) and orientation of the vessels (to avoid an acute angulation between the donor and recipient vessels, and facilitate suturing both walls of the recipient artery).

The arachnoid over the potential recipient vessel is opened; the MCA M4 branch is prepared for anastomosis by placing a high visibility background material underneath the vessel. Larger perforators can be spared by including their origin from the MCA segment in the temporary vessel clips. Before temporary clipping, blood flow is measured in the MCA branch and the cut STA using a Transonics, Charbel ultrasonic flow probe. After the temporary clip is applied to the proximal STA, the STA is cut at a 45° angle to create a fish mouth. The cut STA segment is then flushed with heparinized saline.

MAP is gently raised to over 90 mmHg. Burst suppression is achieved using propofol. Specially designed Anspach-Lazic temporary mini-clips are placed proximally and distally on the recipient vessel. An arteriotomy is then made over the recipient MCA using microscissors, and the lumen flushed with heparinized saline. Indigo-carmine dye (or a sterile marking pen) is used to stain the walls of the donor and recipient vessel and allow the lumen to be seen more easily and facilitate the microanastomosis. 10-0 sutures are first placed to anchor the apices of the arteriotomy (toe stitch, followed by heel stitch). Sutures should be passed from outside the donor artery to inside the recipient artery, and then tied on the outer surface of the anastomosis. Once the donor STA has been anchored, interrupted sutures are place on each side of the anastomosis at close intervals, making sure not to catch the back wall of the vessel. Once the anastomosis is complete, the temporary clips on the recipient artery are released, followed by opening of the clip on the proximal STA (Figure 2). Occasionally additional sutures are needed to seal the anastomosis. Blood flow in the STA, proximal MCA and distal MCA to the anastomosis is then measured with the Transonics Charbel flowmeter, and intraoperative indocyanine green (ICG) as well as intraoperative Doppler are performed to confirm patency and quantitative function of the bypass graft (Figure 2). During closure, the dura is loosely replaced, the inferior burr hole enlarged to accommodate the entering STA graft, the bone is replaced avoiding any kinking or pressure on the vessel, the temporalis muscle is approximated, and the skin is closed with care. The patency of the STA trunk is verified with a Doppler probe at the end of the procedure.

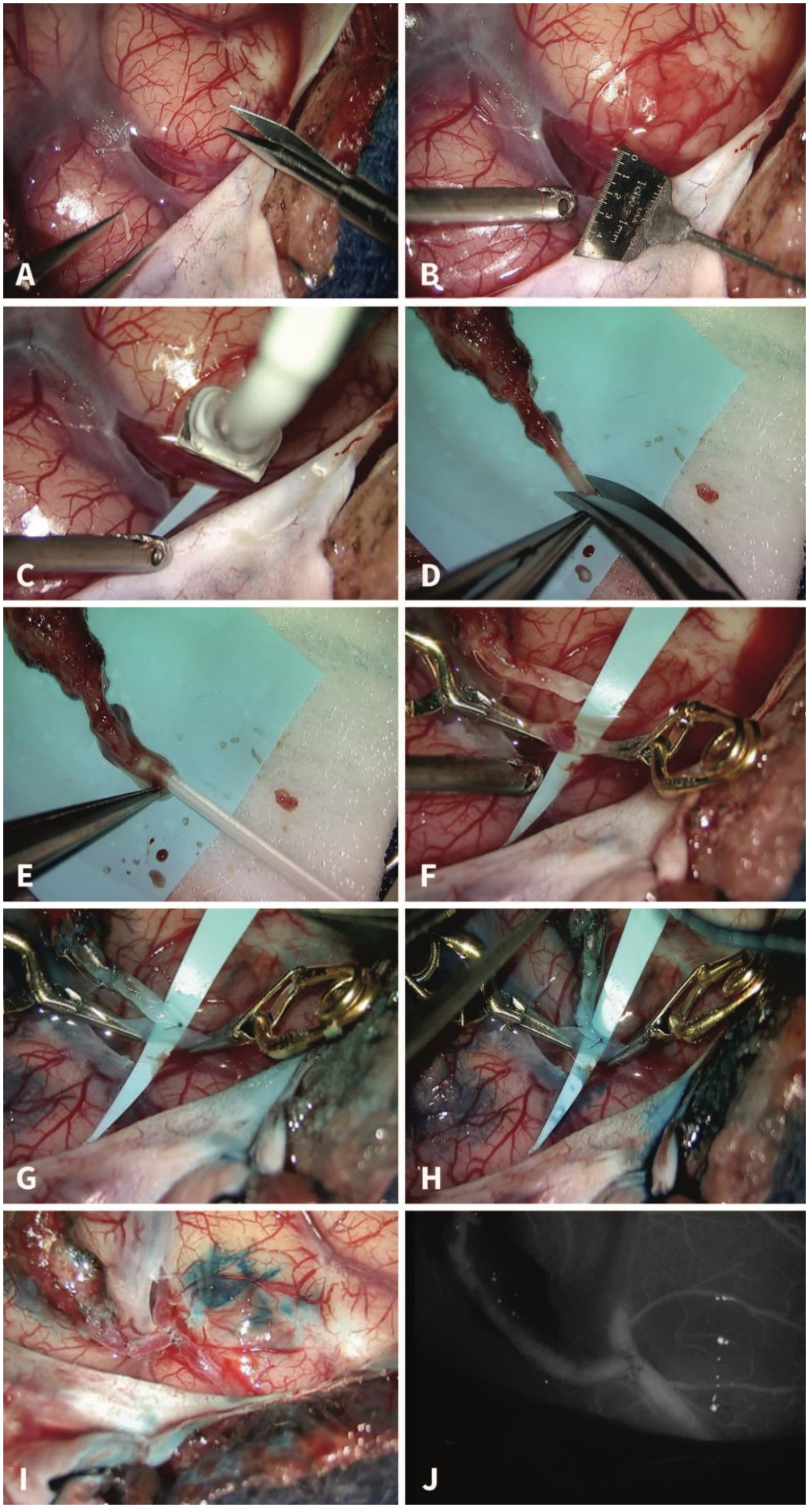
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***Figure 2**. Intradural stage of direct STA-MCA bypass.*

(A) Opening of the arachnoid over the potential recipient MCA vessel, exposing 7mm of M4 branch.

(B) Measurement of the diameter for the recipient vessel.

(C) High visibility background material is passed beneath the recipient vessel, and blood flow is measured using a Charbel Transonics ultrasonic flow probe.

(D) The distal STA is divided at a 45-degree angle,

(E) The cut STA segment flushed with heparinized saline

(F) After temporary clips are applied to MCA vessel, an arteriotomy is made and the lumen is flushed with heparinized saline.

(G) The donor and recipient vessels are tinted with indigo-carmine or a marking pen to better visualize the microanastomosis. Monofilament sutures (10-0) are used to anchor the apices of the incision, toe stitch first, (H) followed by the heel stitch.

(I) The side walls of the anastomosis are sutured in an interrupted fashion, also using 10-0 monofilament sutures. Once the anastomosis is complete, the temporary clips on the recipient artery are released, and then the proximal clip on the STA is removed.

(J) Blood flow in the STA, and proximal and distal MCA to the anastomosis is measured with a flow probe, and intraoperative ICG angiogram is performed to confirm patency and function of the bypass graft.

Adopted from *Teo MK, Johnson JN, Steinberg GK. "Direct Superficial Temporal Artery to Middle Cerebral Artery Bypass" In: Operative Cranial Neurosurgical Anatomy, F Gagliardi, P Mortini, C Gragnaniello, A Caputy Eds. Thieme 2017.*

1.2. Objective

The postop stroke risks are considered high, therefore direct STA-MCA bypass is rarely performed in modern day neurosurgical practice. We aim to identify the risk factors associated with post-bypass stroke risk, to stratify patients' surgical morbidity.

Methods

We studied a large STA-MCA bypass database consisting of 769 MMD patients with 1250 bypasses (1991-2014), and analysed the 30-days stroke risks. Univariate and multivariate logistic regression analyses were performed to determine the risk factors for postoperative morbidity.

Suzuki stage was assigned as proposed (Suzuki and Takaku, 1969).

A simplified cerebral angiogram (DSA) score was applied (Czabanka et al 2016):

Stenosis/occlusion = 1 point
Stenosis/occlusion + intracranial-intracranial (ICIC) collateralisation = 2 points;
Stenosis/occlusion + ICIC + extra-intracranial (ECIC) collateralisation = 3 points.

mMRI brain score was assigned:

No sign of ischemia/hemorrhage/atrophy = 0 point;
Signs of ischemia/hemorrhage/atrophy = 1 point;
DWI +ve infarct within 1 month of surgery = 2 points.

Haemodynamic reserve (HDR) studies to assess cerebrovascular reserve (CVRC) include MRI perfusion, SPECT, Xe-CT with acetazolamide challenge, due to technological and practice changes (Figure 3). HDR score:

Good augmentation = 0 point,
Impaired augmentation with acetazolamide = 1 point,
Steal phenomenon = 2 points.

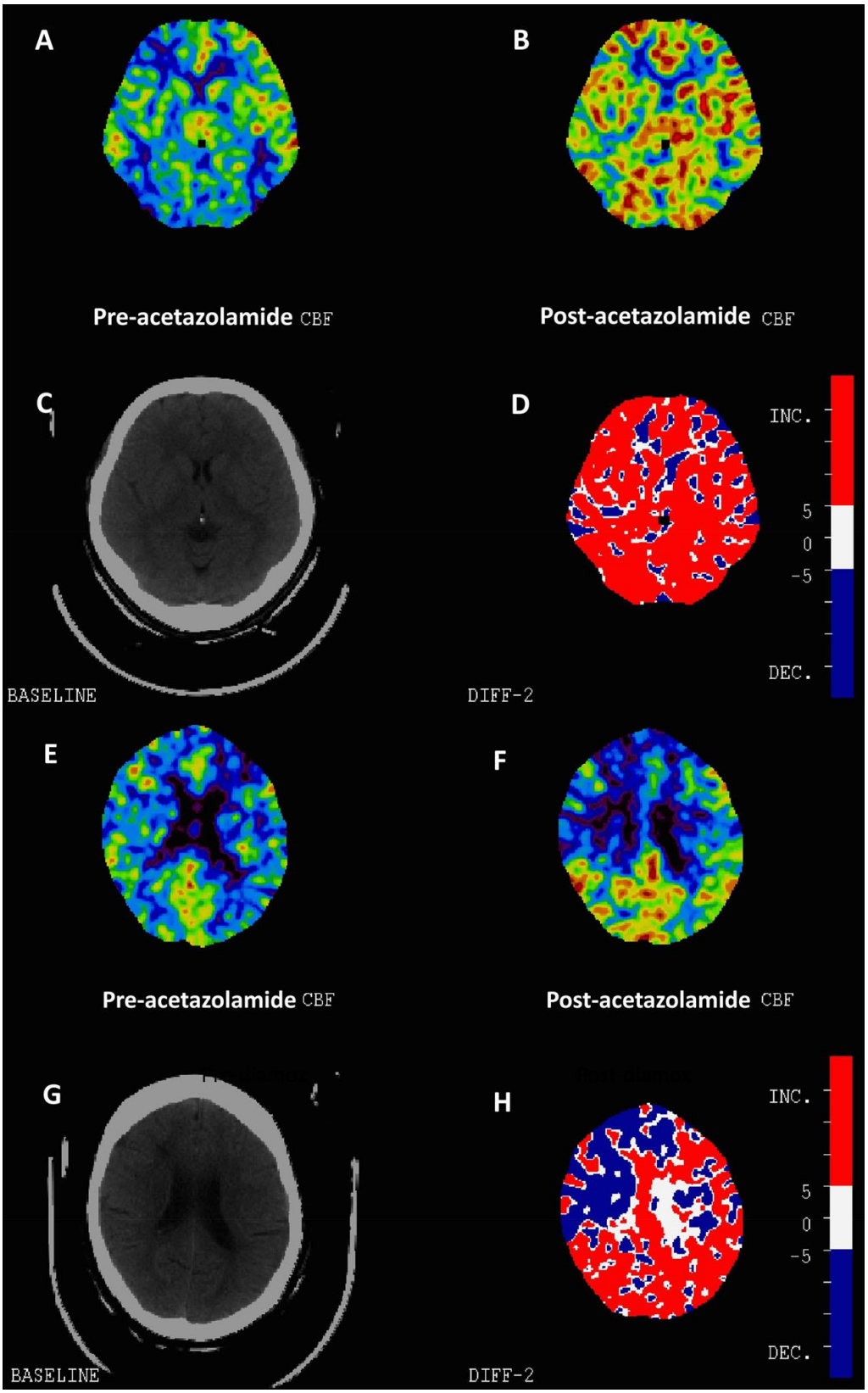

Figure 3. *Xenon CT*

(A) Pre-acetazolamide cerebral blood flow (CBF) measurement
(B) Post-acetazolamide CBF on the corresponding axial slice after administration of 15mg/kg body weight of acetazolamide to calculate stimulated CBF.
(C) Baseline acquisitions of CT brain slices to ensure no underlying infarction.
(D) A specialized, dedicated software (XeCT System; DDP Inc) is used to determine the percentage difference of CBF pre- and post- acetazolamide challenge. Red color corresponds with over 5% CBF increase, white color corresponds with no CBF changes (+/- 5%), blue corresponds with over 5% CBF decrease (steal phenomenon). Overall red in the axial slice, HDR score = 0 point.

A 65 year-old MMD patient with worsening cognitive impairment.
(E) Pre-acetazolamide cerebral blood flow (CBF) measurement using stable xenon-CT technology,
(F) Post-acetazolamide CBF on the corresponding axial slice, where increased CBF was mainly noted in the posterior circulation.
(G) Baseline acquisitions of CT brain slices to ensure no underlying infarction.
(H) A specialized, dedicated software (XeCT System; DDP Inc) is used to determine the percentage difference of CBF pre- and post- acetazolamide challenge, where steal phenomenon was noted in bilateral MCA territories, worse on the right.

HDR score = 2 points.

Results

769 patients with 1250 bypasses (1991-2014) were identified from the moyamoya database. Follow up of at least 6 months was available on 95% (730/769) of patients, with a mean follow up of 7 years (0.5 – 25 years).

548 females, 357 males, age range 0-69 years underwent 1250 bypasses (1118 direct, 132 indirect revascularisations) for MMD. The bimodal peak age distribution of 6-10 years in paediatric cohort, and 31-40 years in adult cohort is shown in "Figure 4". The gender and ethnicity distribution for the whole MMD cohort is shown in "Figure 5".

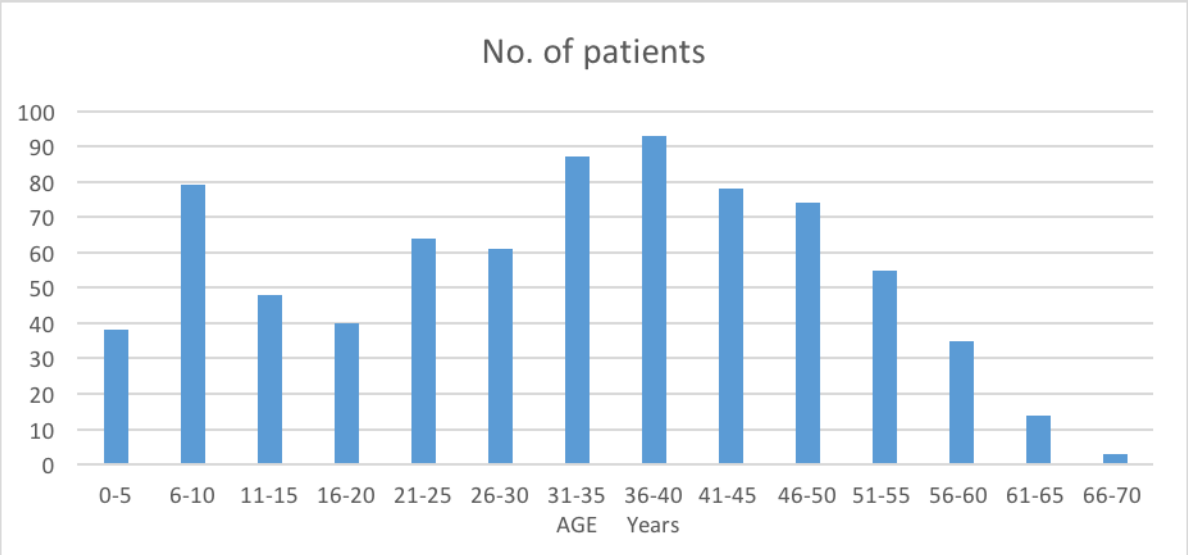

Figure 4. *Age distribution of MMD patients at first bypass surgery. Note the bimodal peak age distribution of 6-10 years in paediatric cohort, and 31-40 years in adult cohort.*

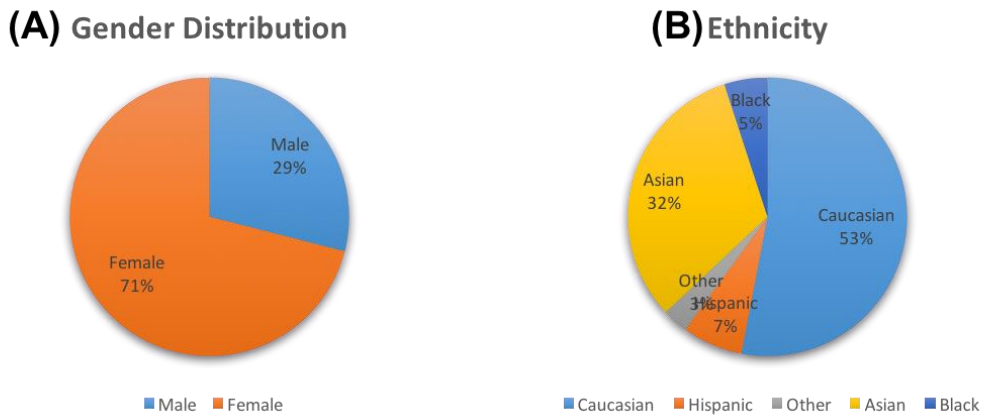

Figure 5. *(A) Gender distribution for MMD patients, with female predominance. (B) Ethinicity distribution with Caucasian predominance in western MMD.*

Over the last 25 years, the number of MMD bypass cases per year from Stanford University Medical Center is shown in "Figure 6", with approximately 100 procedures per year in the 10 years between 2006-2015.

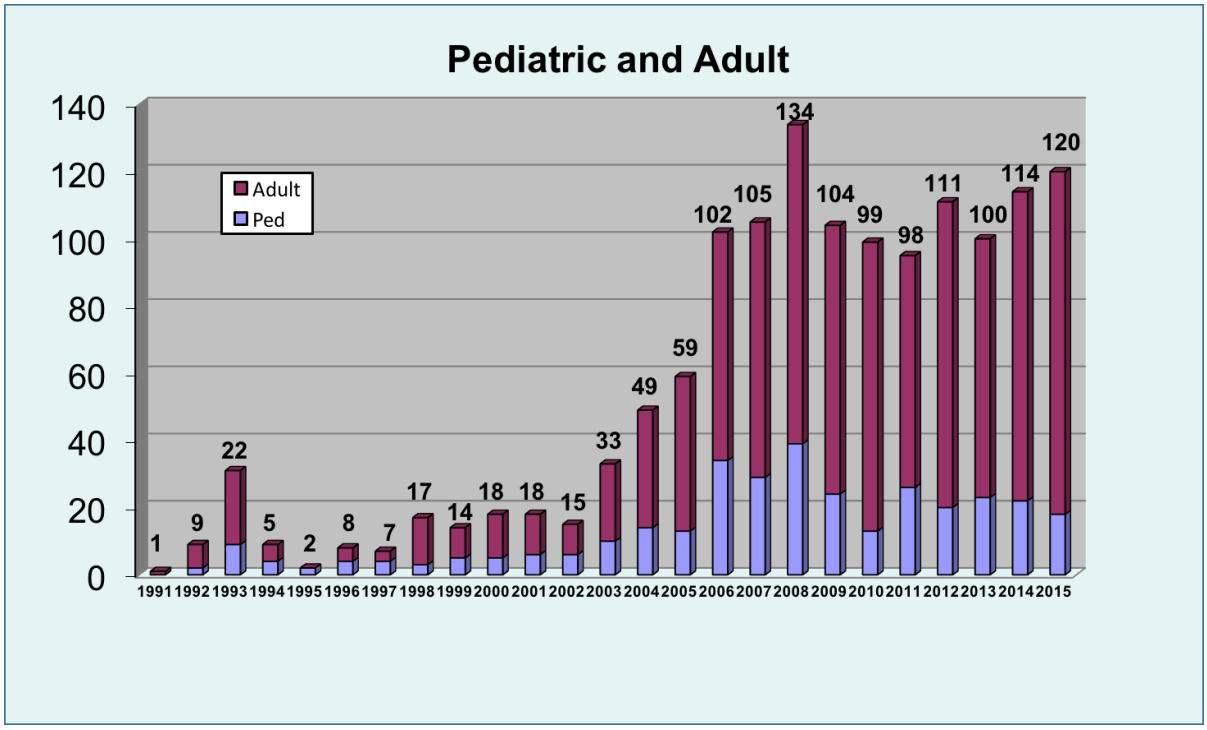

Figure 6. *The number of MMD bypass cases per year from Stanford University Medical Center from 1991-2015.*

80 patients (10.4%) developed ischaemic strokes within 30-days postop. Including intraparenchymal haemorrhage (IPH) and ischemic stroke risks, the combined postop stroke risk is 84/769 (10.9%). 10 patients

had postop extraaxial haematoma (subdural or extradural haematoma) requiring evacuation surgery. 5 patients (0.6%) died of stroke within 30 days postop.

The 30-days ischaemic stroke risk is 7.8% (60/769) and 6.2% (29/467) after the first and second bypasses respectively. With a total of 1250 bypasses, 92 strokes (ischaemic and haemorrhagic) were recorded, leading to a 7.3% per procedure stroke risk.

In "Table 1", younger age groups are associated with lower postop stroke risk, 5.4% (11/205) in paediatric cohort, compared with 12.9% (73/564) in adults. Furthermore, the older the age category, the higher the postop stroke risk, p=0.001. Other statistically significant factors associated with higher postop stroke risks include ischemic presentation, diabetic, hyperlipidemic, higher Suzuki stage, DSA score, modified MRI score, haemodynamic reserve (HDR) score, types of bypass surgery.

Table 1. Univariate analysis of risk factors associated with 30 days postoperative ischaemic and haemorrhagic stroke.

		30Day Postop Ischaemic / Heamorrhagic CVA				
		No		Yes		p-value
		No. of Patients	Row %	No. of Patients	Row %	
Age Category	**<18 yr**	194	94.6%	11	5.4%	0.001*
	19-39 yr	262	90.7%	27	9.3%	
	40- 59 yr	213	83.5%	42	16.5%	
	>60 yr	16	80.0%	4	20.0%	
Gender	**Female**	483	88.1%	65	11.9%	0.189
	Male	202	91.4%	19	8.6%	
Ethnicity	**Caucasian**	373	90.5%	39	9.5%	0.257
	Asian	220	88.4%	29	11.6%	
	Others	92	85.2%	16	14.8%	
Family Hx of MMD	**No**	104	90.4%	11	9.6%	0.324
	Yes	26	96.3%	1	3.7%	
Presentations						
Haemorrhagic	**No**	589	88.2%	79	11.8%	0.039*
	Yes	96	95.0%	5	5.0%	
Ischaemic	**No**	132	96.4%	5	3.6%	0.003*
	Yes	553	87.5%	79	12.5%	
Headache	**No**	360	86.7%	55	13.3%	0.025*
	Yes	325	91.8%	29	8.2%	
Seizure	**No**	604	89.0%	75	11.0%	0.765
	Yes	81	90.0%	9	10.0%	

PMHx						
Diabetes	**No**	469	90.5%	49	9.5%	<0.0001*
	Yes	61	75.3%	20	24.7%	
	Unknown	155	91.9%	15	9.1%	
Hyperlipidemia	**No**	415	90.8%	42	9.2%	0.004*
	Yes	108	81.8%	24	18.2%	
	Unknown	162	90.0%	18	10.0%	
Radiological Findings						
Suzuki stage	**2**	28	100.0%	0	0.0%	<0.0001*
	3	276	93.9%	18	6.1%	
	4	327	86.3%	52	13.7%	
	5	34	70.8%	14	29.2%	
	6	1	100.0%	0	0.0%	
DSA score	**1**	16	100.0%	0	0.0%	<0.0001*
	2	526	92.3%	44	7.7%	
	3	123	75.5%	40	24.5%	
mMRI score	**0**	148	96.7%	5	3.3%	<0.0001*
	1	506	90.4%	54	9.6%	
	2	12	33.3%	24	66.7%	
HDR score	**0**	166	98.8%	2	1.2%	<0.0001*
	1	328	89.9%	37	10.1%	
	2	69	67.6%	33	32.4%	
Types of Surgery First Bypass	**Direct**	644	91.2%	62	8.8%	0.046*
	Indirect	62	98.4%	1	1.6%	

To address the issue of confounding factors, logistic regression analysis "Table 2" was performed, and only older age, DSA score, mMRI score, HDR score, are clearly associated with higher postop stroke risks. Haemorrhagic presentation is still showing a trend towards lower stroke risk (OR 0.279, 95% CI 0.069-1.124, p=0.072).

Table 2. Logistic Regression Analysis for risk factors associated with 30-days postoperative stroke risk.

Variable	Coefficient	Standard Error	P-value	Odds Ratio	95% Confidence Interval
Age	1.295	0.579	0.025*	3.650	1.173-11.359
Haemorrhagic presentation	-1.277	0.711	0.072	0.279	0.069-1.124
Ischaemic presentation	2.172	1.072	0.043	8.774	1.074-71.711
Diabetes	0.527	0.479	0.271	1.693	0.663-4.327
Hyperlipidaemia	0.025	0.435	0.955	1.025	0.437-2.403
Suzuki Stage	0.335	0.685	0.625	1.398	0.365-5.349
DSA score	1.294	0.415	0.002*	3.648	1.618-8.222
mMRI score	2.740	0.765	<0.0001*	15.494	3.462-69.335
HDR score	2.866	0.805	<0.0001*	17.559	3.626-85.037
Surgery Types	-1.227	1.119	0.273	0.293	0.033-2.631

Conclusion

With the standard direct STA-MCA bypass technique as shown, 4 factors are highly correlated with postbypass morbidity (age, DSA score, mMRI score, HDR score). With the uni- and multivariate logistic regression analyses, multiple risk factors were associated with higher postoperative stroke risks, including older age group, higher DSA score, mMRI score, HDR score. We showed very convincingly that younger patients have lower postop stroke risks (5% in paediatric compared to 20% of over 60 years-old). Furthermore, patients with recent DWI +ve infarct within a month of surgery has the highest postop stroke risk (67% in our study), therefore we recommend delaying surgery for these patients to avoid such risks. Based on the 30-days logistic regression analysis, we plan to continue the work on predictive modelling on postop stroke risk using the various risk factors identified, and assigned the appropriate scores. This new scoring system would then be validated prospectively in another cohort of MMD post bypass patients. This information will help to stratify patients' surgical morbidity, is invaluable in the consent, decision making process, and with the right patient selection, we can reduce the post bypass stroke risks.

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Intraventricular Transplantation Of Stem Cells In Chronic Hemorrhagic Stroke

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Abstract

Stroke is a very dangerous disease, the main cause of death and disability throughout the world and also associated with emotional and economic problems. This study aims to determine the clinical outcome of the intraventricular transplantation of bone marrow mesenchymal stem cells (BM-MSCs) in post-hemorrhagic stroke patients.

This study was done consisting of eight patients with supratentorial hemorrhagic stroke, who had undergone 24 weeks of standard treatment of stroke with stable neurological deficits. All of the patients were managed with intraventricular transplantation of BM-MSCs obtained from their own bone marrow. Then, the cells were transplanted intraventricularly (20 x 10^6 cells / 2.5 ml) using the Ommaya reservoir and then repeated transplants were carried out after 1 and 2 consecutive months. The safety and efficacy of this procedure were evaluated at 6 and 12 months after treatment. The National Institute of Health Stroke Scale (NIHSS) is used to evaluate the neurological status of patients before and after treatment. It was found that the improvement of NIHSS score values before and after the treatment in five patients. No adverse effects or complications were detected during the 1-year observation.

Through this study, we demonstrated that intraventricular transplantation of BM-MSCs is safe to do and can improve the neurological status of post-hemorrhagic stroke patients with no adverse effect. Repeated transplant procedures are easier and safer to do through the Ommaya reservoir which is planted subcutaneously.

Keywords: Hemorrhagic stroke, bone marrow mesenchymal stem cells (BM-MSCs), intraventricular transplantation.

Introduction

Stroke is a very dangerous disease, the main cause of death and disability in the world [1]. In 2015, there were 15 million deaths caused by strokes, second only to ischemic heart disease. Even so, in the last 15 years, stroke is still the main cause of world death [2]. 10-20% of stroke cases with worse outcomes by spontaneous intracerebral hemorrhage (ICH). When compared with ischemic stroke, spontaneous ICH is far more at risk for patients [3,4,5]. Based on the causes of spontaneous ICH can be divided into two types, primary and secondary types [4]. Secondary spontaneous ICH is less common. This type is often caused by vascular abnormalities, tumors, drug side effects, and blood clotting disorders and coagulation [3]. Primary spontaneous ICH is more common than secondary spontaneous ICH. 70 - 80% of cases are primary spontaneous ICH caused by hypertension or amyloid angiopathy [4].

In the case of ICH, the risk of nerve damage is greater. ICH can cause blood clots in the area around the brain, oxidative stress, inflammatory reactions, thrombin, excitatory neurotransmitters, and hemoglobin lysis [3,6,7]. These risks can expand cell death so that damage to brain tissue after ICH will feel more severe and can be permanent [6,8]. To prevent severe and permanent damage, several neuroprotective agents have been developed. Neuroprotective works to suppress the excitotoxicity of glutamate, induces antioxidant effects, prevents apoptosis, inhibits the inflammatory process and suppresses matrix metalloproteinase (MMP) activity [3,9].

Several therapies have been developed to deal with damage after ICH, namely hyperbaric therapy, hypothermia, hormonal therapy, neuroprotective drugs, and operative approaches with sophisticated and safe techniques. But even so, there is no one type of therapy that works optimally. Disabilities and deaths from stroke remain the highest [6,10].

As the type of therapy develops after ICH, neurorestorative therapy, including stem cell transplantation, has been a focused effort in the last 10 years [11]. Stem cell transplantation can stimulate the healing process by activating endogenous neurogenesis, synaptogenesis and angiogenesis [3,12]. By replacing damaged cells and restoring damaged nerve circuits, stem cell transplantation is expected to cure stroke patients [1,3]. Based on the report submitted by Chop, et al., Stem cell therapy can avoid the formation of scar tissue

after stroke, preventing the occurrence of gliosis. Even if this therapy is given earlier, it can prevent apoptosis and suppress inflammation [13]. This study aims to determine the safety and feasibility of the intraventricular transplantation method of bone marrow mesenchymal stem cells (BM-MSCs) in post-hemorrhagic stroke patients.

1.1. Case Presentations

This study received legal/ethical clearance from the local medical research ethics committees of Dr. Soetomo General Hospital, Surabaya, Indonesia, following the regulatory guidelines of the country. Moreover, a research permit was obtained from the Research and Development Division of East Java, Indonesia Provincial Government. Informed consent documents, details of the medical treatment and other necessary approval documents were delivered to all patients involved in the study prior to the start of the study.

This study recruited patients aged 45 to 65 years who were diagnosed with hemorrhagic stroke in the last 12 months, a stable neurological condition in the last 6 months and a diagnosis of early supratentorial hemorrhagic stroke. The researchers did not choose patients who had a history of seizures during the stroke, severe co-morbidity, bleeding disorders, and whose neurological conditions improved in the last 12 weeks. Patients who withdrew from standard therapy after a stroke and who were reluctant to participate in this study were also excluded.

Patient Characteristics

The youngest patient in this study was 45 years old and the oldest was 63 years old. The average age of patients was 53.44 ± 6.02 years. There were eight patients involved, six of them were male (75%) and two were female (25%). All patients involved in this study carried out standard therapy for patients with hemorrhagic stroke including medical care and physical rehabilitation. Two patients included surgery (craniotomy and clot removal). Based on a history of supratentorial bleeding, five patients (62.5%) had bleeding in the basal ganglia, one patient (12.5%) had it in the right parietal and one patient (12.5%) had it as the right parieto-occipital bleeding. The characteristics and clinical outcomes of patients are further detailed in Table 1.

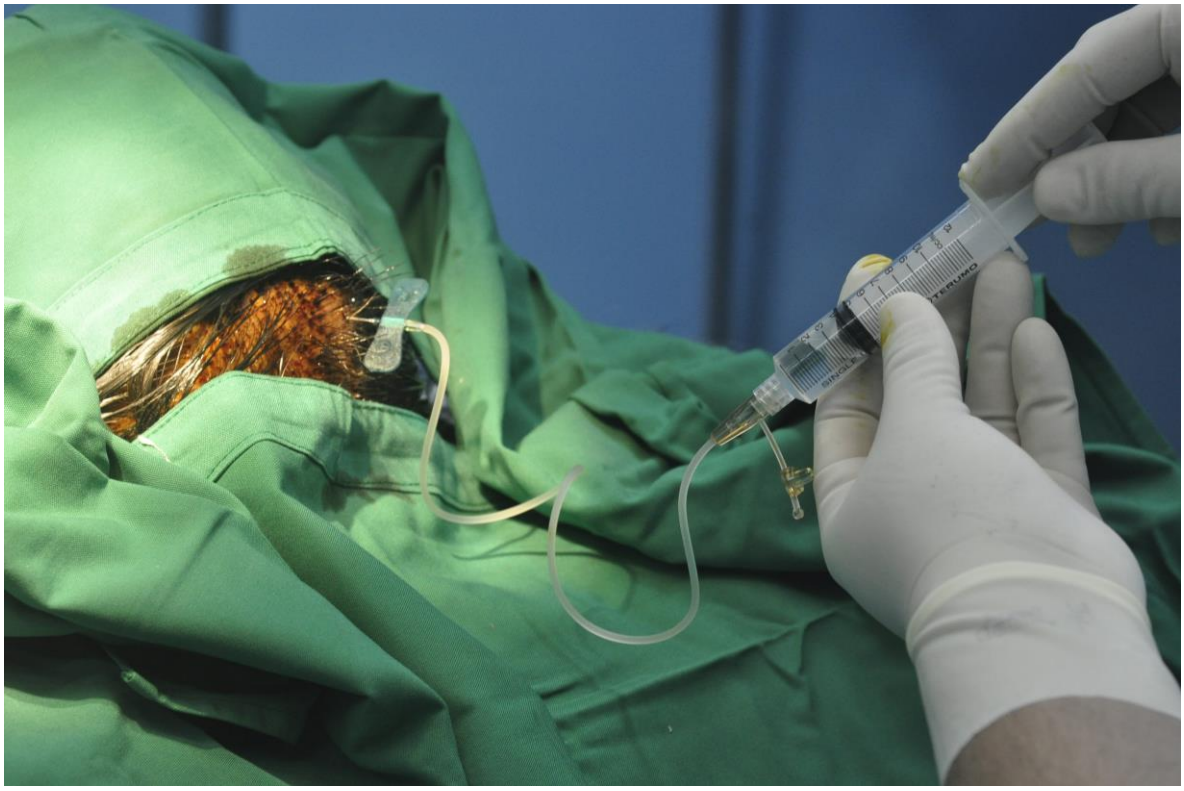

Figure 1 Booster transplantation is done by injection of BM-MSC through subcutaneous transplanted Ommaya reservoir.

Table 1 Data progress of post-hemorrhagic stroke and post-treatment patients.

No.	Age/Sex	Location	NIHSS			Clinical Improvement
			Baseline	6-Months After Stroke	12-Months Evaluation	
1.	45/ F	Left Basal Ganglia	8	8	6	• Severe aphasia → Mild-to-moderate aphasia • Severe dysarthria → Mild-to-moderate dysarthria
2.	63/ M	Right Parietal	2	2	2	-
3.	50/ M	Left Basal Ganglia	5	5	5	-
4.	61/ M	Left Basal Ganglia	4	4	3	LOC Questions; Answer one question correctly → Answer both question correctly
5.	56/ M	Left Frontoparietal FP	23	22	19	• Left & Right Arm, some effort against gravity → Drift • Left & Right Leg, some effort against gravity → Drift
6.	52/ M	Right Basal Ganglia	17	17	15	• Level of consciousness; not alert level 2 → Not alert level 1 • LOC Commands; Performs neither task correctly → Performs one task correctly
7.	59/ F	Right Parieto-occipital	5	5	5	-
8.	48/ M	Left Basal Ganglia	5	5	4	Limb Ataxia; present in one limb → Absent

From the eight patients observed during the 12 months of development, five patients showed neurological improvement, while the other three patients had no significant changes. One patient showed motor repair and two patients showed improvement at the conception level. Two other patients showed improvement from ataxia and increased aphasia and dysarthria. During the observation, we also observed possible signs or side effects such as the incidence of increased intracranial pressure, infection, seizures and other signs of rejection. As a result, no patient experienced these effects.

1.2. Discussion

Patient Characteristics

Based on previous research, men have a higher risk of stroke compared to women [14]. This is consistent with the number of patients involved in this study, 75% male and 25% female patients. It is estimated that the ratio of occurrence of stroke between men and women is 1.3 : 1 [15]. In this study, there were three patients (37.5%) aged 51 - 60 years, three patients (37.5%) aged 45-50 years, while two patients (25%) were aged over 60 years. In terms of age, many reports have revealed that stroke now occurs more often at a younger age [8]. In 1994, 12.9% of stroke occurred in patients aged 20-55 years with an average age of 71 years. In 2005, 18.6% of stroke occurred in patients aged 20-55 years with an average age of 69 years [16]. Of the eight patients, the results showed five patients had improved after evaluation for 48 weeks. Patients 1, 4, and 6 showed cognitive improvement, patient 5 showed motor improvement, and patient 8 showed postural stability. Overall, treatment showed a strong safety profile with little-reported improvement after 48 weeks of evaluation. About 10-15% of all stroke cases are Intracerebral hemorrhagic strokes. The condition caused by Intracerebral hemorrhagic stroke has a higher rate of permanent disability compared to ischemic stroke or subarachnoid hemorrhagic stroke [4]. ICH tends to occur in the basal ganglia (40-50%), lobar regions (20-50%), thalamus (10-15%), pons (5-12%) and cerebellum (5 - 10%) [17]. Previous research revealed that basal ganglia bleeding is a more common pathology. Basal ganglia bleeding is usually associated with hypertension, whereas lobar ICH is often found in older patients with pathological cerebral amyloid (CAA) angiopathy [18].

Autologous BM-MSCs

Neural stem cells and BM-MSCs, including several other cell types, have been widely studied through studies involving animals with strokes [5]. BM-MSCs is reported to have an optimal therapeutic potential for stroke patients. To avoid ethical problems, bodily rejection reactions and other complications, BM-MSCs can be taken from the patient's own body [5,9,19,20]. The results of the study reported by Kondziolka, et al. Of 14 ischemic stroke patients with intraparenchymal transplantation of human allograft cells in the basal ganglia showed patients had no complications at all after the procedure. In the procedure, all patients were given immunosuppressant drugs and anti-seizure drugs [15]. Another study reported by Savitz et al. Showed that of five patients involved, one patient had a seizure, and three patients experienced a decrease in neurological conditions. The five patients have received an intraparenchymal transplantation of fetal pig nerve cells, an allograft from animals. This study was stopped because of ethical problems and complications [21].

Current research uses autologous BM-MSCs (BM-MSCs was taken from patients themselves). Ethically, it is possible to carry out procedures. In addition, it can prevent further complications due to stem cells originating from the patient's body. Thus, it is expected that the body's rejection reaction will be minimal and do not need to use immunosuppressant drugs. BM-MSCs is given via the intraventricular route to avoid epileptogenic effects and permanent pressure on brain tissue. Research on the use of adult mesenchymal stem cells (MSCs) with various models of disease in animals has been carried out experimentally [9]. MSCS taken from the bone marrow is used in the process of tissue repair. MSCS can stimulate the proliferation, migration and differentiation of endogenous progenitor cells in all body tissues. In addition, MSCS can suppress the inflammatory process, immune reactions and prevent apoptosis [5,9].

At present in stem cell therapy there is no standard dose that is referred to [5]. In previous studies, the doses used for stem cell transplantation were also quite varied [1,15,22]. Wang et al. in their study comparing stem cell doses. The study showed that for therapeutic stem cell transplantation optimal dosage needs to be determined, but that does not mean that larger doses always show better results [5]. For example, in intraparenchymal transplantation too high doses can affect the nutrition of grafted cells, and if given intravascularly, cause micro-emboli and occlusion vessels [5]. In this study, we used higher doses than previous studies, as much as 20 x 10^6 BM-MSCs was applied directly to the intracranial space via the intraventricular route. The advantage of using this route is that it can adjust the dosage according to the needs of the transplantation by reducing ventricular fluid. This method can also reduce the risk of intracranial pressure and the effects of body mass. To avoid very concentrated doses and excess fluid volumes, a dose of 20 x 10^6 BM-MSCs is given in 3 ml of liquid. The results observed have no complications such as signs of increased intracranial pressure, infection or seizures. The combined stimulus of intrinsic and extrinsic signals affects neurogenesis in the subventricular zone (SVZ) [23,24]. The SVZ may be a local source of extrinsic signals [23]. Through BM-MSCs fluids, extrinsic signals can stimulate ventricular ependymal cells. This can increase cell proliferation in the SVZ. The stimulus or dose is given also affects the number of neural stem cells involved and the quality of proliferation [24]. The quality of neurogenesis will be more optimal if given a more optimal dose. The next recovery process depends on the dosage.

Intraventricular Transplantation

Inside the thin walls of the ventricular system, there are ependymal cells [23,26]. These cells have permeable properties. For cell stroke patients this is very useful as a treatment including stem cell therapy in the brain parenchyma [26]. New neurons will be consistently produced by SVZ that surrounds the ventricular wall in the lateral ventricle [27,28]. SVZ, which is now known to exist in the human body, has previously been found in large mammals, even in a mouse [23,26]. This SVZ stimulation is very easy to give because the location of the lateral ventricles is easily accessible. In addition, the method of administering stem cells via intraventricular is also quite effective for stem cell therapy in stroke, because the location of the lateral ventricle is very close to the neurogenesis niche area. And during the regeneration process after brain injury and during brain development is affected by substances produced by the choroids plexus in nerve regeneration. In nerve regeneration itself, cerebrospinal fluid is also needed which supports the endogenous regulatory process of neuron differentiation [16]. Two previous reports were cases of children with post-hypoxic encephalopathy and one case of amyotrophic lateral sclerosis (ALS). Intraventricular transplantation by Jozwiak et al. 16-month-old infants who have post-hypoxic encephalopathy use autologous cord cells, showing good clinical results [29]. Intraventricular transplantation carried out by Baek et al. in the case of ALS using the Ommaya reservoir showed good results and there were no complications [30]. Many studies report on the occurrence of endogenous neurogenesis [28]. But there have never been reports of such events in studies of stem cell intraventricular transplantation in hemorrhagic stroke patients.

Safety Result

This research is the first in an effort to repeat stem cell transplantation through the intraventricular route. The application of this therapy is to replace and repair brain tissue of patients with damaged strokes [19]. A recent theory revealed that adult nerve stem cells can be stimulated exogenously or endogenously [28,31]. Some important problems that require further research are based on the conclusions of previous studies, namely: 1) optimal stem cell sources, 2) the most effective route of labor, 3) the most effective time, and 4) the optimal dose [13].

In this study, five patients showed that NIHSS had increased in various types of neurological status. The NIHSS value in stroke patients is used to evaluate neurological status. Thus the patient's prognosis can be predicted and make it easier to determine which drug is best used in the therapy process [32]. By knowing the severity of the stroke, a patient's prognosis can also be predicted, including the age of life, time of hospitalization, improvement in neurological status and functional recovery. Williams et al. conducted research that demonstrated the reliability of NIHSS in analyzing patient conditions both prospectively and retrospectively [33]. In the retrospective process, even no bias is found on the scale, although in the medical record there are several missing elements [33]. Some side effects that might occur after treatment are seizures, infections, increased intracranial pressure and rejection reactions by the body. However, in the eight patients, there was no decrease in neurological status or other complications. During the study, this technique was considered quite safe. Another plus, with the reservoir of repeated injections, booster therapy can be facilitated properly.

Kondsziolka et al. conducted research on planting human nerve cells cultured using stereotactic techniques in ischemic stroke patients. This study resulted in functional improvements in stroke patients after observation for 18 months and 24 months [15]. This study also shows consistent findings. There is a functional improvement between before and after stem cell transplantation. In a study by Bang et al. evaluation of transplantation of intravenous BM-MSCs in patients with stroke infarcts were carried out in the third, sixth and 12th months. The results showed that patients treated with stem cells had a significant increase in NIHSS scores compared to patients without stem cells [11]. Bhasin et al. who also conducted research on stroke infarction patients. In the study, evaluation was carried out after eight weeks after treatment and resulted in a significant difference between patients given BM-MSCs intravenous transplantation and non-patients [11]. The evaluation carried out in this study was after 48 weeks after treatment. Previous research focused on stroke infarction patients, while in this study the patients involved were hemorrhagic stroke patients. Intracerebral hemorrhagic stroke has a higher mortality rate, more severe complications and a worse prognosis compared to ischemic stroke and subarachnoid hemorrhage [3]. Intracerebral hemorrhagic stroke also has more severe tissue damage than ischemic stroke [3]. Permanent damage or encephalomalacia often occurs in the chronic phase, so physical therapy is needed [3]. Under these conditions, stem cell transplantation tends to function as neuroprotective agents and neuronal plasticity stimulators through the paracrine effects of trophic factors to improve neurological function [3]. This study shows the results of increased neurological status in some supratentorial hemorrhagic stroke patients after transplantation procedures.

1.3. Conclusion

The clinical evaluation applied in this study used the NIHSS score observed after 6 and 12 months of treatment, showing a tendency to improve without side effects and complications. Follow-up carried out also revealed the security of the procedure. Based on previous studies, this study was the first to examine the autologous intraventricular BM-MSCs transplantation using the Ommaya reservoir in stroke patients. This treatment can be developed as a therapy for stroke patients in the future. Greater further research related to this study is needed to determine the effectiveness of this therapy as an alternative treatment for a post-stroke disability.

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Interim Report And Study Protocol Of Clinical Trial Of Granulocyte Colony Stimulating Factors For Treatment Of Spinal Cord Injuries

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Abstract

INTRODUCTION: Granulocyte-colony stimulating factor (G-CSF) is a well-known growth factor that has been widely and safely employed by hematologists for treatment of neutropenia and different hamatological conditions over many years. The objective of this study was to evaluate the safety and efficacy of G-CSF administration for neurological and functional improvement in subacute, incomplete Traumatic Spinal Cord Injury (TSCI).

METHODS: The study design was a randomized, double blind, placebo-controlled clinical trial. TSCI cases with American Spinal Injury Association (ASIA) Impairment Scale B/C/D, within 1-6 months after injury were included. Patients were randomly allocated into treatment and placebo groups. Each group included 30 patients (60 total patients). The treatment group received 300 μg/day of subcutaneous G-CSF for 7 consecutive days, while the control group received placebo. Patients were assessed by ASIA, Manual Muscle Testing (MMT), Persian version of Spinal Cord Independence Measure (P-SCIM III), and Functional Assessment Measure (FAM), just before intervention and at 1, 3 and 6 months follow-ups.

RESULTS: Neurological changes including motor, light touch, pin prick and MMT scores showed significant improvement in the treatment group compared to placebo group ($p<0.05$). Functional assessment showed better P-SCIM III and FAM scores changes in the treatment group ($p<0.05$).

CONCLUSION: The promising results regarding neurological and functional outcomes in our cases, may pave the way for clinical application of the treatment.

Introduction

Recently many novel treatments including cellular, cytokines, and neuroprotective treatments have been proposed as an adjunct to classical rehabilitation protocols, all being mentioned as neurorestorative treatments. Widespread clinical application of such treatments requires high quality peer reviewed evidence, being reported from multiple centers. Availability and ease of application of such treatments is amongst the important features for such treatments to be chosen. Granulocyte-colony stimulating factor (G-CSF) is a well-known cytokine that has been widely and safely employed by hematologist for treatment of neutropenia and different conditions over many years(1). It is a recombinant growth factor, having FDA approval for hematological applications. It has been reported to promote neurological and functional recovery after incomplete Spinal Cord Injury (SCI) (2-5).

Previous experimental studies revealed that G-CSF could promote neurological recovery after traumatic spinal cord injury (TSCI) (6, 7). Based on these studies, we shifted to early phases of clinical intervenion. In a phase I trial on 19 patients with chronic motor complete TSCI, very mild adverse effects were observed indicating that G-CSF administration is safe (8). Next, we conducted a non-randomized, non-blinded, comparative phase I/II trial on 74 cases, suggesting the efficacy of G-CSF for promoting neurological recovery for motor-incomplete chronic TSCI (2). Thereafter, we performed a double-blind, randomized, placebo-controlled, clinical trial, phase III study on 120 patients with incomplete chronic TSCI, concluding that G-CSF administration is associated

with significant motor, sensory, and functional improvement (3). Based on these results, we are now presenting the interim results about safety and efficacy of G-CSF administration for neurological and functional changes in subacute, incomplete TSCIs and study protocol of this double blind Randomized Clinical Trial (RCT).

Methods

The trial included TSCI cases with severity of American Spinal Injury Association (ASIA) Impairment Scale B/C/D, being enrolled within 1-6 months after injury.
Sixty incomplete subacute traumatic spinal cord injuries were randomly allocated into treatment and placebo groups. Patients were not aware of the treatment group and independent evaluators accomplished neurological assessment by ASIA (9), Manual Muscle Testing (MMT) score, functional assessment by Persian version of Spinal Cord Independence Measure (P-SCIM III)(10), and Functional Assessment Measure (FAM)(11) questionnaire, just before intervention and at 1, 3 and 6 months follow-ups. Our primary outcome measures were changes in ASIA motor and sensory scores from baseline to 6 months.
The treatment group received 300µg/day of subcutaneous G-CSF for 7 consecutive days and the control group received 1cc normal saline 0.9% subcutaneously. The white blood cell counts were kept under 50.000 by daily complete blood count checks.

At the same time classic rehabilitation program was provided for six months in both groups. Follow-up visits were performed 3 times within the six month period after treatment.

Results

Demographic and neurological features of the included patients have been tabulated in table 1.

Neurological changes including motor, light touch, pin prick and MMT scores showed significant improvement in the treatment group compared to placebo group ($p<0.05$).

Five patients improved from AIS B to C, 5 other cases from AIS C to D, and one case from AIS D to E. There was no AIS change in the placebo group. Also functional assessment showed better P-SCIM III and FAM scores changes in the treatment group ($p<0.05$). No important side effect was observed in the treatment group during the follow-up period.

Discussion

Early institution of neurorestorative treatments after TSCI may have greater effect on the final neurological outcome. However, autorecovery may be responsible for part of neurological improvement in the acute period. A randomized double blind study design would be necessary for establishment of the net effect of the treatment.

Therefore Granulocyte-colony stimulating factor may be administered either on an outpatient (2, 3, 8) or inpatient (4, 5, 12) basis. Finally, we suggest further multicenter studies for establishment of the treatment protocol, and clarify the clinical indications for G-CSF treatment in the subacute setting. The obtained results regarding neurological and functional outcomes in our cases, may pave the way for clinical application of the treatment.

Table1. Demographic and clinical characteristics of patients in the G-CSF and placebo groups.

characteristics	**G-CSF group (n=28)N (%)**	**Placebo group (n=26)N (%)**	**p value**
Age at the time of injection (in years) Mean (±SD)	36.5 (13.3)	31.0 (9.9)	0.096
Gender, *Male*	25 (89.3 %)	24 (92.3%)	>0.90
Duration after SCI (in months) Mean(±SD)	3.7 (1.97)	3.9 (1.77)	0.754

Etiology of SCI			
MVA	14 (50.0 %)	14 (53.8 %)	0.718
Fall	10 (35.7 %)	8 (30.8 %)	
Sport	1 (3.6%)	2 (7.7%)	
Violence	1 (3.6 %)	2 (7.7%)	
Heavy drop	2 (7.1%)	0 (0.0%)	
Neurological level of injury			
Cervical	13 (46.4%)	10 (38.5%)	0.554
Thoracolumbar	15 (53.6%)	16 (61.5%)	
AIS Grade			
B	11 (39.3%)	11 (42.3%)	0.939
C	11(39.3%)	9 (34.6%)	
D	6 (21.4%)	6 (23.1%)	

Abbreviations: G-CSF, Granulocyte-Colony Stimulating Factor; N, Number; SD, Standard Deviation; SCI, Spinal Cord Injury; MVA, Motor Vehicle Accident; AIS, ASIA Impairment Scale.

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Lipid Quantification In Predicting Survival Outcome Of Glioma

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Abstract

Purpose
Evaluation of the predictive values of lipids as prognostic marker for glioma using MRI in-and opposed-phase (IOP) sequence.
Materials and Methods
The analysis of the clinical and imaging data of thirty-three histologically proven glioma patients was carried out. Lipid quantification indicated by lipid fraction was obtained from lipid map constructed from IOP imaging. The lipid fraction of the tumour regions were stratified into three groups using a three-group analysis approach based on volume under surface (VUS) of receiver operating characteristics. The survival outcomes of the stratified lipid fraction were evaluated using Kaplan-Meier survival method.
Results
The lipid fraction of solid non-enhancing region demonstrated significant differences between the three groups (low, medium, and high lipid fraction groups) stratified by VUS for overall survival (OS) ($p=0.01$) and time to progression ($p=0.048$). The high lipid fraction groups had poorer survival compared to the low and medium lipid fraction group.
Conclusion
Lipid fraction of solid non-enhancing region has potential as feasible prognostic tool for glioma patients. Lipid quantification have implications on survival outcomes and prognostication of glioma patients.

Keywords: Glioma, lipid, survival, prognosis, MRI, in-and opposed-phase.

Introduction

Prognostic evaluation is important for patient counseling, treatment strategy planning, and disease management [1]. The heterogeneous nature of glioma and differing levels of sensitivity to treatment further influence patient outcome. The factors used to determine prognosis are age, gender, Karnofsky Performance Status (KPS), tumor morphology, extent of surgery, histopathological correlations and overall treatment protocols [2-4]. However, the prognostic factors were not feasible for pre-treatment planning or counseling. Magnetic resonance imaging (MRI) technique remains the standard of care for treatment planning but has not reached the level of confidence to be used in outcome predictions [5,6].

The regulation of lipid metabolism is one of the important characteristics of cancer cells to sustain rapid tumor growth [7-9]. Lipid has important roles in cell growth, cell membranes generation, signal transduction, apoptosis, necrosis, immunity, metabolism regulation, and reproduction [10,11]. The elevated lipid levels correspond to aggresiveness and worse prognosis [8,12]. The reprogramming of lipid metabolism result in lipid level changes in glioma. However, the mechanisms that lead to changes of lipid composition in gliomatous tissues remain ambiguous. Lipid quantification is a potential biomarker for prognostication of glioma with the important role of lipid in cancer metabolism and tumor development.

In-and opposed-phase (IOP) imaging is an imaging technique for lipid detection that was commonly used in body imaging. Lipid fraction of tumour regions has been shown viable for discrimination of different tumor grades [13]. This study extends the application of lipid quantification into prognostication of glioma by evaluating the survival outcomes of glioma patients. The volume under surface (VUS) method was applied for stratification into three lipid fraction group.

Materials and Methods

1.1. Review of clinical and MRI data

The MRI images of 33 histologically proven glioma cases of different grades (grade II, III, and IV) were extracted from the hospital database. Clinical data were retrieved from the electronic medical records. The patient medical records were carefully reviewed. The inclusion criteria include patients referred for preoperative assessment of intracranial tumors, histologically proven glioma (grade II-IV) and full sequences of MRI brain tumour protocol, and follow-up records of more than 1 year. The exclusion criterion was death unrelated to surgery such as infection.

1.1. Quantification of Lipid Fraction

The tumor regions comprising of solid enhancing, solid non-enhancing, and cystic were segmented on post-contrast T1 images using a semi-automated segmentation method in ITK-SNAP, as described in our earlier work [14,15]. The lipid map was generated via subtraction of the opposed-phase images (Fig 1c) from in-phase images (Fig 1b) that were obtained from IOP [14]. The lipid maps were skull-stripped and registered along with the structural T1 and tumoral masks as described in the methods section of our earlier work (Fig 1d) [14]. The mean lipid fractions of tumor regions were acquired after superimposing the masks onto the lipid maps with reference to the T1 images after registration to IOP images.

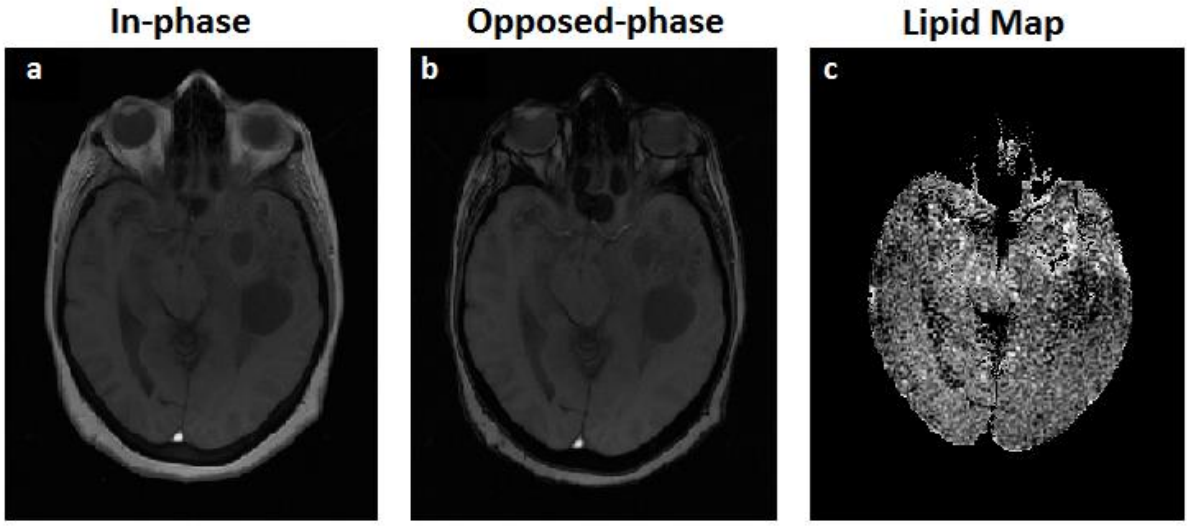

Fig. 1: Axial MRI images showing a) in-phase image, b) opposed-phase image, and c) the skull-stripped lipid map constructed from the subtraction of in- and opposed-phase MRI images.

1.1. Survival Analysis

Statistical analyses were performed using SPSS (version 22, IBM, New York, USA) and R (R Foundation for Statistical Computing, Vienna, Austria). A three-group volume under surface (VUS) receiver operating characteristics (ROC) curve was performed to determine the two optimal cut-off points for three lipid fraction groups stratification (low, medium and high lipid fraction group) [16]. The survival outcomes in terms of OS and TTP were evaluated using Kaplan-Meier analysis [17]. The period for OS was defined (in months) from the day of first diagnosis defined by histopathology analysis until the (i) date of death or (ii) censored at the last date of assessment. Patients who were lost to follow up were censored at (i) last visit or (ii) last follow-up found in the medical records. The duration for TTP was recorded (in months) from the first diagnosis until the date of (i) the appearance of new symptoms or (ii) radiological changes. The occurrence of event was death for OS and progression for TTP. A log-rank test was carried out to determine differences in the survival distribution for the different groups.

Results

1.1. Survival outcomes of lipid fraction stratified groups

Table 1 shows the demographics of glioma patients, with the mean OS and the TTP. Only lipid fraction of the solid non-enhancing region of the tumors showed statistically significant increasing trend with the tumor grades (mean $_{\text{grade II}}$=0.04, mean $_{\text{grade III}}$ =0.06, mean $_{\text{grade IV}}$ =0.08 & p<0.01). The stratification of the lipid fractions was performed using lower cut-off point (LCP=0.05) and the upper cut-off point (UCP=0.07) obtained from VUS analysis [16,18]. The values of lipid fractions less than LCP were classified as low lipid fraction, values between LCP and UCP were classified as medium lipid fraction, while values more than UCP were grouped as high lipid fraction. Fig 2 showed the distribution of the lipid fractions stratified by three groups (low, medium and high lipid fraction groups)

Tab. 1.: *Patient demographics grouped by WHO tumor grades with medians of overall survival and time to progression.*

Clinical Variables		**WHO Grade (n=33)**			**Overall Survival (in months)**	**Time To Progression (in months)**
		Grade II (n=12)	**Grade III (n=5)**	**Grade IV (n=16)**	**Median (range)**	**Median (range)**
Gender	Male	7 (58.30%)	3 (60.00%)	10 (62.50%)	14.99 (63.71)	6.57 (63.71)
	Female	5 (41.70%)	2 (40.00%)	6 (37.50%)	12.46 (152.01)	9.40 (152.01)
Age (mean and range, years)	≤50	35.20 (16-48)	36.33 (25-47)	29.60 (10-47)	15.96 (152.01)	9.07 (152.01)
	>50	62.50 (62-63)	60.00 (51-69)	60.18 (52-73)	9.76 (63.71)	6.80 (63.71)
KPS	80-100	10 (83.3%)	2 (40%)	1 (6.3%)	34.71 (152.01)	8.94 (152.01)
	50-70	2 (16.7%)	3 (60%)	7 (43.8%)	11.97 (41.91)	8.55 (42.44)
	0-40	0 (0%)	0 (0%)	8 (100%)	4.14 (45.50)	3.37 (29.82)

KPS: Karnofsky performance score

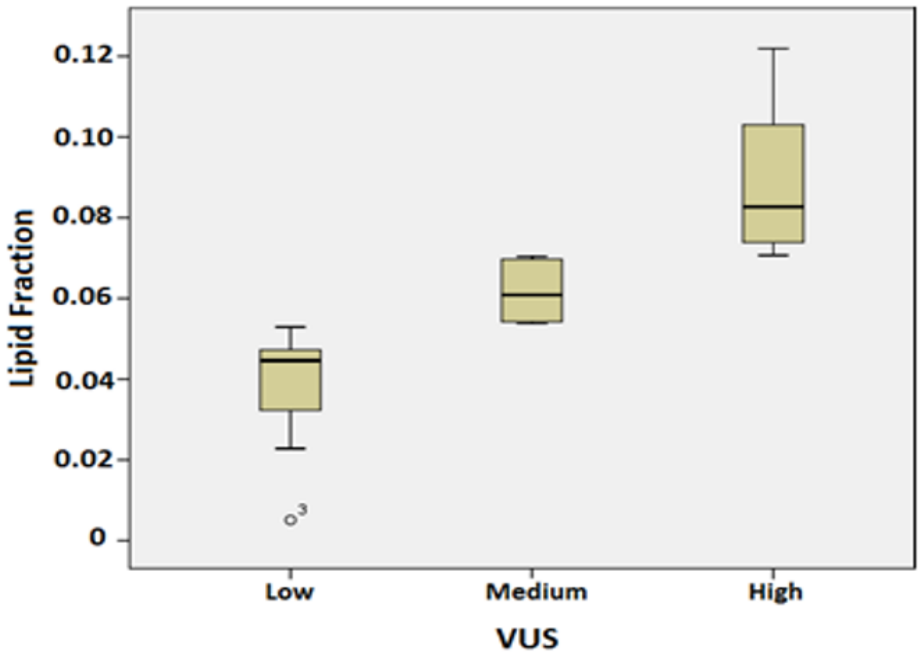

Fig. 2: The distributions of lipid fractions in solid non-enhancing tumor regions across the VUS defined groups

The Kaplan Meier survival analysis for lipid fractions of solid non-enhancing tumor regions demonstrated statistical significant differences between the three lipid fraction groups for both OS and TTP (Table 2). Thirteen patients survived (right-censored) the last assessment date while 20 patients were deceased and 18 patients had disease progression. Favorable overall survival and longer time to progression were seen in the low lipid fraction group as compared to medium and high lipid fraction groups.

Table 2: The survival analysis of the three lipid groups stratified by VUS.

Lipid Fraction	**Kaplan-Meier analysis**	
	Overall Survival	**Time to Progression**
	p-value	**p-value**
Solid non-enhancing of tumour region	0.01*	0.048*

1.1. Discussion

Findings showed that the lipid fraction derived from IOP imaging, particularly from the solid non-enhancing tumour regions has potential for survival outcome prediction in glioma patients. The glioma patients were stratified into three groups based on their lipid fractions (low, medium and high lipid fractions). The overall survival and time to progression of patients were significantly different between the low, medium and high lipid fraction groups. Higher lipid fraction in the solid non-enhancing region also correlated with higher tumor grades.

The stratification of glioma patients for prognostication was useful in grouping of the patients according to outcome for treatment planning strategy and focusing on intervention for the high-risk group [19-23]. The limitations in this study include small sample size, lack of *IDH* mutation status test, different treatment protocols effects not taken into account, and unclear definition of tumor progression based solely on imaging findings.

1.1. Conclusion

Lipid fraction obtained from IOP has potential as a novel prognostic biomarker for glioma patient. The high lipid fraction of the solid non-enhancing tumor region reflects poor survival outcomes. This novel method provides a novel measure for outcome prediction and different approach in personalized medicine.

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Local Corticosteroid Injection Of Sacroiliac Joint, Results Of Three Different Methods.

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Abstract

Background: The sacroiliac joint (SIJ) is considered a common source of low back pain (LBP) and referred pain in the lower limb.

Aim of the work: was to compare the results of local corticosteroid injection for sacroiliac joint by using three different technique which are: Computed tomography (CT), plain C-arm guided and clinical guided.

Material and Methods: One hundred-nine patients, with sacroiliac joint (SIJ) pain, which had not resolved with non-steroidal anti-inflammatory drugs (NSAIDs), were treated with local corticosteroid injected by three different approaches; Computed tomography (CT), plain C-arm fluoroscopy guided and clinical guided. Seventy patients were injected by arthrography-guided approaches (40 by computed tomography and 30 by fluoroscopy), and 39 patients by clinically guided one. They were prospectively assessed for a period of 10 months following the injection.

Results: The arthrographic approaches enabled immediate and adequate pain relief with discontinuation of NSAIDs for more than one-month duration in 89% and 90% of patients in fluoroscopy and computed tomography (CT) guided groups respectively, and only in 43% of those in clinically guided group. Then, along the next 9 months, the pain free state was achieved without NSAIDs in 51 %, 50 % and 16 % of patients in CT guided, fluoroscopy guided and clinical guided respectively.

Conclusion: These arthrography-guided procedures are easy to perform ambulatory patients with accurate access to the SIJ space, but the CT guided procedure is simpler, lesser time consuming and lesser irradiation exposure time and with higher quality of pain relief than the fluoroscopy guided one. Further studies should be done on multiple dose injections of the SIJ under CT control, to see if they prevent the relapse and the subsequent need to the NSAIDs or not.

Keywords: corticosteroid, sacroiliac joint injection, sacroiliac joint, sacroiliitis

Introduction

The sacroiliac (SIJ) is the largest axial joint in the body, with an average surface area of 17.5 cm^2[1]. There is significant variability in the size, shape, and contour of the SI joint, even from one side versus the other within the same individual[4].The sacroiliac joint (SIJ) is considered a common source of low back pain (LBP) and referred pain in the lower limb. When depending on the history and the physical examination alone, it can be difficult to differentiate between SIJ pain and other sources of LBP[5]such as facet syndrome, herniated nucleus palposus, lateral recess stenosis, internal disk disruption, hip joint diseases, and some myofascial syndromes. The true incidence of sacroiliac dysfunction (SD) pain in the general population is unknown[3]. It has been reported to be the primary source of LBP in 22.5 % of 1293 patients[1]. According to the osteopathic literature, one third of LBP occurrence may be directly related to SIJ dysfunction[4]. The physical findings include tenderness over the SIJ sulcus and the posterior SIJ area in general. The muscle adjacent to the SIJ area usually tender as well. Lumbosacral flexion and extension may elicit pain. Neurological findings are usually absent[3]. The specificity of the clinical provocative maneuver to assess SIJ dysfunction is a questionable issue[2].It has been proposed that the most reliable diagnostic test is the fluoroscopy[14]or computed tomography. Computed tomographic guided local anesthetic (LA) injection of SIJ[7] that resulting in immediate SIJ pain relief. Some authors[12]recommended that the procedure be repeated at least twice using two drugs (local anesthetic and corticosteroids), with different durations of action to eliminate false positive responses. The treatment of SIJ

dysfunction should be directed at restoring joint homeostasis. The ideal treatment has not been discovered. Exercise, joint manipulation, and joint injection provide the possibility of re-establishing joint mechanics. Non-steroidal anti-inflammatory drugs

(NSAIDs) may be beneficial and sometimes complement other treatment measures[3]. Direct posterior approach under the posterior superior iliac spine used for puncture aspiration in septic arthritis of the SIJ [12]. Hendrix, et al[10]at 1982 has performed arthrography of the SIJ using the last technique. The fluoroscopic control facilitates the injection of SIJ with LA and corticosteroid as a line of treatment of SIJ syndrome [13], and with LA as a diagnostic block test of SIJ syndrome[9, 12, 14], also with contrast medium as a provocative test[12]. Elgafy, et al[7], has used the CT guided arthrography for LA and corticosteroid injection into the SIJ as a diagnostic measure. The aim of the current work was to compare the results of local corticosteroid injection for sacroiliac joint by using three different technique which are: Computed tomography (CT), plain C-arm guided and clinical guided.

PATIENTS AND METHODS

This study included a total of 109 patients of both sexes who were suffering from chronic SIJ pain which was poorly controlled by NSAIDs, attending at Al-Haram; Ministry of Health Hospital. Approval of the ethical committee and a written informed consent from all the subjects were obtained. This study was conducted between May 2016 and July 2018. All patients were of ASA physical status I and II grading, not pregnant (if female) and not having neurological deficit, previous fractures, tumors, infection or low back pain surgery. They had localized pain in the buttock area over the SIJ. The pain was increased by inward pressure 2. 5 cm below the posterior superior iliac spine by the examiner thumb while the pelvis was holding immobile (to exclude lumbosacral pain) and was relieved after LA injection of the SIJ under CT or fluoroscopic control. The patients of negative block test were excluded from this study. Before the procedure, the motor strength of the patient's lower extremities was tested to provide a baseline for comparison with strength after the procedure. Some patients experience transient weakness of the ipsilateral lower extremity after the procedure. Informed consent was obtained from each patient before beginning the procedure. As the soft tissues over the SIJs were able to support the inserted spinal needle at the desired angle in the imaging plane, the operator could withdraw his hands and step behind a lead shield away from the gantry when obtaining CT images or fluoroscopy; other personnel were positioned outside the room to protect the surgeon from radiation.

1- Computed tomography guided technique:

The patient was lying in prone position on the CT table. The SIJ at S2 was localized on the CT monitor. A line was drawn on the patient skin whereas the guiding light that omitted from the CT apparatus meets the patient skin. Under complete aseptic condition, and local infiltration of the skin with 2 % lignocaine at the midline point, a 22- gauge spinal needle was inserted at the midline point, and then directed antero-laterally towards the SlJ. When the joint space was accessed at the level of S2 foramen under intermittent C.T. control, a contrast medium (0.3-0.5 ml. of omnipaque or air) was injected for confirmation (figure, 1). A dose of 20 mg. in 1 ml. long acting corticosteroid (betamethasone sodium phosphate- diprofos, Schering) plus 4 ml. Lignocaine 1 % (Xylocaine, Astra Zeneca) was then injected into the joint space. The capacity of an inflamed SIJ varies from 1-8 ml. depending on the degree of impairment.

2- Fluoroscopy guided technique:

This procedure was described by Aprill CN, 1992[15] and was performed while the patient was lying in prone position on the fluoroscopy table. Under complete aseptic condition, the skin was penetrated 1-3 cm. below the inferior margin of the SIJ, at this point the skin was infiltrated with 2 % lignocaine. Under intermittent fluoroscopic control, a 22-gauge spinal needle was introduced and directed cephalic to strike the ilium 1 cm. above the inferior margin of the SIJ. The tip of the needle then was manipulated with fluoroscopic guidance until it entered the joint space (figure, 2). The needle assuming a distinct bend as it confirmed to the joint contour, often, indicated entry through the joint space. Contrast medium (0.3-0.5 ml. Omnipaque) was injected for more confirmation. A dose of 20 mg in 1 ml. long acting corticosteroid (betamethasone sodium phos-phate) plus 4 ml. lignocaine 1 % was then injected into the joint space.

3- Clinically guided technique:

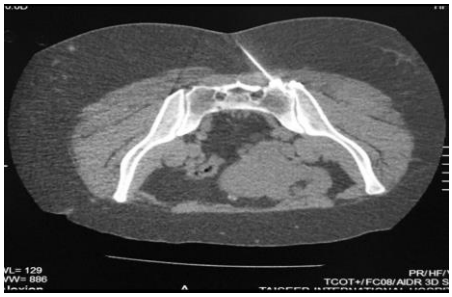
The procedure was described in some literature [5] and was performed with the patient was lying prone, and a pillow beneath the pelvis and the lower abdomen. With standing opposite the SIJ that to be blocked, and after aseptic skin preparation and LA skin infiltration, a 22-gauge spinal needle was inserted by the dominant hand in an anterior-lateral direction along an arc extending between the superior and inferior posterior iliac spines at a

45-degree angle until the deepest point between the sacrum and the ilium was reached. Then, a dose of 20 mg. in 1 ml. of betamethasone sodium phosphate plus 4 ml. Lignocaine 1% was injected, that may find a way into the joint space. According to the technique used the patients were divided into 3 groups; CT guided, fluoroscopy guided and clinically guided group. The studied parameters of this study were; the percentage of patients who experienced complete pain relief with stopping of NSAIDs for one-month duration following the injection, the time of restarting the NSAIDs and their new doses and frequencies to achieving pain free state, the time consumed by each technique, and the time of irradiation exposure to the patients and the medical staff.

Post-Procedure Plan:

• Observe for 15 min to confirm absence of major hematoma.

• Instruct the patient to be aware of the possible complications such as infection, hematoma, or neurapraxia.



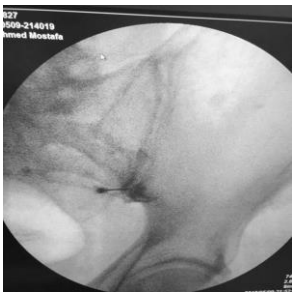


Fig 1: .Shows CT guided injection using Dye to identify SI Fig. 2: Fluoroscopy guided SIJ.

STATISTICAL ANALYSIS

The data collected from the study contained continuous and categorical variables. Continuous data were examined for normality of distribution using Kolmogorov–Smirnov test. Continuous data with normal distribution were summarized as means and standard deviations, and data with non-normal distributions were summarized as medians and interquartile ranges. Categorical data were summarized as numbers and percentages. Variables with normal distribution were analyzed using t-tests, and those with non-normal distribution were analyzed using Wilcoxon rank-sum tests. Categorical variables were analyzed using chi-square test (or Fisher's exact test when 25% or more cells had expected counts of less than 5). A P-value of < 0.05 was accepted as significant. All data spreader on Microsoft excel 2010. Statistical analysis was done using SPSS 24.

RESULTS:

The demographic data of the patients in each group included the number, the age in years, the sex and the number of joints injected, and some pain characters as duration of SIJ pain in months, nocturnal pain that awaken the patient from sleep and radiating pain to the thigh and calf were summarized in (Table 1), and revealed no significant difference between the 3 group.The CT scans showed no abnormality in 38 % of symptomatic SIJ with a positive SIJ block test, subchondral sclerosis (more in the iliac side) in 30 %, osteophytes in 27 %, narrowing of joint space less than 2 mm: in 4 % and subchondral cysts in 2 % of patients. The block was considered successful (70-100 % improvement) when the pain relief was complete and sustained more than one month without or with smaller doses of NSAIDs or fair (50-70 % im-provement) when the patient required NSADs but in their previous doses and frequencies to achieving complete pain relief. However, it was considered failed when the complete pain relief was not sustained one-month duration. Subsequently, the successful block was subdivided according to the need to NSAIDs within the next 9 months into; a) an excellent block (90-100 % improvement); when the patients were still pain free without NSAIDs, b) a very good block (80-90 % improvement); when they were reduced by more than 50% at the same previous frequency. According to that evaluation, the results of this study were analyzed and were shown in (table, 2) which revealed; 90 %, 89 % and 43 % of patients had successful block, 51 %, 50 % and 16 % of patients experienced excellent block, 30 %, 29 % and 20 % of patients had very good block, 9 %, 10 % and 7 % Of patients had good block, 3 %, 4 % and 23 % of patients showed fair block and 7 %, 8 % and 34 % of patients experienced failed block in C.T., fluoroscopy and clinically guided groups, respectively. Those results showed significant ($P<0.05$) increase in quality and duration of pain relief in arthrography guided groups than in clinically guided one, insignificant ($P>0.05$) changes between the two arthrographic groups, except in the time at which the patients will restarted the NSAIDs, which was earlier in the fluoroscopy guided group than the CT guided one. The patients restarted NSAlDs, at 6±2.5 month, 5±3 month and 2.5±1.25 month after corticosteroid injection in CT, fluoroscopy and clinically guided groups, respectively.About the total time that was consumed by each arthrographic technique,

it was significantly (P<0.05) shorter in the CT (10±3 minutes) than in the fluoroscopy (15±5 minutes) guided procedure. Also, the irradiation exposure time was significantly (P<0.05) longer in fluoroscopy (90+35 seconds) than in CT (30±10 seconds) guided technique. There were no notable complications except 3 patients (1 in fluoroscopy and 2 in clinically guided groups) said the procedure was very painful, 4 patients (1 in each arthrographic group and 2 in clinically guided group) had transient anesthesia of the perineum after injection and 2 patients in clinically guided group had reported transient acute pain at the first night following the procedure.

Table (1): shows the demographic data and some pain characters of the three groups and revealed insignificant variations between them.

Item	CT guided group	Fluoroscopy guided group	Clinically guided group
Number of patients	40	30	39
Age in years (M± SD)	(38+12.1)	(37.6±13.5)	(35.5±13)
Male/female	22/18	20/10	26/13
Number of joints injected	50	36	44
Duration of SIJ pain in months (M+SD)	(24±16)	25±18	26+12
Nocturnal pain (patients)	(10)	(9)	(8)
Radiation pain (patients)	(8)	(6)	(9)

M= mean SD= standard deviation

Table (2): shows the pain relief response pattern by patients in each of the three group and revealed significant changes between the clinically guided group and each of the two other groups, but insignificant changes between the arthrography groups.

Item	% of patients in CT group	% of patients in fluoroscopy group	% of patients in clinical group
Successful injection (lasting > 1 month)	90%	89%	43%*
a) Excellent block (90-100% improvement)	51%	50%	16%*
b) very good block (80-90)	30%	29%	20%*
c) Good block (70-80 % improvement)	9%	10%	7%
d) Fair block (50-100 % improvement)	3%	3%	23%*
Failed injection (lasing < month)	7%	8%	34%*

- Means P value < 0.05 (significant).

DISCUSSION:

Low back pain located around the para-sacral area is a common presenting complaint of many patients. The diagnosis for the etiology and the source of this pain is varied. One of the causes of LBP that often is overlooked by clinicians is SIJ dysfunction. A lack of awareness of this potential etiology for LBP results in inappropriate and inadequate treatment. Sacroiliac joint pain is resistant to identification by the history and physical examination[5]. Even the pain provocation test of the SIJ by extending it by injection of contrast medium was not suitable for this joint. This leaves the diagnostic block test as the only available as a criterion standard for the

SIJ dysfunction[14]. So; this study had mainly depended on the block test for diagnosis of SIJ pain. The treatment strategies of SIJ pain include exercise, joint manipulation, NSAIDs, steroids, muscle relaxants, opiates, fluoroscopy guided intra-articular long acting corticosteroid inject[13], and fluoroscopy radio-frequency[8].

Arthrography of SIJ was previously described by[11]for aspiration of septic arthritis, and then by[13], for corticosteroid injection as a therapeutic measure, and by Fortin, et al, 1994[9], for injection of contrast medium as a pain provocation test. However, scientists had used it to inject LA as a diagnostic block test[6, 9, 12, 14]. Lastly, CT guided LA injection of the SIJ for diagnostic attempt as described by[7].

This study compared between the CT, fluoroscopy and clinically guided SIJ injection with LA and corticosteroid and revealed immediate and adequate pain relief in CT and fluoroscopy groups while in clinical group it was inadequate. The percentages of patients who experienced successful block with excellent, very good, and good impairment were equal in CT and fluoroscopy groups and were significantly ($P<0.05$) higher than those in clinically guided group. While the fair results were approximately the same in arthrographic groups and lower than that of the clinically guided group. However, the failure rate was very higher in the clinically guided

procedure than in arthrographic guided one. These results were explained by the complete entering of the injected drugs into the joint space and producing their maximal effect in arthrographic groups, unlike, in clinically guided group only little amount of the drugs can find a way to reach inside the joint space. For the same reason the patient in clinically guided group restarted the NSAIDs earlier than those of the arthrographic one, however, patients in CT guided group restarted the NSAIDs later than those in fluoroscopy guided one, this might be due to blocking of one of the roots that innervate the SIJ, which is S2 as the injected drugs can enter the second sacral foramen in CT guided procedure (Figure 1), that might accentuate the blockage.The immediate pain relief which revealed by this study was in agree with the results of Elgafy et al, (2001)[7], who used lignocaine under CT guided SIJ diagnostic arthrography, but these results were differed from those of Maugars and coworkers (1992)[13], who did not use LA, and they used corticosteroid which gave its effect after 2-3 days following the injection. However, the overall results of the arthrographic procedures in this study were in the same direction of that of[13], but with higher percentage of successful block that was lasting more than one month (89-90 % in the present study and 79 % in their study), and with lower block failure rate , which was lasting less than one month (7-8 % in the present study and 16 %in their study). This may attribute to the usage of the SIJ diagnostic block test and exclusion of patients of the negative result in this study to decrease the ratio of false diagnosis of sacroiliac pain, and this test was not considered by the study of[13].

No adequate explanation can be given as to why results were always parallel when both SIJs were treated by corticosteroid injection. Because the arthrographic techniques ensure intra-articular administration of drugs, failures might have been related to the occurrence of pain in the extra-articular portion of the joint due to sacroiliitis or to an associated lumbar pain or may be due to false diagnosis because the SIJ block test may be positive in some painful conditions other than sacroiliitis as groin pain. So, some authors[12] recommended the repetition of the block test, at least, twice using two LAs with different durations of action to eliminate the false positive results.

The use of the arthrography guided techniques described here, although presenting some difficulties (especially in the fluoroscopy one) for an inexperienced doctor, would seem essential for improved therapy of sacroiliitis. If corticosteroid is injected near the SIJ in the absence of arthrographic control, there is little likelihood that the drugs will penetrate through the thick posterior sacroiliac ligament and to the joint, as what was occurred in the clinically guided technique, which revealed the high failure rates in clinically guided group in this study.The present study revealed that the fluoroscopic control is more difficult and more time consuming than CT control. About irradiation exposure time, it was longer in fluoroscopy than in CT guid-ed procedure.

CONCLUSION

Corticosteroid injection of the SIJ is indicated for patients who having acute or persistent SIJ pain that is not adequately controlled by NSAIDs and should be done under arthrographic control which enabled accurate intra-articular injection, adequate pain relief and discontinuation of NSAIDs. These arthrography-guided procedures are easy to perform ambulatory patients with accurate access to the SIJ space, but the CT guided procedure is simpler, lesser time consuming and lesser irradiation exposure Lime and with higher quality of pain relief than the fluoroscopy guided one. Further studies should be done on multiple dose injections of the SIJ under CT control, as they prevent the relapse and the subsequent need to the NSAIDs, or not?

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Minimally Invasive Puncture With Use Thrombolytic Evacuation Of Spontaneous Intracerebral Hemorrhage

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Abstract

Our purpose was to investigate the safety and efficacy of minimally invasive surgery using tissue-type plasminogen activator (tPA) in patients with intracerebral hemorrhage.

Keywords: plus recombinant tissue type plasminogen, intracerebral hemorrhage, minimally invasive surgery, thrombolytic evacuation, hemorrhage stroke

Introduction

Optimal management of spontaneous intracerebral hemorrhage (ICH) remains one of the highly debated areas in the field of neurosurgery. Earlier studies comparing open surgical intervention with best medical management failed to show a clear benefit. Thrombolytic evacuation with urokinase-type plasminogen activator (uPA) or tissue-type plasminogen activator (tPA) has been shown to be a hopeful treatment for ICH. We report our experience in treatment of ICH by minimally invasive surgery with recombinant tissue type plasminogen. Thus, we investigated safety and efficacy of minimally invasive surgery (MIS) plus recombinant tissue type plasminogen (tPA) in patients with intracerebral hemorrhage.

Materials and Methods

Our study was a single-center retrospective clinical trial performed in the department of general neurosurgery, the Municipal clinical hospital #1 of Astana city.

In the present study we treated a total of six patients with spontaneous intracerebral hemorrhage (ICH) in basal ganglia from December 2017 to March 2018. The following was taken into account: patient age, gender, Glasgow Coma Scale (GCS), hematoma volume (HV), Blood pressure (BP), intraventricular hemorrhage (IVH), intracerebral hemorrhage score (ICH score), Glasgow Outcome Score (GOS).

Inclusion criteria for patients in the present study were as follows: spontaneous ICH in the basal ganglia, (HV) ≥ 30 mL; GCS score ≥7; age range: 18–80 years.

Exclusion criteria for patients in the presents study were ICH induced by intracranial arteriovenous malformation, aneurysms, tumors, trauma and patients with coagulopathy.

We performed emergency surgery within 24 hours after the hemorrhage. For the beginning, we performed external ventricular drain (EVD) or minimally invasive puncture hematoma, then drained catheter connected to active drain system.

CT head scan a control after 12 hours. If the CT is negative for new hemorrhage administer 2mg of intrathecal tPA (alteplase) mixed in 3-10 ml sodium chlorine 0, 9 %. After each appointed dose, the system closed for 1 hour to allow drug-clot interaction, and then reopened to allow for active drainage.

Following day control CT to check hematoma volume. We did repeated administration of tPA using previous protocol if the clot is more 30 ml. Usually we repeat the procedure several times until hematoma do not become less 30 ml. Fig.1

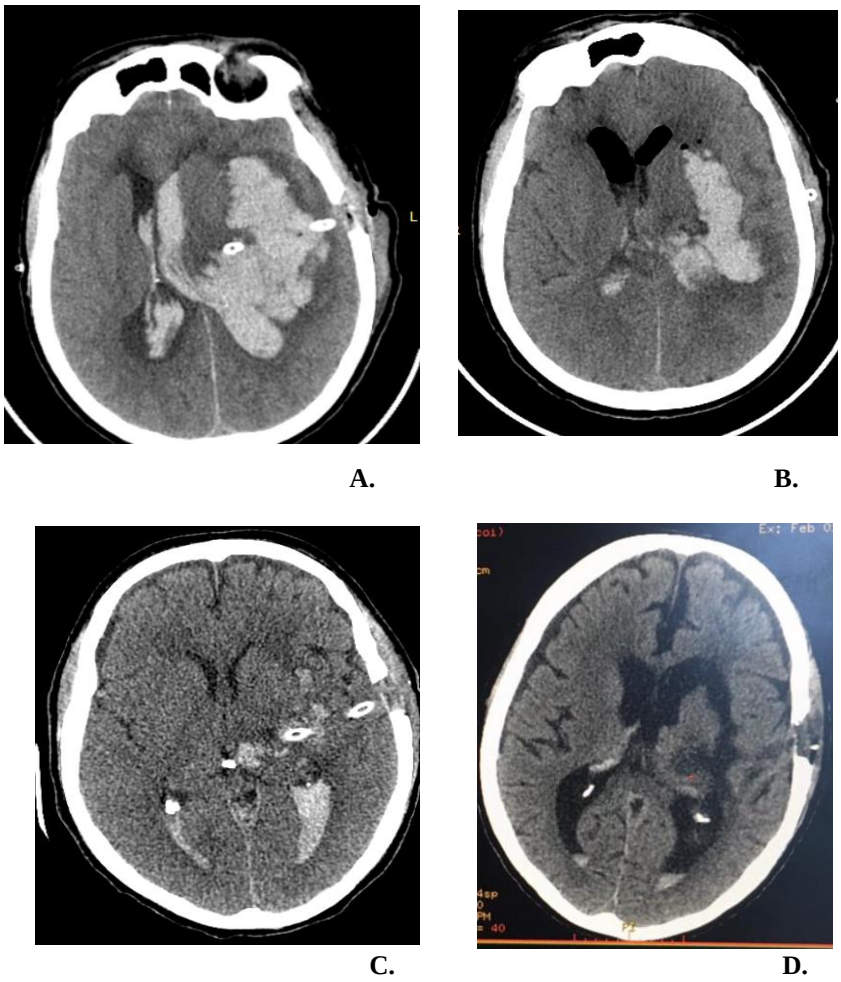

Fig.1 CT scan before and after the administration of the tPA.

(A) Before the administration of tPA, (B) Two times administration of the tPA, (C) Five times administration of the tPA, (D) 20 days after stroke.

Results

We performed surgery on 6 patients (3 males, 3 females) with spontaneous intracerebral hemorrhage (ICH). All patients had a hemorrhage located in basal ganglia. The mean age of patients was 56 years (from 47 to 72 years).

All case had mean hemorrhagic volume 58 mL (from 30 to 150mL) with intraventricular hemorrhage. Most the hemorrhages occurred on the right side (right - 4 patients (67%), left - 2 patients 23%)). At the time of admission BP ranged from 150/90 to 220/100 (mean 185 mmHg).

In addition, we used clinical and neuroradiology characteristics for GCS and ICH score.

Before the operation of consciousness the patients had 2 patients (33%) had 13 score and 2 patients (33%) 8 score, 1 patient (17%) - 10 score and 1 patient (17%) - 9 score of GCS.

The ICH score showed most patients (5 patients/82 %) had 3 point it means 72% mortality risk, and 1 patient/17% - 2 point, that is 26% mortality risk. (Table 1).

After treatment clot was reduced an all patients. No post-operative complications.

For measuring the degree of disability and recovery we used Glasgow Outcome Score and

Modified Rankine scale. After our treatment on the Glasgow Coma Scale 3 patients in result had moderately severely disability, one patient with moderately disability, one patient vegetative, and In the one patient died. The outcome in terms of Rankin Score showed that of 6 patients 5 patients/83% had severe disability (5 score) and 1 patient/17% had moderately severe disability (4 score).

Results are shown below in table format.

Patient	Age/sex	HV (volum, ml)	Site	BP (mm/Hg)	Location	GCS (before operation)	ICH score (before operation)	VH	Rankin Score	GOS
1	72/F	73	left	150/90	Basal ganglia	9	3	yes	5	3
2	55/M	81	right	190/70	Basal ganglia	10	3	yes	5	1
3	53/M	49	right	200/100	Basal ganglia	13	3	yes	5	3
4	61/M	150	left	180/90	Basal ganglia	8	3	yes	5	2
5	53/F	53	right	200/100	Basal ganglia	8	3	yes	5	3
6	47/F	30	right	220/100	Basal ganglia	13	2	yes	4	4

Tabl 1 Clinical characteristics

Results

The non-traumatically induced intracerebral hemorrhage is one of the most devastating subtypes of cerebrovascular diseases with extremely high mortality [1-3]. Hitherto, the 30-day mortality rate of ICH is 30-52% with half of such deaths occurring in the first 2 days, and only 20% of those surviving within 6 months [4, 5]. This statistic indicates imperfect treatment methods. Therefore, to date there is no clear standard for the management of spontaneous ICH.

Compared with conservative medical treatment, attempts at hematoma removal via conventional aggressive surgical treatment have failed to show more benefits for most ICH patients [2, 6].

Recently, alternative methods of surgical treatment have appeared, one of which is minimally invasive surgery with use of thrombolytic agents. That method is very encouraging for good treatment results.

The minimally invasive surgery plus recombinant tissue type plasminogen activator (tPA) helps with evacuation of clot, in this way decreasing the clot size and perihematomal edema thereby reducing brain compression.

In conclusion, with our study, this treatment at high rates of ICH score mortality showed low death rate. Predictors of favorable outcome are youth and smaller hematoma. Use of external ventricular drain with tPA allows drainage of hematoma regardless of depth.

In summary the minimally invasive surgery plus tPA help in evacuation if hematoma is more effective than surgical treatment or medication alone [7].

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MRI CINE Study In Chiari Malformation With Syringomyelia

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Abstract

Chiari malformation is often associated with syringomyelia, up to 85% being reported. It is a disorder of medosdermal origin with mixed neuroectodermal component. Surgical bony decompression remains the first line treatment in symptomatic patient with headache or medullary dysfunction. We looked specifically into the surgical outcome of Chiari malformation with syringomyelia in relation to clinical symptoms, functional grade and radiological features. We utilised statistical analysis to appraise the relationship between clinical findings and radiological parameters. This included length of tonsillar herniation, syrinx thickest diameter and length, syrinx: cord ratio, and cerebrospinal fluid (CSF) flow dynamics CINE sequence. Result showed significant correlation between clinical symptoms improvement and return of CSF flow in CINE study. There was no clinical correlation to other parameters despite its radiological improvement. Conclusion, CINE sequence is a useful tool. We recommend it as an adjunct to assess the adequacy of surgical decompression during long term follow ups and to anticipate early intervention.

Keywords: Chiari malformation, syringomyelia, MRI, CINE, posterior fossa decompression size.

Introduction

Chiari malformations were first described by John Cleland in 1882, then was later classified by Hans Chiari in 1891, into four major groups.[1] The term "Chiari malformation" has been used in recognition of the work of Hans Chiari, a Viennese pathologist, who practised medicine in Vienna, Prague and Strasbourg. He reported a case of 17 year-old woman with elongation of the tonsils and medial division of the inferior lobules of the cerebellum into cone shaped projections which accompany the medullar oblongata into the spinal canal.[2] It is a disorder of mesodermal origin with mixed neuroectodermal component. It has been hypothesised that para-axial mesoderm insufficiency after closure of the neural folds could lead to underdevelopment of the basichondrocranium, resulting a "crowded" posterior cranial fossa which can be of normal or small size.[3] A small posterior fossa and short clivus have been observed in two-thirds of Chiari I cases.[4] It is often associated with syringomyelia, up to 85% had been reported in Chiari I malformation.[5] It is a condition of fluid containing cavities in the parenchyma of the spinal cord.[6] For a long time, evolution of hypothesis from Gardner's hydrodynamic theory to William's craniospinal pressure dissociation and recent Oldfield or Ball and Dayan's Virchow Robin Space theory, many had attempted to describe the pathophysiology of syringomyelia and yet these theories are difficult to reconcile with clinical findings.[1,6] Posterior fossa foramen magnum decompression remains the standard surgery to restore CSF flow at the craniovertebral junction. However, there is currently no consensus about the best operative technique especially in the context of the extend of suboccipital bony decompression and use of dural graft.[7] There are no literature review on optimal size of posterior fossa suboccipital craniectomy. An inadequately small decompression likely unable to resolve the Chiari symptoms, likewise, excessive decompression will lead to cerebellar ptosis. Thus, surgical outcome remains variable and unpredictable. Those that experience poor long-term clinical outcome often require more surgery.[8] In this series, we evaluate the radiological features of Chiari malformation with syringomyelia, correlating to the surgical outcome in terms of headache symptoms, motor weakness, sensory deficit and clinical function. By utilising MRI Cine sequence, we study the CSF flow at level of foramen magnum before and after surgery, therefore, determining adequacy of the decompressive craniectomy that may influence the postoperative outcome.

Methods

2.1. Patient selection

Cross sectional study. Nine patients with symptomatic Chiari malformation type I and syringomyelia were included in a clinicoradiological study at Hospital Universiti Sains Malaysia, between January 2015 and June 2016. Radiographic criteria of inclusion were defined as tonsillar herniation of at least 4mm below the foramen magnum (McRae′s line) on mid-sagittal T1-weighted MR images. Patients with craniovertebral junction abnormalities, hydrocephalus, and syndromic craniosynostosis were excluded. All the 9 cases had posterior fossa foramen magnum decompression and C1 laminectomy. The characteristic for the 9 patients are summarised in Table 1.

2.2. Neurological Assessment

Preoperative clinical examinations were conducted by author or neurosurgeon. Functional grade was determined using modified rankin scale (MRS). The preoperative symptoms and signs were summarised in Table 1. The nine patients were followed-up in neurosurgical clinic postoperatively at six and twelve months and clinical assessment was conducted. Patients were classified as having improvement, similar or worsening of clinical symptoms. Improvement is defined as complete or partial clinical recovery of motor, sensory deficit or both.

2.3. Radiological Imaging

Radiological measurements pre and post operatively were conducted by a radiologist or neurosurgeon. MR images were stored in Picture Archiving and Communication System (PACS). Using T2-weighted imaging at mid-sagittal plane, tonsillar herniation, syrinx length, vertebral level of thickest syrinx diameter and syrinx: cord ratio were measured. Pre and post operative Cine CSF flow study were compared to assess the CSF flow at the anterior and posterior foramen magnum. Postoperative imagings were obtained between six and twelve months after surgery.

2.4. Surgery

All 9 patients underwent posterior fossa foramen magnum decompression and C1 laminectomy, in 3-pin Mayfield head clamp, prone position. Posterior midline incision, extending from inion to the C2 spinous process. Subperiosteal dissection to exposed suboocipital bone and posterior arch of C1. Standard suboccipital craniectomy was performed, 30mm height by 30mm width from the lip of foramen magnum. C1 laminectomy encompassed removal of posterior arch, measured at 15mm in length. Dura was opened in ″Y″ shape till cervical spinal cord. Atlanto-occipital band was released. Arachnoid layer was protected with cottonoid petty during durotomy. The arachnoid layer was kept intact to prevent CSF leak or pseudomeningocoele. Tonsils were not resected and obex not opened. Durofascioplasty was performed using harvested fascia, measured about 20mm x 20mm. Care was taken during the closure to ensure no blood spilled intradurally. Cottonoid petty remained to cover the arachnoid plane till duroplasty complete. Layers were approximated in layers in an order of muscle, fascia, subcutaneous and skin. Interrupted sutures were used in all layers except fascia plane in which continuous suture was applied. The mean duration of operation 90 minutes.

2.5. Statistical Analysis

IBM SPSS version 24 was utilised to analyse the data to appraise relationship between radiological signs and clinical symptoms or functions (MRS) to evaluate the adequacy of surgical decompression. P value of less than 0.05 was considered significant.

Results

3.1. Demographic data

Nine cases were surgically treated. There were 6 females and 3 males, with their age ranged 15-41 years old (majority were adolescent age group, 55.6%). Six patients had headache or neck pain as presenting symptoms, which were valsalva or cough exertional in nature. The headache was either occipital in origin or at nape of the neck. The onset of symptoms was gradual and most of them were not able to accurately tell when the symptoms started. Mean duration symptoms was 24 months. Their symptoms progressively worsened over the years to associate with limb weakness and sensory deficit. Four had quadriparesis, 3 had bilateral upper limb weakness and 2 had unilateral upper limb weakness. Two of the quadriparetic patients had poor functional MRS of 5. Majority (n=5) of them had MRS of 3, 1 had MRS of 2 and another had 4. In case 5, the patient presented with relatively short history of 2-month progressive quadriparesis and admitted in acute setting for type 2

respiratory failure, requiring ventilatory support. In case 9, the patient had scoliosis progression with chest discomfort and neck pain, associated with small hand muscles wasting and bilateral upper limb numbness. None had cerebellar symptoms. Refer table 1.

Tab. 1. Demographic, clinical and radiological data

Case No.	Age (yrs), Sex	Duration of symptoms (mos)	Headache/ Neck pain	Motor deficit	Sensory loss	MRS (Preop)	Radioimaging (MRI)			
							Tonsillar herniation	Syrinx length (Total level)	Syrinx thickest level	Syrinx: Cord ratio
1	24, F	66	Y	Quadriparesis	C4-S4 (Both)	5	10.3mm	C2-T10 (16)	C6	0.68
2	15, M	36	N	UL weakness (L)	C5-C8 (L)	3	11.6mm	C1-T12 (19)	C6-C7	0.88
3	52, F	240	Y	Quadriparesis	C5-S1 (Both)	4	11.0mm	C4-T10 (14)	T3	0.48
4	41, F	24	Y	UL weakness (Both)	C6-T1 (Both)	2	5.1mm	C2-C6 (5)	C5	0.83
5	19, F	2	N	Quadriparesis	C2-L5 (Both)	5	9.0mm	C2-T11 (17)	T2-T3	0.61
6	23, F	20	Y	UL weakness (Both)	C8-T1 (Both)	3	11.3mm	C1-T8 (15)	C5-C6	0.91
7	15, M	21	Y	Hemiparesis (R)	C4-T4 (R)	3	4.8mm	C2-T8 (14)	T3-T4	0.68
8	20, M	6	N	Quadriparesis	C5-S1 (Both)	3	16.0mm	C1-C6 (6)	C4-C5	0.75
9	16, F	24	Y	UL weakness (Both)	C4-T1 (Both)	3	10.0mm	C3-L3 (20)	C6-C7	0.83

*Y = Yes, N = No, UL = Upper limb, L = Left, R = Right

Tab. 2. Surgical outcome in Chiari series

Case	Pre Op	Post Op							
		Functional grade/ Clinical symptoms				Radiological (MRI and CT)			
	MRS	MRS	Headache	Motor	Sensory	CINE CSF flow study	Syrinx length	Syrinx: Cord ratio	Decompression (cranial & C1 laminectomy)
1	5	5	C	S	S	No	Same	0.58 (Reduced)	B35mm, C17mm
2	3	3	NA	S	S	Return	Same	0.82	B30mm, C16mm
3	4	2	C	I	R	No	Reduced	0.32 (Reduced)	B34mm, C15mm
4	2	2	C	S	S	No	Resolved	0.20 (Reduced)	B36mm, C13mm
5	5	5	NA	S	S	No	Reduced	0.67	B33mm, C16mm
6	3	2	C	I	R	Return	Reduced	0.69 (Reduced)	B40mm, C14mm
7	3	2	C	R	S	Return	Same	0.57 (Reduced)	B35mm, C13mm
8	3	2	NA	I	R	Return	Reduced	0.45 (Reduced)	B35mm, C13mm
9	3	3	C	S	I	Return	Same	0.88	B31mm, C15mm

**NA = Not applicable, C = completely resolved, S = Similar, R = Recovered, I = Improved

3.2. Preoperative radiological findings

All the 9 cases were Chiari type 1 with tonsillar herniation and syringomyelia. None had hydrocephalus or other associated cranial anomalies, especially craniovertebral junction disease. Mean tonsillar herniation was 9.9mm. The syringes were large, spanning at mean length of 14 vertebral level and thickest at cervical region.

3.3. Preoperative radiological findings and clinical symptoms correlation

We analysed the preoperative radiological parameters to the severity of clinical symptoms and functional grades. The parameters included syrinx: cord diameter ratio, syrinx length, length of tonsillar herniation and thickest area of syrinx. There was no strong correlation between the radiological signs and pre-operative clinical symptoms or functional grades.

3.4. Radiological outcome

Mean suboccipital bony decompression diameter was 33.8 mm ± 3.18, and C1 posterior arch diameter of 14.8 mm ± 1.38. These were measured from computed tomography (CT) brain conducted a day after the surgery. Seven patients (77.0%) showed radiological improvement after the surgery. They either showed reduction in syrinx length (n=2), syrinx: cord diameter ratio (n=1), or both (n=4). The syrinx length reduction ranged from complete resolution to 6 vertebral body levels. The post-operative syrinx: cord diameter ratio ranged from 0.20 to 0.69, showing up to 75% of significant reduction. The mean pre-operative syrinx length in vertebral level and syrinx: cord ratio were 12 ± 0.22 and 0.74 ± 0.14 (minimum 0.48, maximum 0.91). After the surgery, the syrinx length and syrinx: cord ratio were 14 ± 5.24 and 0.58 ± 0.22 (minimum 0.20, maximum 0.88). There was statistical significant improvement in the syrinx length and syrinx: cord ratio and after the surgery, p-values were less than 0.05.

Tab. 3. Pre and Post operative syrinx: cord ratio

		Mean (SD)	Mean diff (95% CI)	df	p-value
Syrinx length in vertebral level	Pre-op	14.00 (5.24)	2.00 (0.16, 3.84)	8	0.037
	Post-op	12.00 (0.22)			
Syrinx: cord ratio	Pre-op	0.74 (0.14)	0.16 (0.01, 0.33)	8	0.040
	Post-op	0.58 (0.22)			

*Paired T-test, data was normally distributed

3.5. Neurological outcome

All the 6 patients who experienced headache or neck pain had complete resolution of symptoms post operatively without analgesia. Five out of 9 patients (55.6%) had neurological improvement after the surgery, either motor (n=1), sensory (n=1) or both (n=3). Those 3 patients that showed both symptoms improvement had full recovery of sensory loss and residual weakness with motor power of 4 to 4+/5 (Medical Research Council Grading). Whereas for the other 2 patients, one had full motor recovery with similar sensory deficit and another had only slight sensory deficit recovery. The remaining 4 patients (44.4%) reported no improvement. None had worsening of neurological deficit after the surgery. Four patients (44.4%) showed improvement in functional assessment after the surgery. Three had MRS grade 3 improved to 2 and one had MRS grade 4 improved to 2. They were able to ambulate and carry out daily living without assistance despite some disability. Five other patients function remained the same after surgery, in which 2 patients who had poor MRS 5 pre-operatively remained bed ridden and fully dependent.

3.6. Neurological outcome and radiographic correlation

In this series, 7 patients achieved radiological improvement after the surgery, but only 4 showed clinical neurological and functional improvement at 1 year. We did subgroup analysis and divided into 2 groups based on CSF flow. For those that clinically improved, CINE CSF dynamic study demonstrated good return of CSF flow at anterior and posterior craniovertebral junction, see figure 1. This is statistically significant in the Fisher's exact test (X^2=5.76, $p<0.05$). Peak velocity CSF flow waveforms at foramen magnum showed normal bidirectional sinusoidal waveform. On the other hand, those with only radiological improvement had restricted or no CSF flow at the level of foramen magnum. Its peak velocity CSF flow showed multiple short upward and downward pulsations indicating spatial inhomogeneity in velocities without sinusoidal pattern.

Otherwise, we found no correlation between the degree of improvement in functional grades to the other radiological parameters changes through Fisher's exact test ($p>0.05$). This included syrinx length and syrinx: cord ratio reduction.

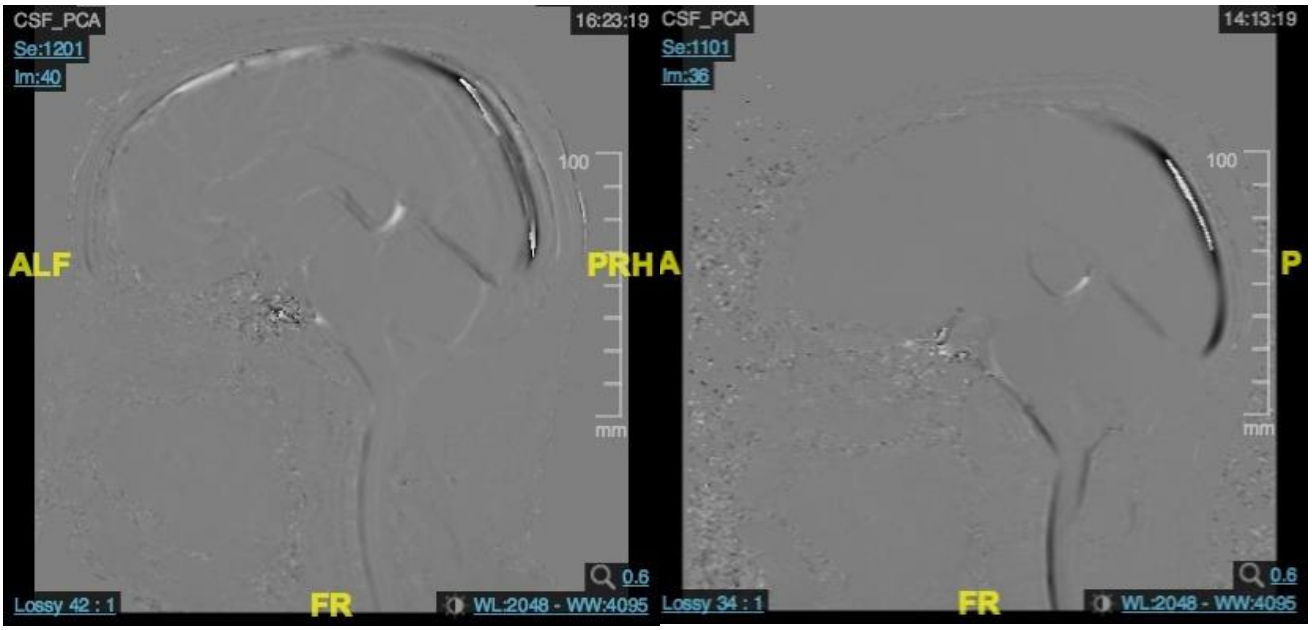


Figure 1. MRI CINE showed pre and postoperative CSF flow at posterior foramen magnum (right).

3.7. Surgical complications

We encountered no major bleeding, cerebellar ptosis, CSF leak or meningitis postoperatively.

Discussions

Chiari surgery involves a surgical decompression of the craniovertebral junction to provide space necessary to decompress the cerebellar tonsils and allow the CSF to flow freely between the posterior fossa and the upper portion of the spinal subarachnoid space.[9] Each individual patients require a different degrees of surgery for a successful outcome. This include the size of bony decompression, C1 laminectomy, durotomy, arachnoidotomy, tonsillar resection, obex exploration or shunt. It has to be balanced by weighing the risk of complications such as CSF leak, pseudomeningocoele and arterial injury.[10] Although least amount of surgical procedure is less likely to be associated with complications, it is also less likely to accomplish the goals of the procedure in 5-20% of Chiari patients. This leads to another surgery.[10] Magnetic resonance imaging (MRI) era has revolutionised the Chiari surgery. Many techniques had developed. The commonest being a simple bone decompression which is usually effective with minimal complications. On the other hand, posterior fossa decompression and durofascioplasty provide the advantage of visual access to subarachnoid space to inspect for arachnoiditis, dural or arachnoid band and arachnoid cyst. Through this technique, some may preserve the arachnoid membrane in the consideration of greater incidence of complications.[9]

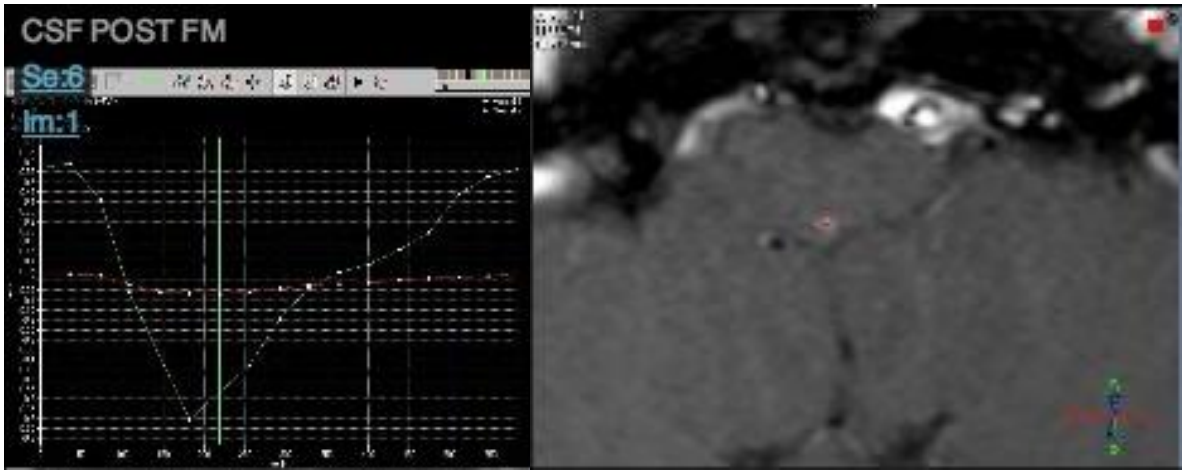
4.1. Size of posterior fossa bony decompression

Many studies had reported various sizes of bony craniectomy leading to optimal foramen magnum decompression. However, it has been known that large bony decompression is associated with complication of cerebellar ptosis.[9, 11, 12] Holly and Batzdorf reported 4 of their 7 cases who underwent second surgery for cerebellar ptosis, had previous bony decompression more than 40 x 40mm.[11] Duddy and Williams observed cerebellar ptosis in 59% of their case, but only 2 had worsened symptoms. Their posterior fossa bony decompression size was 40-50mm in height and 30-45mm in width. Asymptomatic cerebellar ptosis was more common following Chiari surgery, however, majority of those cases were not severe trigger craniospinal pressure dissociation.[12] Cerebellar ptosis is also more common in cases without durotomy repair.[13] Likewise, a small bony decompression does not serve its purpose in the case of Chiari with syringomyelia. Noudel et. al. addressed that 30 x 30mm bony decompression prevents cerebellar ptosis but with higher rate of additional surgery or intervention, up to 30%. Caldarelli et. al. reported overall good clinical outcome in limited suboccipital craniectomy in Chiari malformation, approximately 20mm in height, 25mm in width. However, only half of their 12 cases with syrinx showed mild clinical improvement.[14] Sindou et. al. performed triangular shape (size about 35mm in height x 30mm in width) with extreme lateral opening of the foramen magnum rim till the occipital condyles on either side. Good outcome (Kanofsky more than 60) was reported in 74% of Chiari patients with syringomyelia though only 60% showed radiological improvement.[15] Noudel et. al. reported 36%

excellent outcome in a 11 patients series that underwent bony decompression of 30mm in width and C1 laminectomy 15mm. Those 4 completely recovered patients achieved at least 14% increment of posterior fossa volume. Outcome was better in patients with smaller starting volume. The remaining patients had partial treatment response achieved less than 9% of posterior fossa volume increment.[16] Quon et. al. had otherwise revealed no significant correlation between change in posterior fossa volume and clinical improvement.[17] Nonetheless, we performed bony decompression at size of more than 30 x 30mm but no greater than 40 x 40mm. Literature review showed the Chiari surgical outcome with different technical modalities ranged from 53-100%.[18] Each technical modalities demonstrated its limitations due to the wide range clinical variability of Chiari patients.

4.2. Supplementary MRI CINE for CSF flow study

Our series performed similar surgical procedure to all the 9 patients. The result showed that radiological improvement does not equate to clinical or functional recovery. Standard posterior fossa bony decompression may provide anatomical correction, however, clinical outcome remains variable if the CSF flow dynamic is not restored. MRI provides the capacity to assess the CSF spaces beyond the bony margins.[9] The impact and extent of decompression on the overall CSF flow can be assessed by utilising phase-contrast MRI as a useful non-operative tool in CINE sequence. This sequence captures pulsatile flow dynamics to measure the amplitude and direction of CSF and blood flow relative to anatomical structures, particularly in patients with CSF obstruction. CSF flow during cardiac cycle demonstrates bidirectional craniospinal displacement. In pulsatile flow theory, during systole, increase in cerebral blood volume and CSF is displaced caudally via dorsal subarachnoid space of foramen magnum. when diastole comes, the elastic recoil of spinal dura propels the CSF in a reverse caudocranial direction towards the intracranial compartment via ventral subarachnoid spaces.[19] Ventrureyra et. al. showed that symptoms correlated well with abnormal CINE flow imaging as compared to anatomical changes. It is commonly used in asymptomatic Chiari patients when there is uncertainty of surgical benefit based on anatomical abnormality.[20] Quon et. al. reported 3 Chiari patients with postoperative obstructed CSF flow only showed slight clinical recovery despite good radiological improvement. Size of the standard bony decompression was no mentioned in the study. Overall, Quon et. al. had showed 88.9% of Chiari patients with CSF flow restoration had some improvement in their headaches. These patients achieved partial or complete clinical improvement.[17] Our series had demonstrated that the standardised size of bony decompression was not adequate in 5 patients. They did not show clinical improvement even though the syrinx became smaller. There was no return of CSF flow in CINE study at level of foramen magnum. Conventionally, longer duration follow-up up to 2 years may be required to observe the clinical outcome or functional recovery. On the other hand, patients with CSF flow restoration with sinusoidal pattern showed both clinical and radiological improvement as early as 3 to 6 months, see figure 2. Thus, with the use of serial CSF flow studies as adjunct, it can provide a guide to anticipate neurological recovery, meanwhile also act as an early assessment tool to those



potential Chiari patients that require early re-intervention.

Figure 2. Peak velocity CSF flow waveforms at foramen magnum shows normal bidirectional sinusoidal waveform.

Conclusion

Chiari with syringomyelia is a challenging disease in neurosurgery and its surgical outcome remains variable despite many technical modalities. The standardised surgical bony decompression is not adequate in all Chiari cases. CINE CSF flow study provides an early assessment to clinical recovery. Therefore, second look surgery or alternatives can be anticipated and tailored to individual patient to achieve early intervention and better surgical outcome.

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Neuronavigation Versus Traditional C-Arm Flouroscopy In Transsphenoidal Surgery For The Excision Of Pituitary Macroadenomas: A Comparative Study From The University Of Santo Tomas Hospital, Philippines

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Abstract

INTRODUCTION: Transsphenoidal surgery (TSS) with C-arm fluoroscopy for excision of pituitary adenomas remains one of the safest procedures in contemporary neurosurgical practice. However, it is not without complications. The most severe, potentially fatal, complication of this surgery is injury to the internal carotid artery (ICA) causing intra- and postoperative bleeding and among others, optic nerve injury, hypothalamic injury, and CSF leaks. Since the most likely cause of these serious complications during transsphenoidal surgery is localization and misdirection, neuronavigation may be beneficial, if not, a better instrument to aid surgeons in transspehnoidal surgery.

OBJECTIVE: To determine any significant surgical advantage of using neuronavigation as compared to the traditional C-arm fluoroscopy in transsphenoidal excision of pituitary adenomas in terms of (1) intraoperative blood loss, (2) operative duration and (3) complication rate.

METHOD: This is a retrospective cohort study from the University of Santo Tomas Hospital of all cases of non-functioning pituitary macroadenomas from January 2014 to July 2016 who underwent transsphenoidal surgery whether by C-arm flouroscopy or neuronavigation. Both groups were compared and analyzed to determine any significant statistical differences.

RESULTS: A total of 37 patients were included in this study divided into 2 groups namely, TSS + C-arm (n=25) and TSS + NN (n=12). The mean blood loss for the latter group was 220.8 mL which was significantly lower to the 284 mL mean blood loss of the former (p=0.005) at 95% level of significance. The mean operative duration of patients under the TSS + NN group was 2.6 hours which was shorter than that of the control group at 2.9 hours but was not significantly different (p=0.077) at 95% level of significance. There were 2 cases with complications noted from the TSS + C-arm group and none for TSS + NN group. However, these did not show any statistical significance.

CONCLUSION: It can be concluded that neuronavigation for the transsphenoidal surgery of non-functioning pituitary macroadenomas is not a requirement, but an advantageous adjunct that may be beneficial to both surgeon and patient.

Keywords: pituitary adenoma, transsphenoidal surgery, neuronavigation, C-arm fluoroscopy

Introduction

Transsphenoidal surgery (TSS) for excision of pituitary adenomas remains one of the safest procedures in contemporary neurosurgical practice. It must be taken into account that even if carried out its "classical" way, with the use of a speculum, it has always been considered minimally invasive. In this approach, a small sublabial incision is created and the nasal aperture dissected and enlarged to allow the surgeon access through the natural anatomical corridor of the sphenoid sinus and eventually the sella. The surgeon's line of sight is defined by the long and narrow tunnel through which the beam of the microscope reaches the region of interest and thus, the most common problem and most likely cause of serious complications during transsphenoidal surgery is localization and misdirection.[1]

Traditionally, the C-arm fluoroscope has been the companion of choice to guide the surgeon through the bony passage leading to the sella. It is still the most frequently practiced method of both navigation and intraoperative imaging. This has been effective and vastly used however, only bony structures of the skull are visible with the use of an image intensifier. It at least allows an anatomical orientation of the surgeon by visualization of radiopaque instruments such as steel, curettes and forceps in relation to the bony skull base. It is also generally used to direct the nasal speculum towards the sella thus, minimizing the effort of dissection. Most transsphenoidal surgeons have used this to date as the standard procedure allowing orientation. The major disadvantage is that it does not directly visualize soft tissues or vascular structures. Radiation exposure and the space consuming size of the C-arm within the operating room are other concerns.[2]

The advent of image guided surgery was one of the major innovations of the past decade. Conceptually, the generated 3D preoperative image data is merged with the patient's anatomy by registration. Once registration is accurate, the surgeon can work in the mathematical space (Cartesian coordinate system) of the brain image that is the same as the physical space under optimum conditions.[3] In other words, in the operating theatre, this technology allows the surgeon to navigate to any anatomical landmark or radiologically evident pathological target with precision and safety. Thus, the realistic image of the operative field can be related to the virtual reality of the 3-dimensional data set as it is delivered by the imaging procedure. One of the major advantages of these systems is that selected anatomical landmarks, vascular structures, tumor dimensions and other targets can be manually or automatically segmented and finally superimposed on the surgeon's field of view. Hence, potential operative hazards can be readily recognized by the surgeon while he is carrying out the dissection.[2]

With the use of the neuronavigation system, many problems of using the C-arm alone can be addressed. The anatomical structure of the sphenoid sinus and sella can be precisely and dynamically identified during the surgery and excision of the tumors can be accurately judged and therefore the surgical outcome improved.[1] A definite advantage of such a system is the ability to accurately locate the tumor and surrounding structures at any given time thus, effectively avoiding misdirection.[4] Moreover, because of its surgical advantages in the operative field, various intra- and postoperative complications may be avoided. This study aims to determine the surgical advantages of using neuronavigation in terms of intraoperative blood loss, operative time, and complication rate for patients undergoing transsphenoidal surgery for pituitary macroadenomas.

Objectives

2.1. General Objective

To determine any significant surgical advantage of using neuronavigation as compared to the traditional C-arm fluoroscopy for excision of pituitary macroadenomas in the University of Santo Tomas Hospital.

2.2. Specific Objectives

1) A. To determine if there is significantly lower intraoperative blood loss in transsphenoidal surgeries assisted by neuronavigation (BRAINLAB) as compared to the traditional C-arm fluoroscopy

B. To determine if there is significantly shorter intraoperative duration in transsphenoidal surgeries assisted by neuronavigation (BRAINLAB) as compared to the traditional C-arm fluoroscopy

2) To determine if there is a significantly lower complication rate between transsphenoidal surgeries assisted by neuronavigation (BRAINLAB) as compared to the traditional C-arm flouroscopy

Methodology

3.1. Study Design

This is a retrospective cohort study of all cases of non-functioning pituitary macroadenomas from January 2014 to July 2016 who underwent transsphenoidal surgery at the University of Santo Tomas Hospital in either Private or Clinical Divisions. Information was collected and reviewed from the medical records and the database of the section of Neurosurgery. Two groups emerged, namely (1) control group (TSS + C-arm), encompassing those who underwent transsphenoidal surgery assisted by C-arm flouroscopy; and (2) treatment group (TSS + NN), those who underwent transsphenoidal surgery assisted by the neuronavigation system (BRAINLAB). Out of the 37 patients included in this study, 25 underwent TSS with C-arm flouroscopy while 12 proceeded with TSS with neuronavigation (NN).

Patients were eligible for inclusion if they were 18 years of age or older, diagnosed with pituitary macroadenoma (tumor diameter > 1 cm) and supported by a contrast-enhanced cranial CT or MRI. Exclusion criteria entails patients with concomitant bleeding diasthesis, tumor histopathology other than pituitary adenoma, an endocrinologic functioning pituitary tumor, had undergone previous transsphenoidal surgery and those with clinical or radiological diagnosis of apoplexy.

All transsphenoidal surgeries were performed at the University of Santo Tomas Hospital (USTH). Neuronavigation as provided for by BRAINLAB (Medtronic) was rented from RBMB Medical Inc. Data collection was mainly through the hospital's medical records and the census from the Section of Neurosurgery.

3.2. Statistical Analysis

Categorical Variables were presented in Counts (Percentages %). Fishers Exact Chi-Square Test was used to determine significant association. Continuous Variables were presented in Mean ± Standard Deviation (Minimum, Maximum). Non-Parametric Mann Whitney Test was used to compare the two groups. The statistical software used to compute significance was SPSS v21.

Results

4.1. Demographics and Patient Profile

A total of 37 patients were included in this study, all of whom underwent transsphenoidal surgery for excision of a non-functioning pituitary macroadenoma. After further data gathering, 2 groups emerged namely, TSS + C-arm or the control group (n=25) and the TSS + NN or treatment group (n=12). Gender differences in both groups are not significant as shown in Table 1 (p=1.000) making both groups comparable. Other variables such as age and size also do not show any significant differences (p=0.883, p=0.140), respectively.

Tab 1. Patient Profile

	Total n=37	TSS + C-arm (n=25)	TSS + NN (n=12)	P-value
Gender				
Male	14 (37.8%)	9 (36%)	5 (41.7%)	1.000

Female	23 (62.2%)	16 (64%)	7 (58.3%)	
Age (years)	46.8 ± 11.2 (26, 71)	47.2 ± 11.7 (28, 71)	46.1 ± 10.3 (26, 61)	0.883
Size (cm)	3.7 ± 0.4 (3, 4.5)	3.7 ± 0.4 (3.1, 4.5)	3.5 ± 0.3 (3, 4)	0.140

Tab 2. Other statistics

	Total n=37
Group	
TSS + C-arm	25 (67.6%)
TSS + NN	12 (32.4%)
IBL (mL)	263.5 ± 64.2 (200, 400)
Duration (hour)	2.8 ± 0.5 (2, 4)
With Complications	2 (5.4%)
DI	1 (2.7%)
Hematoma	1 (2.7%)

4.2. Intraoperative Blood Loss

When intraoperative blood loss (IBL) of each patient included in the study were gathered, the following information were obtained. First, the range of blood loss for the TSS + C-arm group was from 200 – 400 mL while for the TSS + NN group, 200 – 300 mL. Second, the mean blood loss for the latter group was 220.8 mL which was significantly lower to the 284 mL mean blood loss of the former (p=0.005) at 95% level of significance (Table 3).

Tab 3. Intraoperative Blood Loss (IBL)

	TSS + C-arm (n=25)	TSS + NN (n=12)	P-value
IBL (mL)	284 ± 65.7 (200, 400)	220.8 ± 33.4 (200, 300)	0.005

4.3. Operative Duration

When comparing the operative duration of both groups, different results were obtained. The mean operative duration of patients under the TSS + NN group was 2.6 hours which was shorter than that of the control group at 2.9 hours but was not significantly different (p=0.077) at 95% level of significance. However, at 90% level of significance (significant if p-value < 0.10), the operative duration of patients who underwent TSS + NN becomes significantly shorter than that of the control group as seen in Table 4.

Tab 4. Operative Duration

	TSS + C-arm (n=25)	TSS + NN (n=12)	P-value
Duration (hours)	2.9 ± 0.6 (2, 4)	2.6 ± 0.3 (2.3, 3)	0.077*

**Significant if p<0.1 at 90% confidence interval*

4.4. Complication Rate

Only 2 complications were noted in the entire study namely, Diabetes Insipidus and postoperative hematoma. Both of these complications were observed from the TSS + C-arm group while none were noted from the TSS + NN group. Diabetes Insipidus in one patient was diagnosed through a laboratory panel while patient with postoperative hematoma was evidenced by a plain cranial CT scan. The latter patient eventually required a reoperation to evacuate the hematoma. There is no significant difference between the complication rates of both study groups (p=1.000) (Table 5).

Tab 5. Complications

	TSS + C-arm (n=25)	TSS + NN (n=12)	P-value
Complications	2 (8%)	0 (0%)	1.000
Diabetes Insipidus	1 (4%)	0 (0%)	
Postoperative Hematoma	1 (4%)	0 (0%)	

Discussion And Conclusion

Over the years, transsphenoidal surgery with C-arm fluoroscopy is the most widely used surgical modality for the removal of pituitary tumors aided by the 2-dimesional image generated through fluoroscopic x-ray technology. Though several reports and studies show low morbidity and mortality rates with the C-arm used, there are still pitfalls with this method. The most severe, potentially fatal, complication of this surgery is injury to the internal carotid artery (ICA) particularly during dural incision in the sellar base, which has a reported incidence of 0% - 3.8%. When the ICA is injured, even if hemostasis is achieved intraoperatively, development of stenosis, fistulas or pseudoaneurysms of this artery may ensue.[5] Another such complication is inadvertent hypothalamic and optic nerve injury which can also be brought about by suboptimal definition of the borders and depth of tumor resection. Since C-arm fluoroscopy only gives a 2-dimensional image of the osseus anatomy of the skull, its use is limited only to guide the surgeon from the surgical opening to the sella and not much with vascular and soft tissue visualization, more so, tumor resection. Surgeons may have disorientation during transsphenoidal surgery due to patient anatomic variation and the mere sagittal orientation of fluoroscopic image

guidance.[6] With the advent of neuronavigation technology which provides accurate intraoperative localization of even soft tissue and vascular structures at anytime, the aforementioned complications can theoretically be avoided.[4, 12]

Neuronavigation has been gaining popularity as an aid for better tumor resection of different intracranial locations including masses of the pituitary gland. The University of Santo Tomas Hospital, Section of Neurosurgery is one of these institutions which continue to tap the various applications of this technology in the field of pituitary surgery. In lieu of this recent endeavour, data from the last 3 years were gathered and analyzed in this retrospective study and showed statistically significant difference in intraoperative blood loss at 95% confidence interval in favor of the group with neuronavigation. This may be attributed to prompt localization and evasion of vascular areas which the neuronavigational system can accurately provide. Normal vital structures such as the internal carotid arteries and venous sinuses can be identified and avoided thus, vascular hemorrhages prevented and maximal safe resection achieved.[10] In the study of Seyithanoglu et al. in 2016, where 141 cases of transsphenoidal surgery were included, 69 patients for the fluoroscopy group and 72 for the neuronavigation group. He then noted 2 cases of ICA injury in the first group which contributed to significant blood loss and required profound hemostasis, while no case of neurovascular injury was noted in the neuronavigation group. Operative duration on the other hand was also measured and compared between the two groups. A significantly shorter operative duration for the TSS + NN group was shown at 90% confidence interval but not at 95%. One of the pillars to effective and efficient transsphenoidal surgery is proper directionality from incision to tumor excision. Neuronavigation eliminates difficulties in localization and guides the surgeon across the operative anatomy to reach the sella. This holds true especially during revision surgery where normal anatomical structures may be distorted or in situations dealing with sphenoid sinus pneumatization, multiple sphenoid sinus septae and even kinking of the internal carotid arteries.[9] Once at the tumor site, avoidance of vascular structures providing faster hemostasis and immediate localization of areas of interest may reduce overall operative time. In a paper by Zhao et al in 2006, it was stated that although an additional 16-20 minutes is added for preoperative setup and registration, neuronavigation is able to help surgeons tremendously through precise localization during surgery hence, the entire operative duration would not be prolonged at all. Due to the data gathered from this study, the advantage of neuronavigation regarding blood loss and operative duration in transsphenoidal surgery cannot be ignored. Although some experienced surgeons and experts are more comfortable and efficient doing it the traditional way, neuronavigation can be a vital tool in assisting less experienced surgeons. Based on literature by Sun et al in 2012, intraoperative neuronavigation systems can reduce post-operative complications associated with transsphenoidal surgery, especially the incidence of CSF leakage and the size of residual tumors. Conversely, in this local study, no statistically significant findings were noted regarding the complication rate of both groups despite the control group having 2 cases with complications and the treatment group having none. The difference may have been masked due to the limited number of subjects and may be recorded more accurately once a larger population is studied.

The advantages that neuronavigation may provide are not limited to the aforementioned parameters alone. Since neuronavigation makes use of preoperative imaging only, there is no radiation exposure involved as opposed to using C-arm fluoroscopy.[7] Moreover, surgeons are not required to use heavy lead gowns which are a hindrance for mobility during the operation. The absence of a large bulky C-arm in the operating room would also allow added mobility for the surgeon and surgical assists. These are some unquantifiable factors which further affirms the benefit of neuronavigation.

To further assess the effectiveness of this modality, the ideal parameter to measure would be completeness of tumor removal. In future research, pre- and postoperative imaging must be obtained and compared to determine any significant difference regarding the amount of tumor excised between the two methods. Moreover, functioning pituitary adenomas can be included in future studies, using pre- and postoperative hormonal parameters as gauge for adequacy of tumor removal. Another recommendation may be increasing the number of subjects to further strengthen the power of the statistical findings.

On the contrary, neuronavigation is far from perfect and has several downsides. All these systems use images, mainly CT or MRI, acquired preoperatively, on which the planning of the operative procedure as well as its intraoperative performance is based. Several potential sources of error may manifest such as inaccurate registration due to scalp movement, geometrical distortion in the images, and movement of the patient with respect to the system during surgery. Another source of inaccuracy is the so-called brain shift or movement of the brain relative to the cranium between the time of scanning and the time of surgery. As dynamic changes of the surgical field regularly occur during the surgical procedure, the surgeon is faced with a continuously changing intraoperative field for which the preoperative data does not provide any information.[3] Other disadvantages are the additional expenses that it entails. Preoperative imaging used must at the specifications ready for neuronavigational use. If the CT or MRI is not compatible, then one has to be repeated accordingly. The use of the system's machine and instruments also involves additional costs.

With the data and outcome shown in this study, and despite this technology's limitations, it can be concluded that neuronavigation for the transsphenoidal surgery of non-functioning pituitary macroadenomas is not a requirement, but an advantageous adjunct that may be beneficial to both surgeon and patient.

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New Cannula For Brain Delivery Drugs, Experience With Oncolytic Virus Infusion For DIPG

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Abstract

Purpose: Drugs infusion in the brain needs special cannulas to ensure proper delivery and to avoid back flow.

Oncolytic viruses are an emerging new treatment for brain tumors that must be injected into the tumor to be effective.

Alcyone MEMS cannula (AMC) has been designed to provide a precise convection-enhanced delivery directly to a neurological target. It has two lumens that can be used to infuse two different drugs at the same time.

Material and methods: A phase I clinical trial for pediatric DIPG with an oncolytic adenovirus, DNX-2401, uses the AMC to inject the virus directly into the pons.

Gadolinium (Gd) was infused through the second channel. Procedure overview was as follow: Dilution of the Gd (Gadovist 1.0M) with saline to 5-20mM, insertion of the AMC on a planned trajectory. Infusion of 150uL of Gd. Then infusion of 1mL of the DNX-2401. Removal of AMC and performance of a magnetic resonance (MRI).

Results: 4 patients have been treated following this clinical protocol. MRI following Gd and virus infusion showed a ring of contrast in the planned target in all the patients with no back flow. A Gd concentration of 5mM was infused in the first patient, with a slight signal in T1 3D sequences, so it was increased to 20mM for the next patients, with a more intense signal. No complications have been registered.

Conclusion: The AMC is a useful device for drug delivery into the brain, which can be used to infuse one or two drugs, avoiding back flow.

Keywords: Convection enhanced delivery, oncolytic virus, diffuse pontine gliomas.

Introduction

Malignant brain tumors are very aggressive tumors that frequently have a very dismal prognosis. New therapies are needed to fight against the tumor cells. New therapies are emerging, as oncolytic virus, that can infect tumor cells but not normal ones. Diffuse Intrinsic Pontine Gliomas (DIPG) are among the most malignant type, with an overall survival (os) of 12m [1].
The brain blood barrier (BBB) is supposed to be an obstacle for some drugs with big molecules, and systemic toxicity is other obstacle that limits the drugs concentration in brain tumors. Direct brain infusion treatments would avoid both limitations, opening more options for new therapies in these tumors. However, brain parenchyma is delicate and to avoid damages and neurological deficits, new cannulas are needed.

Convention enhanced delivery (CED) is a drug delivery method where the drug is introduced in the brain with one or multiple microcatheters and a pump. The materials and designed of the tip will be very important for the drug distribution[2].
CED has not been successful yet in brain tumors, because 1-we have not the right agent to be delivered, 2-tumors cells have or develop multiple mutations, being resistant to certain drugs, 3. The catheters employed where not appropriate, because they had back-flow and a poor volume distribution.

In this report we want to present a new cannula (Alcyone MEMS Cannula, AMC®) designed for brain infusion and used to deliver an oncolytic adenovirus in brain tumors[3].

Material and Methods

All the patients enrolled until August 2018 in the phase I clinical trial for pediatric DIPG with an oncolytic adenovirus, DNX-2401, were included along with compassionate use patients following the same protocol. During the trial the AMC was used to inject the virus directly into the pons.

Gadolinium (Gd) was infused through the second channel, as a surrogate marker to see the infusion volume in the intraoperative MRI performed after the virus infusion.

Procedure overview was as follow: Dilution of the Gd with saline to 20mM, insertion of the AMC on a planned trajectory. Infusion of 150uL of Gd. Then infusion of 1mL of the DNX-2401. Removal of AMC and performance of a magnetic resonance (MRI).

Results

From December 2017 to August 2018, 5 patients have been treated following this clinical protocol (Clinical trial.gov: NCT03178032) [4] and 4 as compassionate use. A transcerebellar, transpeduncular trajectory was performed in all the patients.

The infusion of the contrast was 10 minutes long, and the 1 mL of virus took 67 minutes.

The MRI performed after the Gd and virus infusion showed a ring of contrast in the planned target in all the patients but one and no back flow were detected.

A Gd concentration of 5mM (Magnevist ®) was infused in the first patient, with a slight signal in T1 3D sequences. (Gadavist®) was used in the next patients and it was increased to 20mM with a more intense signal. No complications have been registered.

In the last patient the signal of contrast was not seen in the MRI, we were not sure about its meaning, whether it was because the tumor tissue or secondary to a failed dilution of the gadolinium.

The mean tumor volume was 31.19cc (54.25-16cc) and the Gd plus virus injected volume was 3.07cc (Table 1).

Discussion

Drug delivery directly into the brain tumor opens new options of treatment in brain tumors. Specially, in deep sited tumors.

Oncolytic adenovirus must be injected in the tumor because in the bloodstream could be eliminated before reaching the tumor.

All but one received Gd 20mM and 1mL of virus and the infusion rate was 15uL/min, what is faster than previous publication (10 uL/min published in the literature)[5].

This could not be named as CED since it is a short infusion, so maybe a more proper denomination should be an intraparenchymal fast infusion.

Because the virus replicated in the tumor cells we did not need to cover the complete tumor volume with the infusion. 1 or 2 trajectory were performed in each patient, one for the biopsy one for the virus injection or whenever possible just one trajectory but the virus was infused 1cm deeper from the biopsy site.

There were none or minimal back flow.

Conclusions

The AMC is a useful device for drug delivery into the brain, which can be used to infuse one or two drugs, or one agent plus one marker, through one trajectory.

1mL can be infused in 67min, with a good volume distribution
The AMC avoids back flow so there is no waste of the therapeutic agent.

Table 1.

Patient ID	Tumor type	Tumor volume	Gd volume ioMR
DIPG01	DIPG	41.82	1.53
DIPG02	DIPG	35.71	3.63
DIPG03	DIPG	27.04	2.65
DIPG04	DIPG	29.8	3.01
DIPG05	DIPGexoph	26.59	0
CU01	DIPGrecurrent	33.79	5.11
CU02	DIPGrecurrent	16.14	4.21
CU03	DIPGrecurrent	15.63	3.46
CU04	DIPGrecurrent	54.25	3.01
Mean		31.19	3.07

Legend: Tumor volume of DIPG in cc
Gd volume in intraoperative MRI in cc
CU= compassionate use

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Non Traumatic Intracerebral Hemorrhage: Kuala Lumpur Experience

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1.1 Abstract

Stroke is the third leading cause of death in Malaysia.(1) Up to 25% of stroke cases are due to intracerebral hemorrhage (ICH). The aim of the study is to evaluate the prognostic factors and to mortality rate of spontaneous ICH in Kuala Lumpur, Malaysia. We performed a single center prospective cohort study for patients above 18 year of age with spontaneous ICH whom presented to us from 1st May 2017 to 30 April 2018. Patients who bled due to tumors and rupture of arteriovenous malformations were excluded. Demographics of these patients, clinical parameter, radiologic findings, surgical intervention done, outcome (based on MRS grading) and mortality was recorded at 30 days.

A total of two hundred and ninety two patients were included. Our median age of ICB is 48.9 years. Among our patients with ICH the common risk factors were: hypertension (99.0%), diabetes mellitus (35.6%), ischemic heart disease (IHD) (30.0%), chronic kidney disease (CKD) (7.8%) and valvular heart disease (3.1%). Mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) on admission were 207.4 mmHg and 105.7 mmHg respectively. Most lesion were located in the putamen (45.9%) followed by brainstem (18.2%), thalamic region (15.4%), cerebellar (10.6%) and lobar (9.9%). One hundred and ninety three (66.1%) patient presented with a history of loss of consciousness, 57.2% with headache, 29.0% with muscle weakness, 50.3% with vomiting, 42.8% slurring of speech and 0.7% with seizure. For patients with stable condition, medical treatment is the mainstay of therapy. If the clinical condition deteriorates during medical treatment, surgical intervention was offered if indicated. In our series, 31.8% of our patients with ICH receive surgical treatment.

The mortality rate was 29.1% at 30 days. 61.0% of patient had a good outcome meanwhile 39.0% had poor outcome. The selected variables were incorporated into models generated by binary logistic regression method analysis to define the significant predictors of outcome. In conclusion, IHD, CKD, severe GCS and presence of IVH is significant for mortality.

Keywords: Primary intracerebral hemorrhage, Clinical profile, Outcome, Prognosis, Malaysia

2.1 Introduction

Stroke can be classified into ischemic or haemorrhagic stroke. Ischaemic stroke accounts for up to 79.4% meanwhile haemorrhagic stroke accounts for up to 25.2% percent of overall stroke admission. (1-3) Hemorrhagic stroke or commonly known as intracerebral haemorrhage (ICH) is an important causes of death and disability worldwide. ICH in fact has a significant higher morbidity than cerebral infarction or subarachnoid hemorrhage. (4)

Worldwide, stroke is ranked as the second commonest cause of death and the third most common cause of disability-adjusted life-years (DALYs) from the Global Burden of Diseases, Injuries and Risk Factors Study (GBD) in 2010. (5, 6) Similarly in a Malaysian study, stroke accounts for the third commonest cause of death after ischemic heart disease and cancer. (1) The Malaysian Acute Stroke Registry reported a 1 month mortality of 25.9% for patient presenting with ICH.(2) These data reveal that ICH is a serious non-communicable disease that has a devastating impact towards the individual, family and the community, as well as a burden to the healthcare system and the country.

In addition to higher mortality, the incidence ICH amongst the Southeast Asian population is higher. Studies comparing the Caucasian population in Australia, with Asian population shows a 5 times higher incidence of developing ICH in the latter.(7) The Malaysian stroke registry reconfirms the statement as we had a higher proportion of ICH compared to higher income countries with a mean age for ICH being 60.8 which was 10 years younger than developed countries.(2) Moreover, hypertension (72.5%) was a major risk factor with males affected more at 52.9%. Other associated risk factor identified were smoking (51.5%), diabetes (24.9%),

hyperlipidaemic (21%), ischemic heart disease (6%) and atrial fibrillation (1.3%) (2). Sadly, it is noted that chronic kidney disease and patient with valvular heart disease on anticoagulant were not included in this registry as a significant risk factor for ICH.

Hypertension is defined as a persistent elevation of systolic blood pressure (BP) of 140 mmHg or greater and/or diastolic BP 90mmHg or greater. As a major risk factor of ICH, hypertension has a prevalence of 42.6% above the age of 30 years old in the year 2006 and has increased to 43.5% in 2011, with 60.6% of patients being 'undiagnosed' in Malaysia. (8)

Hypertension is a chronic disease which damages the end target organ if uncontrolled. The organ commonly involved would be the heart, resulting in heart failure, coronary heart disease and left ventricular hypertrophy. The brain on the other hand may develop transient ischemic attack and stroke. This is followed by peripheral vasculature disease and kidney failure.

ICH can be subdivided into primary and secondary ICH. Primary ICH or spontaneous ICH is the term used to describe ICH in the absence of any underlying vascular malformation. Up to 88% of primary ICH is caused by hypertensive arteriosclerosis and cerebral amyloid angiopathy (CAA). (9) Secondary ICH results from bleeding of cerebrovascular vascular abnormalities, tumors, or impaired coagulation.

ICH is derived from spontaneous rupture of small vessels damaged by chronic hypertension or amyloid angiopathy. Chronic uncontrolled hypertension damages the vessel wall long before the rupture. During the asymptomatic period, prolong uncontrolled hypertension leads to smooth muscle proliferation and necrosis which is ultimately replaced by collagen. Subsequently, the vessel becomes stiff and brittle losing the compliance capacity. The vessels tend to dilated due to this process and form Charcot-Bouchard aneurysm. Common vessels that rupture are the arteriole of a diameter of less than 300 micrometer especially the lenticulostriate arteries. (10)

Based on the GBD 2010 findings, there is 47% increase in ICH cases worldwide with death up to 63% occurring in low and middle income countries (LMIC). There were 62.8 million (DALYs) of which (86%) in LMIC lost due to ICH. The worldwide burden of ICH has increased over the last 2 decades in terms of absolute numbers of ICH incident events. The majority of the burden of HS is borne by LMIC as the rate has increase significantly.(11)

ICH is associated with higher risk of fatality from infarct and approximately half of patients with primary ICH die within the first month. Moreover, patients tend to have more deficit upon discharge as hemorrhage stroke tend to not only damage the brain cell but lead to increase pressure or spasm of the vessels. However, certain studies reveal there isn't any statistically significant difference in outcome between ischemic stroke and ICH. (12)

Currently, ICH Score is a simple clinical grading scale which allows risk stratification of ICH to predict mortality at 30 days.(4) However, the factors included in the ICH score are vague and broad. For example, the age cut off for the scoring is 80 years old. Malaysian's median life span is 60 years old. Thus, ICH score would be inaccurate in Malaysian context as younger patients present with ICH.(2, 13, 14) Secondly, a cumulative GCS is used instead or specific scoring system. No exclusion was made if the patient did have an ICH over the Broca's area (which would result in aphasia) thus skewing the result to an unfavourable prognosis due to the poor verbal component in the overall GCS score. Thirdly, no concomitant co-morbid were taken into account. Based on our clinical experience, ICH is more common in patient with renal disease and cardiac problem (atrial fibrillation patient on anti platelet therapy or warfarin) and tend to fare poor.

In view our clinical experience, younger patients present with ICH and patients with associated co-morbid fare poorer. We wanted to investigate and identify prognosticate factors involved in ICH. In the Malaysian context, there is no recent study over the past 3 to 5 years with regards to ICH.

The most relevant recent data was from the Malaysian Acute Stroke Registry Malaysia which was taken from 2010 to 2014. However, concomitant comorbid such as chronic kidney disease or valvular hear disease was not included. Moreover, the registry had minimal data on patient undergoing surgical intervention and outcome based on intervention.(2)1

Other Malaysian study relevant pertaining to surgical intervention of ICH were collected from 1994 to 2003.(13, 14) Based on Sia *et al* which was published in 2007, the important predictors of mortality were GCS score on admission, haematoma volume >30mls, evidence of intraventricular extension and ICH score. (13) Muiz *et al* noted significant predictors of outcome were the Glasgow Coma Scale score on admission, the duration of surgery and the total volume of the hematoma meanwhile the significant predictors of mortality were high total white blood cell differential count, low plasma protein, high plasma lactate dehydrogenase and brain edema.(14) However over the past 10 years since these last neurosurgical local data, there is a possibility that the disease epidemiology may had some changes.

The study is aimed to determine and evaluate the prognosticate factors for ICH in Kuala Lumpur. This will aid us in our clinical practice in order to make better judgement. Upon which more better clinical decision and information can be conveyed to the family members regarding the expected outcome for the patient.

3.1 Material and Method

3.1 Research design

This study is a prospective cohort study done after obtaining approval from the Medical Research & Ethics Committee of Ministry of Health Malaysia and registered in the national register for clinical trials (NMRR-17-730-34957). The main objective is to analyze the prognostic factors of mortality and morbidity of spontaneous ICH at 30 days. The primary endpoint is to establish the prognostic factors for spontaneous ICH.

3.2 Research location and duration

This is a single centre study conducted in Hospital Kuala Lumpur. Data was collected from 1st May 2017 to 30 April 2018.

3.3 Study population

All patients with spontaneous ICH aged 18 and above referred to the neurosurgery Hospital Kuala Lumpur were included in the study. The diagnosis was based on a typical clinical onset and CT. ICH definitions and rules is as specified by the Tenth Revision of the International Classification of Diseases under I61 Nontraumatic intracerebral hemorrhage, unspecified. Patients with secondary intracerebral hemorrhage (due to vascular or brain tumour aetiology) was ruled out. Thus, any patient with less than 45 years of age with no risks for hypertensive haemorrhage will be investigated with a CT angiogram after 6 weeks. (9). Patients who fulfil the inclusion and exclusion criteria are enrolled in this study.

3.4 Method of research

In this study, the analysed parameters were age, gender, race, comorbids (1) hypertension: previous usage of antihypertensive drugs or previous medical diagnosis of hypertension; (2) diabetes mellitus: fasting glucose value 6.7 mmol/l at the time of admission or corresponding value for random plasma glucose 17.8 mmol/l at the time of admission; ischemic heart disease or history of cerebrovascular disease, chronic kidney disease based on Cockgroft Gault formula with Stage 3 and above, valvular heart disease, usage of anticoagulant or warfarin), clinical parameter upon admission which is blood pressure (BP) and Glasgow Coma Score (GCS), radiological imaging (site, location of ICH, presence of IVH and hydrocephalus), surgical intervention performed (craniotomy, craniectomy or EVD) and finally the outcome (mortality or morbidity at 30 days).

Classification of each hematoma location was based on the location of the epicenter of the hematoma whether its supratentorial (lobar, thalamic, putaminal) or infratentorial (cerebellar, or brain stem). Associated condition on the CT scan such as intraventricular bleed and hydrocephalus is documented. The volume of the intracerebral hematoma was estimated by measuring based on greatest diameter "A" and perpendicular diameter "B" of haematoma and the thickness of each CT slices by adding the number of CT slices visualizing the haematoma. These values are multipled and the product (AxBxC) is divided by two to yield the approximated volume ABC/2.(15)

Management of ICH was in accordance of protocol. Medical therapy was performed with BP stabilization as per AHA guidelines and referral to rehabilitation team. Patients with mild symptoms and those who refused surgical intervention were treated conservatively. Surgery was offered for patients with obvious hemiplegia and altered consciousness (based on GCS score) provided a clot size of more than 30cc within 1cm from the cortical surface. The decision to operate was not affected by whether hemorrhage was in the dominant or nondominant hemisphere or by the presence or absence of aphasia. No absolute upper age limit was set for surgery. For patient with hydrocephalus or intraventricular hemorrhage based on CT imaging, ventricular drainage was performed. Outcome was assessed by a clinical follow-up at 1 month using MRS scoring. The clinical outcome was divided into good outcome where patients made a good recovery (correspond to MRS 1 to 3) or poor outcome (based on MRS score 4 to 6).

3.4 Statistical analysis

Statistical analysis was performed with the use of IBM SPSS statistics Version 20.0.0 Differences with a P-value of 0.05 or less were considered as statistically significant. Univariate analysis was performed using x2 for categorical variables while the two-independent-sample t test was used for continuous variables. Numerical variables will be presented in mean and standard deviation whereas categorical variables will be presented in frequency and percentage. Data which was significant was included into binary logistic regression analysis.

Using binary logistic regression analysis with outcome being mortality, prognostic predictors was identified. The results were presented by an appropriate tabulation including adjusted odds ratio (OR) with 95% confidence intervals (CIs) and the corresponding p value.

4.1 Results

4.1. Demographic

During the 12 months period from 1st May 2017 to 30 April 2018, there were a total of 300 patients recruited. However 8 patients were excluded as CTA brain done at 6 weeks revealed AVM (2.7%). Thus, 292 patients were included in this study.

There were one hundred and eighty two men (73.6%) and one hundred and ten (37.7%) female with a male to female ratio of 1.65:1. The age ranged from 28 to 83 years old with a mean age of 48.9 years. The age distribution showed that highest incidence of ICH occurs between the age of 31 to 60 year old. There were 215 Malays (73.6%), 54 Chinese patients (18.5%), 20 Indian patients (6.8%) and 3 others (1.1%). The age, ethnicity and the patient's gender did not show any statistical significant affecting the admission mortality. **(TABLE 1)**

4.2 Clinical profile

There were multiple risk factors associated. Hypertension was the commonest risk factor associated with ICH (99.0%). Other risk factors were diabetes mellitus (35.6%), ischemic heart disease (IHD) (30.0%), chronic kidney disease (CKD) (7.8%) and valvular heart disease (3.1%). There were 52 patient on aspirin (17.8%) and 15 patient on warfarin (5.1%). Presence of IHD, CKD and valvular heart disease was statically significant for mortality.

One hundred and ninety three (66.1) patient presented with a history of loss of consciousness, 167 (57.2%) headache, 143 (29.0%) muscle weakness, 147 (50.3%) vomiting, 125 (42.8%) slurring of speech and 2 (0.7%) with seizure.

On admission, the mean GCS is 11.53. Sixty seven patients (22.9%) had a severe GCS score, 97 (33.2%) had moderate, 69 (23.6%) had mild GCS with 59 (20.2%) had normal GCS score of 15. GCS scoring had a strong statistical association with mortality with p value <0.0001.

Mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) on admission were 207.4 mmHg and 105.7 mmHg respectively. Blood pressure was not significant for mortality. Two hundred and thirty three patients (79.8%) presented with systolic pressure more than 180mmHg. **(TABLE 1)**

		TOTAL PATIENT		GOOD OUTCOME	POOR OUTCOME	P VALUE
		n	(%)	n	n	
Age*		49.81± 12.89				0.740
Sex						
	Male	182	62.3%	105	77	0.142
	Female	110	37.7%	73	37	
Ethnic	Malay	215	73.6%			0.707
	Chinese	54	18.5%			
	Indian	20	6.8%			
	Others	3	1.1%			
Hypertension		289	99.0%	176	113	
	Systolic	207.4				0.808
	Diastolic	105.8				0.155
Risk Factor						
	Diabetes	104	35.6%	58	46	0.178
	IHD	30	10.0%	8	22	0.001
	CKD	22	7.8%	4	18	0.001
	Valvular heart disease	9	3.1%	2	7	0.015
Medication						

	Aspirin	52	17.8%	28	24	0.226
	Warfarin	15	5.1%	7	8	0.246
Symptom						
	LOC	193	66.1%			
	Headache	167	57.2%			
	Vomit	147	50.3%			
	Weakness	143	49.0%			
	Slurring of speech	125	42.8%			
	Seizure	2	70.0%			
GCS*		11.53				0.001
	Normal	59	20.3%			
	Mild	69	23.6%			
	Moderate	97	33.2%			
	Severe	67	22.9%			

Tab. 1 - Association of demographic and clinical profile with ICH and mortality

4.3 Radiological imaging

One hundred and twenty five (42.8%) ICH lesions were on the right side, 86 (29.5%) lesion were on the left and remaining 81 patient (27.7%) with ICH over the midbrain, midline or both side. Most lesion were located in the basal ganglia (45.9%) followed by brainstem (18.2%), thalamic region (15.4%), cerebellar (10.6%) and lobar (9.9%).

About 17 (5.8%) of patient had midline shift (MLS) more than 5mm. Of the patient presenting with ICH 142 (49.6%) had clot size less than 15cc, 111 had clot size between 15 to 30cc (38.0%), 29 patient had clot size between 30 to 50 and about 10 patient had clot size more than 50cc (3.4%).

One hundred and fourty nine patients (51%) had intraventricular hemorrhage on CT scan. Fifty five patients (18.8%) has hydrocephalus (HCP) based on CT scan. Location of ICH, presence of midline shift, clot size, IVH and HCP had a statistical association with mortality. **(TABLE 2)**

		TOTAL PATIENT		GOOD OUTCOME	POOR OUTCOME	P VALUE
		n	(%)	n	n	
Location						0.001
	Putamen	134	45.90%	108	26	
	Thalamic	45	15.4%	21	24	
	Brainstem	53	18.2%	0	53	
	Cerebellar	31	10.6%	26	5	
	Lobar	29	9.9%	23	6	
Side						
	Right	125	42.8%	98	27	0.001
	Left	86	29.5%	56	30	
	Other	81	27.7%	24	57	
MLS						
	Less than 5mm	275	94.2%	174	101	0.001
	More than 5mm	17	5.8%	4	13	
Clot size						
	Less than 15cc	142	49.6%	86	56	0.008
	15 to 30cc	111	38.0%	77	34	

	30 to 50cc	29	9.9%	11	18	
	More than 50cc	10	3.4%	4	6	
IVH						
	Yes	149	51.0%	85	64	0.163
	No	143	49.0%	93	50	
HCP						
	Yes	55	18.8%	24	32	0.003
	No	237	81.2%	154	83	

Tab. 2 - Association of radiological imaging and mortality

4.4 Surgical intervention

Among the surgical group, 54 (18.5%) patients underwent craniotomy and evacuation of clot, 8 (2.7%) underwent craniectomy due to edema and 52 (17.8) patient underwent extraventricular drainage. **(TABLE 3)** Patient underwent craniectomy and EVD for IVH and HCP has a statistical with mortality.

	TOTAL PATIENT		GOOD OUTCOME	POOR OUTCOME	P VALUE
	n	(%)	n	n	
Surgery	93	31.80%	39	54	0.001
Craniotomy	54	18.5%	31	23	0.555
Craniectomy	8	2.7%	0	8	0.001
EVD	52	17.8%	24	28	0.016

Tab. 3 - Association of surgical intervention for ICH with mortality

4.5 Outcome

In general, 178 (61.0%) had good outcome and 114 (39.0%) had poor outcome. 82 patient died (29.1%) at 30 days. **(TABLE 4)** Multivariate analysis showed that the IHD, CKD, brainstem bleed, severe GCS and IVH for ICH is significant. **(TABLE 5)**

MRS		TOTAL PATIENT	
		n	(%)
Good	1 to 3	178	61.00%
Poor	4 to 6	114	39.0%

Tab. 4 – MRS score at 30 days

Variable	p Value	Adjusted OR (95% CI)	
IHD	0.001	13.05	(3.12 - 54.62)
CKD	0.005	11.44	(2.12 - 61.47)
Brainstem	0.015	3.48	(0.62 - 19.62)
IVH	0.035	1.67	(0.50 - 5.59)

Severe GCS	0.04	1.76	(0.29 - 12.71)

Tab. 5 – Multivariate analysis for predictor of ICH mortality and 95% CI relative risk of ICH

5.1 Discussion

There were 73.6% Malay patients, 18.5% Chinese patients, 6.8% Indian patients and 1.1 others whom presented with ICH. Kuala Lumpur population demographic census suggests ethnic Malay being the majority at 41.6%, followed by Chinese at 39.1%, Indians at 9.2% and others at 10.1% in Kuala Lumpur. Thus, it is noted a large number of patients being ethnic Malay which is incongruent with the demographic of Kuala Lumpur.(17) Although race was not found not to be a significant prognostic factor, it would be inappropriate to correlate race with outcome as Malay ethnic is the major racial population of the neighboring states.

Sex was not significant using univariate analysis. The slightly more male preponderance compare to the female by a ratio of 1.65:1 can be explained by the demographic in Kuala Lumpur.(17)

Based on the study, it is noted that the mean age of ICH is 48.9. This is even lower compared to the Malaysian Stroke Registry which was 60.8 years. The age distribution also shows highest incidence of ICH occurs between the age of 31 to 60 year old. Although this has no bearing on statistical significance, the impact of the DALY cannot be argued as younger Malaysian is developing ICH in Malaysia.

Hypertension was consistently seen in most of the patients (99.0%) but statically not significant. It is mainly due to patients whom tend to default their anti-hypertensive treatment. (3) Other reason may be that acute symptoms that occur with stroke without any warning sign as compared to heart disease, where subtle symptoms and signs may be picked up in many patients during regular clinic follow up. (12)

But presence of IHD and CKD has been statistically significant. The risk of myocardial infarction due to IHD is present. The higher rate of ICH in patients undergoing dialysis cannot be denied. Moreover, brain perfusion related injury (hypoperfusion) occurs more frequently with patient with CKD. In the CHOICE cohort, 10 patient had ICH and case fatality was noted up to 90%.(16) Other risk factor was not statically significant in the multivariant analysis.

The most reliable predictor of ICH is the GCS upon arrival. It has been consistently been a good indicator in numerous other studies. However, the presence of aphasia in left sided ICH may obscure the prognosis and provide a false negative impression of ICH. It is difficult to exclude verbal component from the overall GCS in order to prognosticate the mortality. The need for a better more specific scoring system for stroke may need to be considered in the future.

Among the surgical group there was no statically significance for craniotomy. However, it would be only fair is these patient are follow-up at 1 year to see the proper outcome. The presence of IVH was a predictor for poor prognosis which was not evident with hydrocephalus. Our center has a fairly high rate of EVD related ventriculitis which further complicates recovery and possibly contribute for higher false positive results.

Patient with brainstem bleed (18.2%) was noted to fare poorer. This is likely due to the fact patient is ADL dependent and predispose to hospital acquired infection due to the poor mobility.

Our study noted a mortality rate of 29.1%. This rate is consistent with our Malaysian Stroke Registry which reported a mortality of 25.9%. (2)

5.1.1 Limitation

Our study had several limitations. Firstly, the number is small and may account for some of the discordant results when compared to the published literature. Secondly, the rate of ventriculitis related EVD in our center may have contributed for false positive results for poor prognosis patients. We have also noticed that some patient with good GCS with borderline size clot tend to deteriorate later in Day 2 to 3 due to edema requiring surgery. We find it difficult to dichotomize these patients as they deteriorate later. Moreover, GCS scoring

preoperatively which is used as a tool to measure consciousness does not correlate with outcome which is measure by MRS.

6.1 Conclusion

In this study, we are able to review our ICH epidemiology data. This is the largest and latest study involving neurosurgical intervention among ICH patients in Malaysia. The mortality rate of 29.1% at 30 days is fairly acceptable. The commonest risk factor is hypertension which account to 99.0%. Significant predictors of mortality like IHD, CKD, poor motor score upon admission, location of brainstem bleed, presence of IVH or HCP, and craniectomy is noted. Moreover, our mean age of 48.9 years is worrisome. To treat ICH in Malaysia is to treat hypertension aggressively at the all primary care centres and creating more awareness of the disease. It is evident that younger patients in Malaysia present with ICH. The impact to the country via loss of young workforce needs to be address and taken seriously. Moreover, the prognostic factor mentioned above can be used to aid in the decision making and aid clinicians to determine the outcome of ICH. The need for a more refine scoring system to include the comorbids and other parameters may be of help in the near future.

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Orbital Apex Syndrome Cause By Invasive Aspergillosis: A Case Series

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Abstract

Orbital apex syndrome (OAS) may be due to various aetiologies such as sarcoidosis, connective tissue disorders, orbital tumours, optic nerve gliomas, infra-clinoid aneurysm of internal carotid artery and many more (1). Fungal infections are the least common causes of OAS. Invasive aspergillosis in immunocompetent patients is rare. It occurs very often in the granulocytopenic patient and is potentially fatal. Predisposing factors include alcoholism, steroid therapy and diabetes mellitus. The route of infection is usually by inhalation of Aspergillusspores and conidia or airborne metabolites of Aspergillus. The main routes of central nervous system contamination are hematogenous dissemination from a distant primary source, mainly lung, and contiguous spread from an adjacent focus such as orbit or paranasal sinuses (2). It is possible that our patient had a paranasal sinus Aspergillus infection that extended into the orbital apex and carotid artery, although imaging studies did not indicate such an infection. Involvement of the CNS is present in 10-15% of patients with disseminated disease (3). Immunocompromised individuals such as those having acquired immunodeficiency syndrome (AIDS), patients with malignant tumors, diabetes, or on corticosteroids or immunosuppressive agents are at risk of developing aspergillosis. Mukoyamaet al. roughly classified the mode of development of aspergillosis of CNS into five types: 1) meningitis, 2) meningoencephalitis, 3) abscess, 4) granuloma, and 5) vasculitis. It is learned from this experiencethat in an immunocompromised patient having orbital apex syndrome with or without evidence of sinus disease on CT or MRI, fungal infection should be kept in mind. This is true for our patient in case no 1, where by she was exposed to prolonged high dose of steroids. The clinical features of our case suggest that early diagnosis in a case of aspergillosis presenting with visual loss is difficult. In those treated with steroid and whose symptoms and signs do not quickly improve, or the symptoms and signs relapse quickly, repeat imaging may reveal new findings. The ways to establish diagnosis include biopsy and culture of the excised specimen. Early diagnosis and radical resection, combined with antifungal medications is paramount to save this (4). Surgical debridement with antifungal is the preferred modality of treatment (5). The overall case fatality rate is 58%, and it is highest for bone marrow transplant recipients (86.7%) and for patients with CNS or disseminated aspergillosis (88.1%). In patients with invasive aspergillosis, initial therapy with voriconazole is associated with better clinical response, improved survival and fewer severe side effects. The correct diagnosis of cerebral aspergillosis can only be achieved by histopathological examination because clinical and radiological findings including MRI are not specific.

Keywords: Invasive aspergillosis, orbital apex syndrome

Introduction

Cerebral aspergillosis is rare and usually misdiagnosed because its presentation is similar to that of a tumor. The correct diagnosis is usually made intra-operatively. Cerebral abscess with fungal infection is extremely rare and few cases have been reported, but it carries a poor prognosis. A case series of two cases with cerebral aspergillosis were reported. Both patients had lesion in the orbital apex, cavernous sinus andextend to the middle cranial fossa. A high index of suspicion, a comprehensive understanding of the infectious process and advanced laboratory andradiological diagnostic techniques, allow early diagnosis. Surgery, followed by systemic anti-fungal medications, remains the cornerstone of management. Early administration of empirical

anti-fungal agents along with immunomodulators may further improve prognosis. Immunocompetent patients tend to have better outcomes as compared to those who are immunocompromised.

Case Series

1.1. Case Report 1

A 52-year-old male presented with the complaints of headache persisting for 2 months, and presented with progressive visual deterioration and ptosis in the right eye. He had no known disease and no apparent immune deficiencies. On physical examination, he was afebrile. The neurological examination revealed a ptosis, ophthalmoplegia, and impairment of visual acuity on the right eye. His laboratory results white cell count, sedimentation rate, C-reactive protein, peripheral smear and biochemical tests were all in normal range. Viral markers were negative. Magnetic resonance imaging (MRI) revealed a mass in the right cavernous sinus, extended to the anterior cranial fossa and the superior orbital fissure with an iso-signal intensity in T1-weighted iamge. The lesion showed a slightly low signal intensity in T2-weighted sequences and strong enhancement .Based on these MRI findings, the impression was inflammatory abscess, but meningioma or metastatic tumor were also suspected. The patient underwent a pterional approach craniotomy for pathologic diagnosis and decompression of neural structures. During surgery, a well-encapsulated pus pocket was found at the clinoid process, and severe adhesion with the surrounding tissue was encountered. An intra-operative frozen section biopsy revealed a fungal infection. The biopsy material showed inflammatory granulation tissue and micro abscesses containing a large number of hyphae with 45 degree angulations and spores.The pathology result was consistent with aspergillus infection.

1.1. Case Report 2

A 68-year-old lady with underlying hypertension, presented with progressive loss of vision in the left eye with persistent retro-orbital pain aggravated by movement since July 2017. She then noticed dropping of eyelid about 2 weeks prior to admission. She had no history of diplopia, redness, watering or floaters. She was treated with intravenous methylprednisolone, however there was no improvement in the symptoms despite prolonged high dose steroids. Clincally, non tender paranasal sinuses and bilaterally palpable temporal arteries. On examination revealed complete left sided opthalmoplegia with left visual acuity was 6/12 with positive RAPD and reduce extraocular muscle movements and complete ptosis of the left eye. Fundoscopy showed left papilloedema and pallor of right disc. Right eye were normal. WBC and C-reactive protein were within normal limits. HIV, hepatitis B and C screening were negative findings. MRI brain on 3/10/2017 showed dural based lesion involving left orbital apex with extension into the left cavernous sinus and left temporal fossa with local mass effect and compression onto the left optic nerve. She underwent endoscopic sinus surgery, transsphenoidal surgery and optic nerve decompression and tumour biopsy on 9/10/2017.

Post operative contrast enhance CT brain showed residual soft tissue (aspergillosis) of the orbital apex. Histological specimen from optic nerve showed fungal hyphae morphologically compatible with Aspergillus species. She was started on antifungal treatment and her visual and ocular movements improved.3 weeks after, noted to have clinical deterioration along with worsening radiological findings. A second surgery via endoscopic transphenoidal was done 2/11/2017. Her condition remained static. A repeated MRI brain showed soft tissue lesions at orbital apex and cavernous sinus, however a PET scan confirmed no active lesion. She has shown recovery during her follow up in neurosurgery clinic.

Figure A:

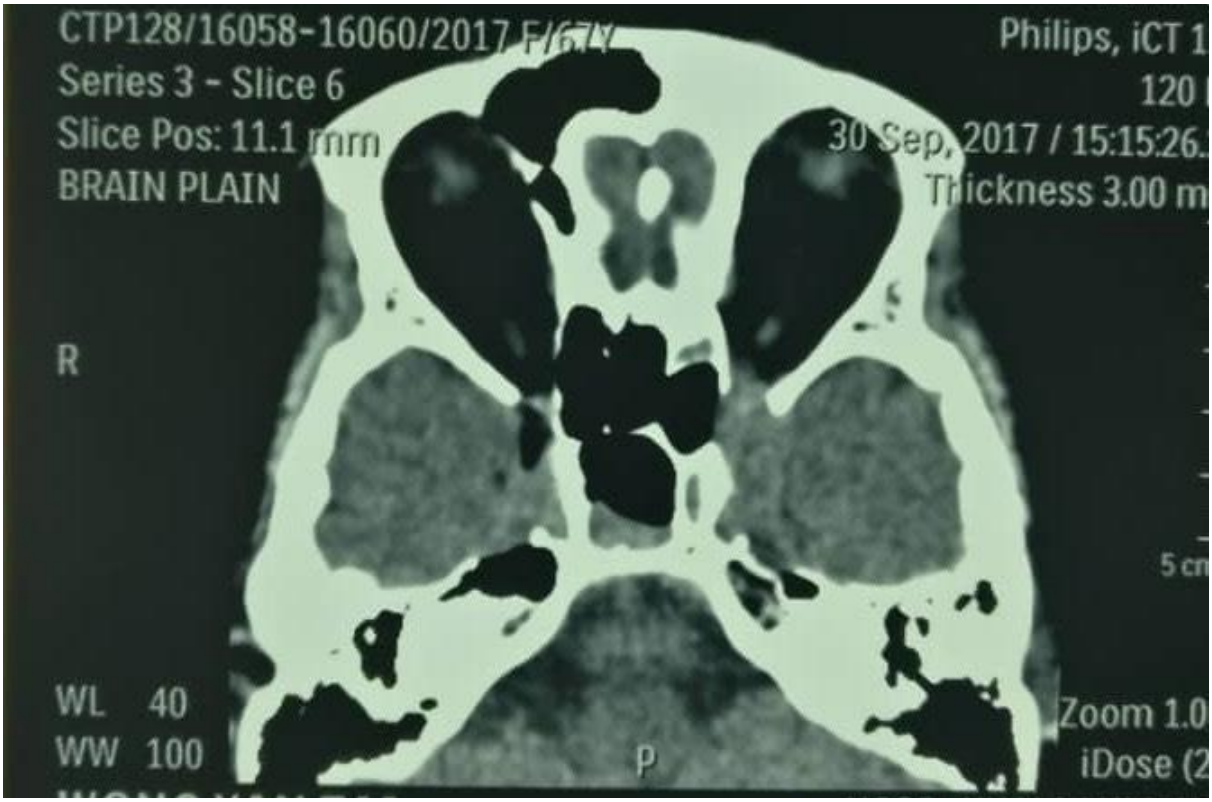

Figure A: CT scan showed soft tissue at the left orbital apex region.

Figure B:

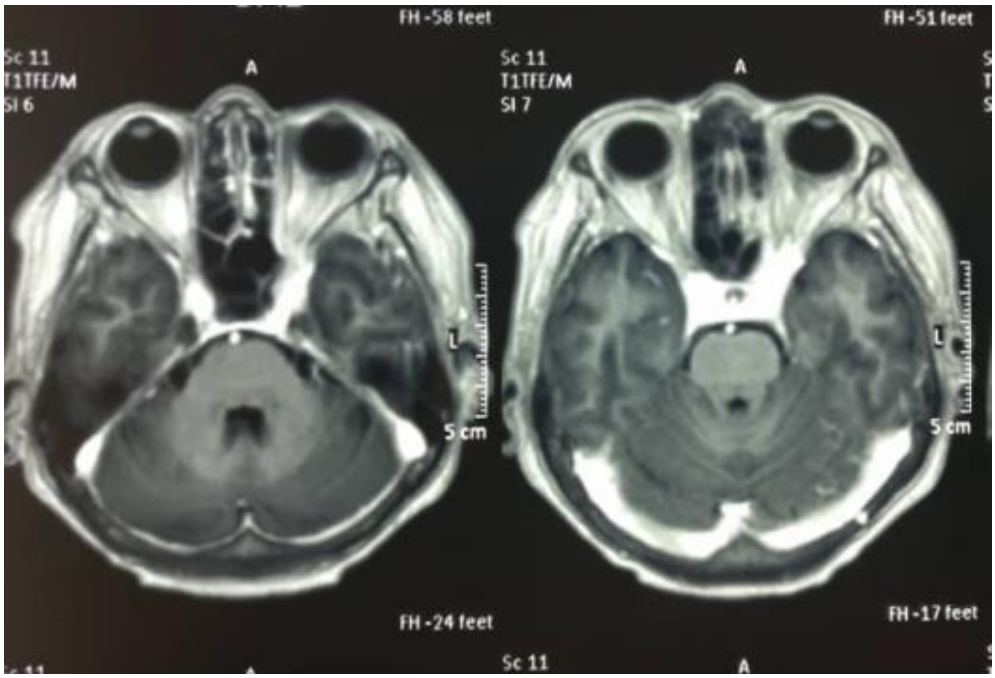

Figure C:

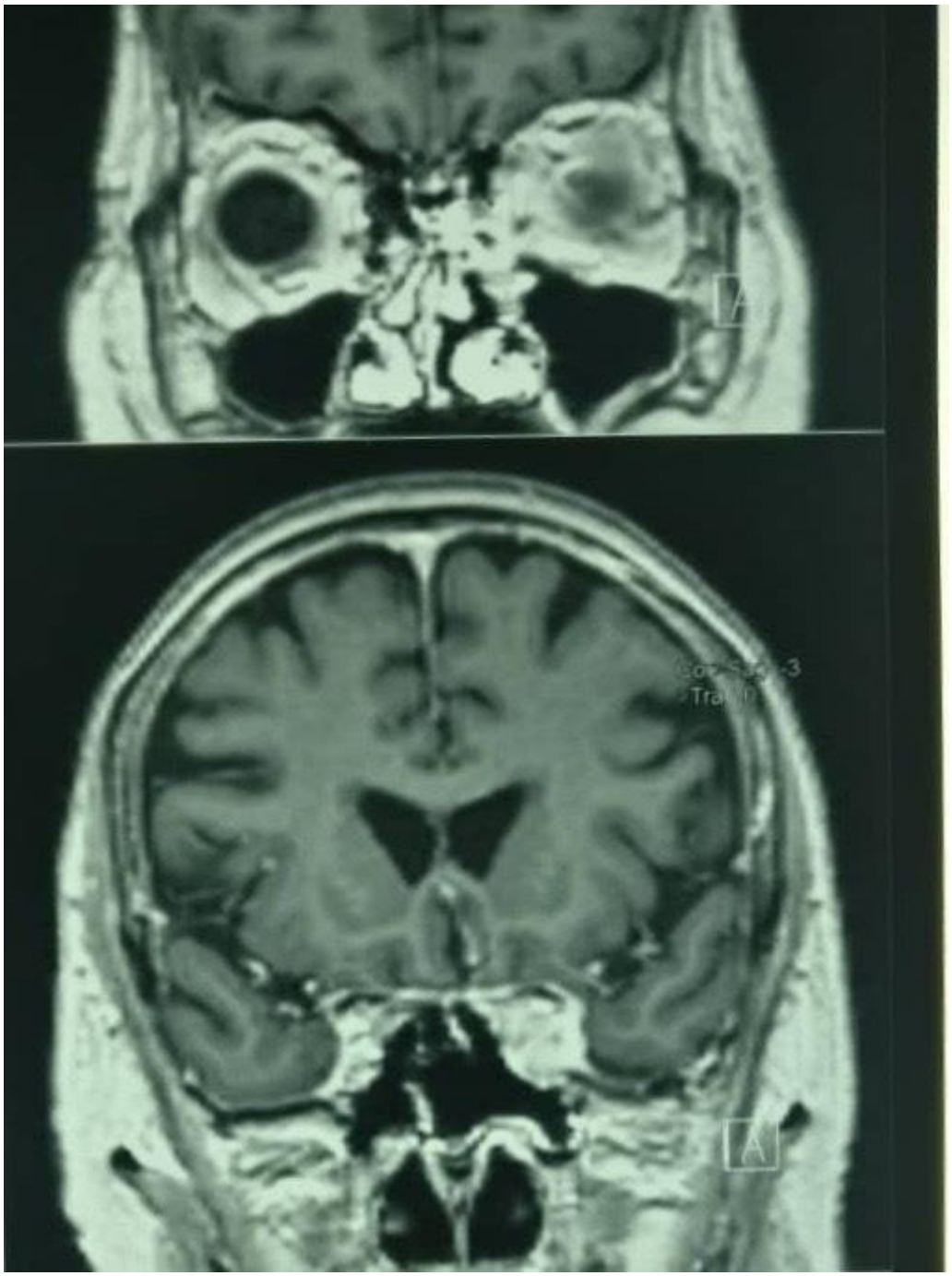

Figure B & C: MRI brain and orbit showed dural based lesion involving left orbital apex with extension into the left cavernous sinus and left temporal fossa with local mass effect and compression onto the left optic nerve.

Figure D:

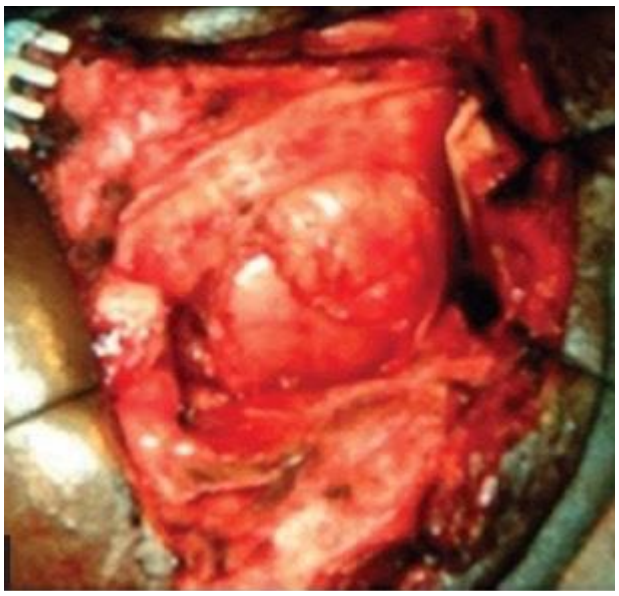

Figure D: Intraoperatively findings of orbital apex lesion which are soft to firm in consistency, moderately vascular and regular margins.

Figure E:

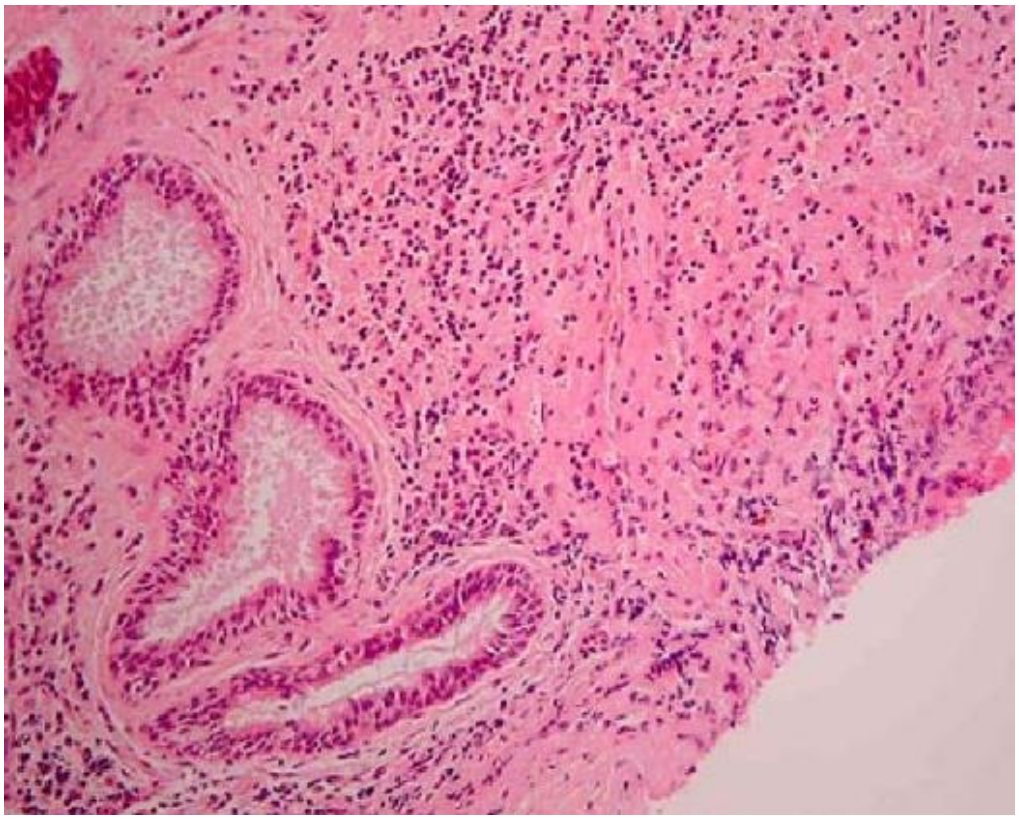

Figure E: Histopathology showed infiltration by inflammatory cells, predominantly lymphocytes and plasma cells (haematoxylin and eosin)

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Pituitary Apoplexy – A Short Case Series

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Abstract

Pituitary apoplexy is a rare neuroendocrine emergency which can occur due to infarction or hemorrhage of pituitary gland. This disorder most often involves a pituitary adenoma. Occasionally it may be the first manifestation of an underlying adenoma. Patients usually present with headache, vomiting, altered sensorium, visual deficits and/or endocrine dysfunction. Hemodynamic instability may result from adenocorticotropic dysfunction. Imaging with either CT or MRI should be performed in suspected cases.

We did a single center retrospective analysis of 62 patients who underwent surgery in our neurosurgical unit for pituitary lesions, out of which 6 were pituitary apoplexy that underwent transnasal endoscopic decompression immediately after the diagnosis of pituitary apoplexy with either deteriorating consciousness or progressing visual impairment. These 6 patients' data was further analyzed. Mean age was 56.3 years (24 – 78 years range), with male preponderance with male to female ratio of 2:1. All 6 patients had headache (100%), progressing visual disturbance in 4 patients (66%), 2 (33%) had diminished consciousness. Radiologically evidence of hemorrhage was seen in MRI in 4 patients (66%), sphenoid sinus invasion seen in 1 patient. Most common endocrinological abnormality was cortisol deficiency that was seen in 5 out of 6 patients (83%). All 6 patients underwent transnasal endoscopic surgery and postoperative period was uneventful in 4 patients, 1 developed CSF leak which was managed conservatively and 1 developed recurrent lower respiratory tract infections later developed sepsis and expired. Postoperatively 2 patients (33%) achieved normal endocrine profile, remaining 4 developed hypothyroidism among which 1 had associated cortisol deficiency and is on steroid replacement and 1 had transient diabetes insipidus. Clinical outcome is good in 5 patients (83%, GOS 4,5) and 1 patient expired.

To conclude early surgical decompression for pituitary apoplexy appears to be a preferred modality of treatment in selected cases of pituitary apoplexy. Transnasal endoscopic approach has the added advantage of minimal invasiveness with short postoperative stay.

Keywords: Apoplexy, Pituitary adenoma, Cranial nerve palsies, Endocrine dysfunction, Visual field defects, Transnasal endoscopic surgery

Introduction

Pituitary apoplexy can be a potentially life threatening condition caused by a vascular process in pituitary lesions like a hemorrhage or an infarct resulting in necrosis, edema and sudden expansion of the contents of sella compressing and compromising the normal neuroendocrine elements[17,18]. The syndrome usually presents with acute onset severe headache with nausea and vomiting, visual field deficits, vision loss and diminished consciousness.

Incidence of pituitary apoplexy is estimated to be around 2% to 20%[1], with larger size favoring the higher incidence of apoplexy. Surgical management is the main modality of treatment in a selected cases with progressing visual impairment and diminishing consciousness, although the difference in clinical and endocrinological outcome in early vs late surgery is still a matter of debate.

Despite the timing of surgical intervention from symptom onset, endocrinological outcome is not satisfactory as indicated by many studies but clinical outcome may be better in those who underwent early surgery. We made an effort to analyze the data of our patients retrospectively to understand the demographic, endocrine, clinical and pathological aspects of pituitary apoplexy.

Patient 1

A 34 years gentleman presented with sudden onset severe headache with vomiting associated with double vision. On examination he was conscious and oriented, hemodynamically stable. Neurologically he had bilateral cranial nerve VI palsy with rapidly progressing vision loss. MRI brain was suggestive of sellar lesion with suprasellar extension compressing the visual axis and hemorrhagic component seen within the lesion (Fig.1).

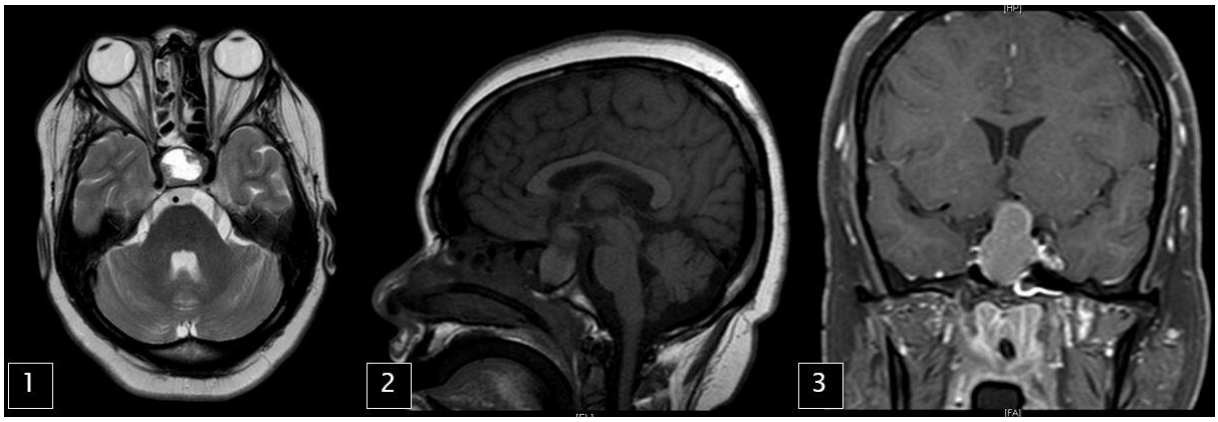

Fig 1: Preoperative MRI of patient 1 [1] T2 axial section showing widened sella, isointense sellar lesion with hyperintense component in the centre suggesting haemorrhage [2] Sagittal Non contrast T1 section showing isointense lesion in sella with significant suprasellar extension [3] Gadolinium contrast enhanced T1 coronal section showing non enhancing sellar and suprasellar lesion with significant optic axis compression

Endocrinologically patient had cortisol deficiency with normal thyroid and prolactin levels. This patient was planned for emergency surgery in view of progressing visual impairment and under general anaesthesia transnasal endoscopic sellar decompression, evacuation of hematoma and lesion was done (Fig.2).

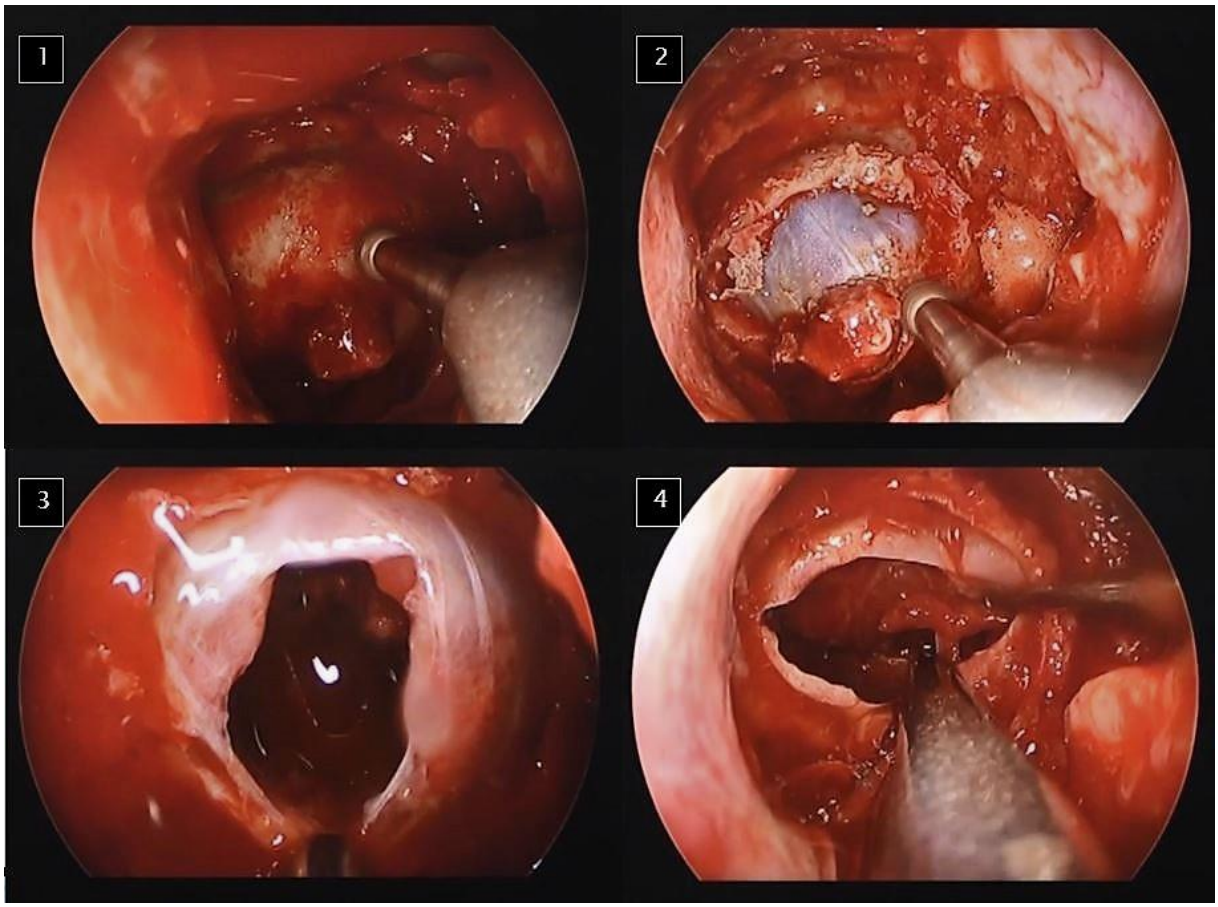

Fig 2: Intraoperative pictures in surgeon's orientation of Patient 1 [1] Drilling sellar floor, lesion can be seen protruding into the sphenoid sinus eroding the sellar floor posterior to the drill [2] After drilling the floor of sella [3] Hematoma can be seen in sella after opening the dura [4] Excising the lesion after completely evacuating the hematoma

Postoperative course of this patient was uneventful. Vision improved with minimal residual bitemporal hemianopia. Patient's endocrine status became normal postoperatively. Patient was on regular follow-up (Fig.3) and asymptomatic.

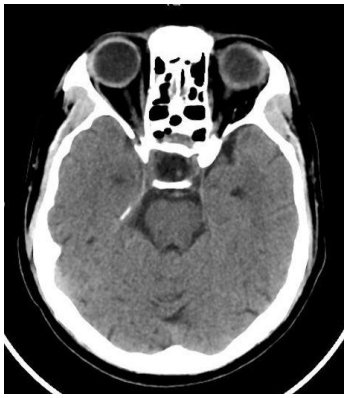

Fig.3: Postoperative CT brain plain axial section after 1 month of discharge

Patient 2

56 years gentleman presented with sudden onset bitemporal severe headache with no history of trauma, seizure or loss of consciousness. On examination he was conscious and oriented and in severe pain. He was hemodynamically stable. CT plain brain was done which showed isodense lesion in sellar region with extension to sphenoid sinus (Fig 4). MRI brain was done which showed a heterogeneous hypo to hyperintense lesion in sellar region eroding the sellar floor extending into sphenoid sinus (Fig 5).

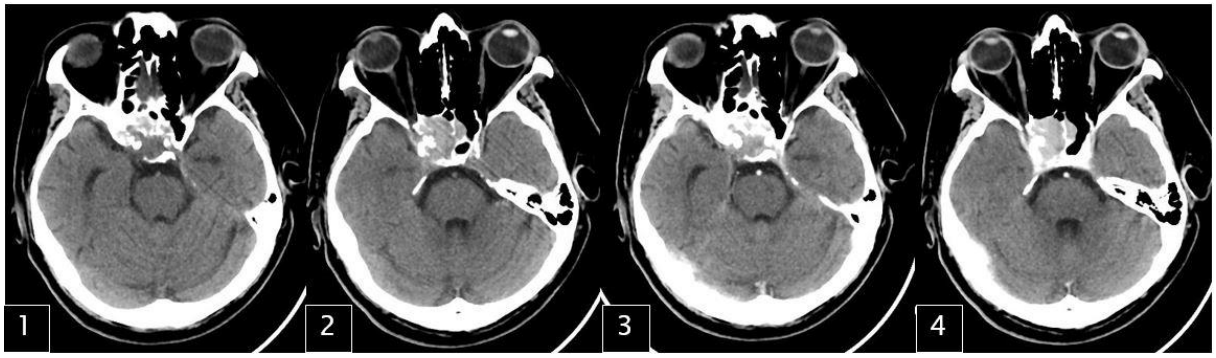

Fig 4: Admission CT brain of Patient 2 [1][2] Plain and [3][4] Contrast enhanced axial sections suggesting Iso to Hyperdense lesion in sellar region with sphenoid extension

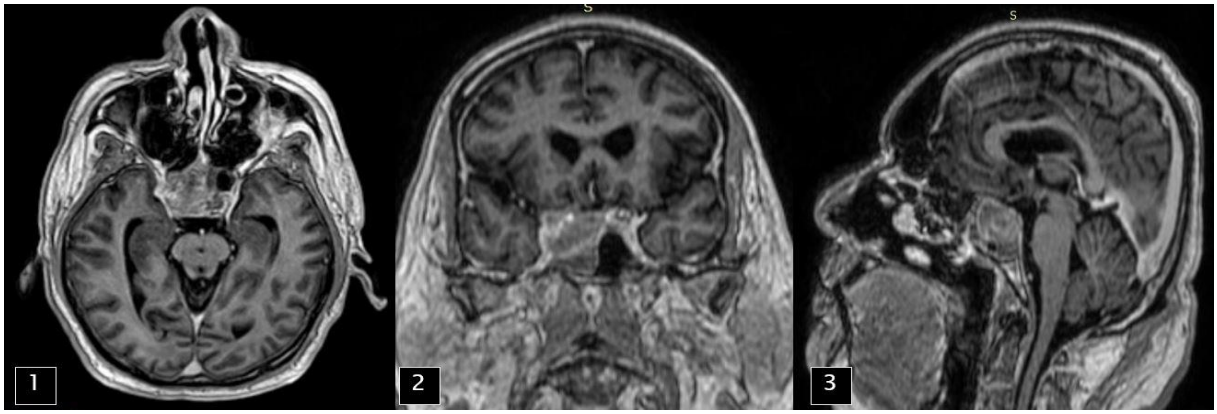

Fig 5: Gadolinium enhanced contrast MRI brain [1] axial [2] coronal and [3] sagittal sections of Patient 2 suggesting hypo to hyperintense non contrast enhancing lesion in sellar region with sphenoid extension

Endocrinological workup showed serum prolactin of 5067ng/ml and cortisol of 2.23µg/ml with normal thyroid profile. He was started on conservative measures but on 2nd day of admission he developed intractable epistaxis with significant blood loss. He was posted for surgery and under general anaesthesia transnasal endoscopy was done. Upon entry into the nasal cavity blood was seen dribbling from the sphenoid. Sphenoid sinus wall was seen eroded and irregularly torn dura is seen along with a blood clot protruding (Fig 6[1]). Blood clot was evacuated and sphenoid sinus was entered, sellar floor was eroded with tumour protruding out of the defect (Fig 6[2]). Dura opened completely and hematoma was found within the sella that was evacuated. Tumour was excised and skull base was packed.

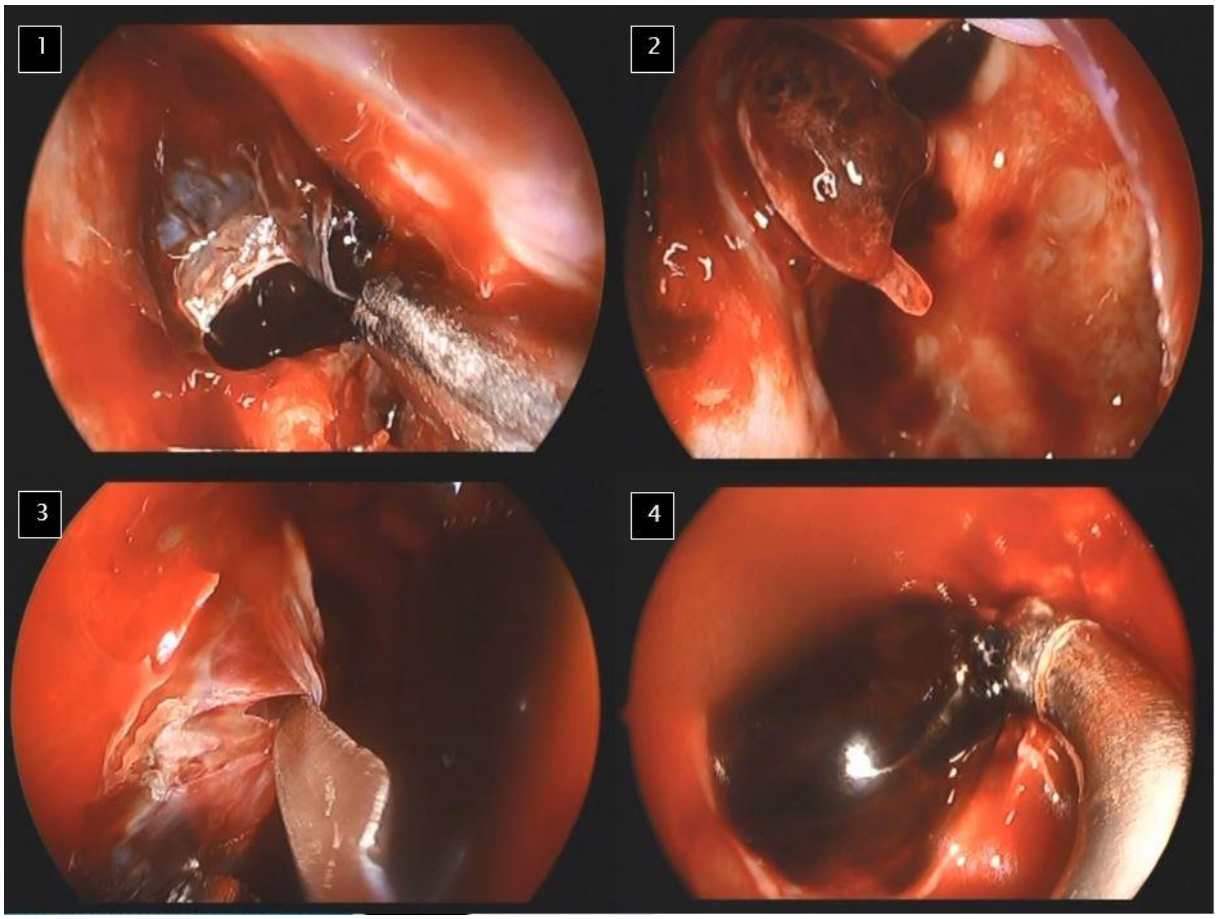

Fig 6: Intraoperative pictures of Patient 2 [1] Appearance of sphenoid sinus with irregularly torn dura and protruding hematoma [2] After evacuation of hematoma in sphenoid sinus, tumour was seen eroding sella floor and protruding into sphenoid sinus [3] Dura opened completely [4] Hematoma within the sella evacuated

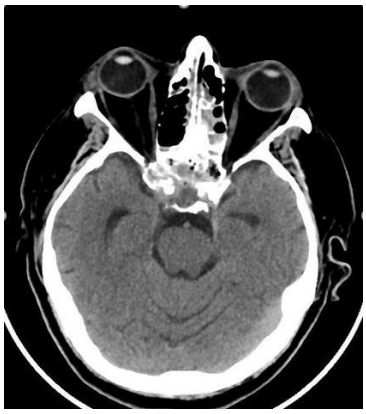

Fig 7: Immediate postoperative CT brain plain of Patient 2

Postoperative period was uneventful. His headache relieved postoperatively, started on Bromocriptin and discharged in stable condition. He is on regular follow-up and asymptomatic.

Results

1.1. Demographics

A total of 62 patients were operated for pituitary adenoma within the study period out of which 6 patients (9.6%) had pituitary apoplexy. Mean age of patients operated for pituitary apoplexy is 56.3 years ranging from 24 years to 78 years. In our series, incidence in females is twice more than males with a female to male ratio of 2:1.

1.2. Presentation

Most frequent presenting symptom is sudden onset severe headache which is present in all 6 patients (100%). Headache is associated with visual symptoms in 4 patients (66%) out of which only field defects is present in 3 patients (50%) and 1 had rapidly progressing loss of vision (17%). Decreased conscious level is seen in 2 patients (33%). Previous history suggestive of endocrine disturbance is noted in 2 patients in which one had amenorrhoea and another had symptoms of hypothyroidism.

1.3. Imaging

All 6 patients underwent initial Computed Tomography Brain out of which most frequent finding was widening of sella seen in all 6 patients (100%). Hyperdensity in CT suggestive of haemorrhage is seen in only 4 patients (66%). Erosion of sella floor with extension into sphenoid sinus is seen in 1 patient.

MRI brain was done in all 6 patients, mean dimensions of sellar lesions is 3.1x2.3x2.2 cm (APxLRxSI). Radiological evidence of haemorrhage in MRI is seen in 4 patients (66%), sphenoid sinus invasion is seen in one patient.

1.4. Endocrinology

Most frequent endocrinological abnormality encountered in cortisol deficiency which is seen in 5 out of 6 patients (83%) and 1 patient had all hormones within normal limits. Along with cortisol deficiency 1 patient had prolactin excess, 1 patient had prolactin deficiency, 1 patient had hypothyroidism and 1 patient had panhypopituitarism.

1.5. Pathology

Operative specimens of all 6 patients were reported to be adenomas on histopathological examination. Endocrinologically 1 patient had prolactinoma as evidenced by markedly elevated serum prolactin levels. Histopathological examination also revealed that one patient, whose radiology did not show any evidence of

haemorrhage, had ischemic apoplexy while rest of the five patients had haemorrhagic component in pathology specimen.

1.6. Operative, Postoperative course and outcome

Out of the 6 patients, only one patient had torrential bleeding intraoperatively which mandated the termination and abandoning of the procedure after which she was stabilized, reoperated after 3 days, procedure was uneventful and discharged in stable condition, the same patient succumbed to death after 6 months due to acute renal shutdown which is unrelated to the pituitary pathology. One patient improved clinically in postoperative period except for hypothyroid status but developed recurrent LRTI leading to sepsis and died on 12th postoperative day. Except for this one patient rest of the 5 patients (83%) had good outcome at 6 months follow-up with one having residual bilateral CN VI palsy.

1.1. Endocrinological outcome

2 out of 6 patients (33%) had their hormonal profile within normal limits at 6 months follow-up. Total of 4 patients developed hypothyroidism for which they are on thyroxin replacement therapy, out of these 4 patients only 1 patient developed transient Diabetes insipidus which resolved spontaneously and 1 patient developed cortisol deficiency for which he is on steroid replacement therapy along with thyroxin replacement.

Discussion

62 patients underwent transnasal endoscopic surgery for pituitary pathologies within the study period in our institute out of which 6 patients had pituitary apoplexy, incidence is 9.6% which is comparable to previous studies. In out short series of pituitary apoplexy cases managed by transnasal endoscopic surgery, 4 patients underwent early surgery[1] (<72 hours of symptom onset), and 2 patients underwent delayed surgery[1] (>72 hours of symptom onset). Due to the small sample size of our series, no statistically significant conclusion could be drawn in relation to timing of surgery from symptom onset as indicated in the previous larger studies[1,2].

Demographically our series had a female preponderance with female to male ratio of 2:1 as opposed to other larger studies[1,3,4,5] all of which shows male preponderance with a male to female ratio of 2:1. Mean age of presentation is 56.3 years which is matching with the previous studies[6].

Patients presented with sudden onset severe headache, visual field deficits, diminishing consciousness, progressive vision loss and epistaxis in decreasing order of frequency which is comparable with the previous studies[1]. Only one patient had preoperative profuse epistaxis which was not reported in the literature to the best of our knowledge. Previous history of endocrine dysfunction is noted in 2 patients on detailed history, 1 had symptoms suggestive of hypothyroidism and 1 had amenorrhoea.

Radiographically all patients had features of a lesion in sella apart from features of haemorrhage which indicates that all are macroadenomas[3,4,5,7,8,9]. As indicated by the larger previous studies[4,6,8,10,11,12,13], tumour size may be directly proportional to incidence of apoplexy which may also suggest that macroadenomas are more prone to present as apoplexy. Endocrinologically 5 out of 6 patients (83%) had non-functional adenomas with only 1 patient having a functional adenoma specifically prolactinoma.

As many previous larger studies[2,4,6,14,15,16] suggest, endocrinological recovery is not so satisfactory as only 2 out of 6 patients attained full hormonal independence at 6 months follow-up. Most frequent hormonal dysfunction postoperatively is hypothyroidism followed by transient diabetes insipidus and cortisol deficiency in the order of decreasing frequency.

Study limitations

As our study is a single center retrospective cohort study with very small sample size, no statistically significant conclusions can be drawn from this study. As most of the results are similar to the previous larger studies, this study may be considered as an adjunct for further studies and meta-analysis, as there is only limited data available in the literature till date.

Conclusion

Pituitary apoplexy can present as a neurological and neurosurgical emergency which affects both neurological and endocrinological systems. Early surgical decompression is beneficial in selected cases where clinical outcome is good but endocrinological outcome is not very satisfactory even in early surgeries.

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Primary Cns Lymphoma In Immunocompetent: Rising Trend, Why?

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Abstract

An increased incidence of Primary central nervous system lymphomas (PCNSL) has been noticed in both immunocompromised and immunocompetent patients with majority of these being diffuse large B cell lymphomas (DLBCL). Our study is aimed to assess the trend of incidence among the immunocompetent patients at our institute.

All histopathologically proven cases of PCNSL were reviewed from 2012 to 2018 and clinical details were obtained from patient records. Immunodeficiency-associated lymphomas were excluded and possibility of systemic lymphoma was ruled out.

Result: Over a 5-year period, a total of 52 cases were reported as primary CNS lymphoma (two were retroviral and one was HBsAg positive). No other cause for immunocompromised state in rest of the patients was identified. A gradual increase in the number of cases every year was noticed. Almost, in all cases histopathology revealed Diffuse Large B Cell Lymphoma(n=47) with high Ki67% but one case was T-cell type.

Conclusion: A rising trend of PCNSL was noticed at our institute over the five years, however, a parallel increase in the incidence in overall CNS tumours especially Glioma was also noticed during the same period (p=0.001).

Key words: Central nervous system, immunocompetent, immunocompromised, incidence, India, Primary CNS Lymphoma

Introduction

Primary CNS lymphoma is a rare, extra nodal Non-Hodgkin's lymphoma (NHL) confined to the brain, leptomeninges, eyes, or spinal cord. WHO classification of hematopoietic and lymphoid tissue has defined it as a diffuse large B cell lymphoma of CNS involving intracerebral, spine and intraocular region (1). The lymphomas of CNS with evidence of systemic disease are secondary CNS lymphoma. PCNSL was first reported in 1929 by Bailey (2) who initially used the term 'perithelial sarcoma' for this rare entity. Later various other names were described - perivascular sarcoma, adventitial sarcoma, malignant reticuloendotheliosis, reticulum cell sarcoma, and microglioma. It was much later recognized as neoplasia of lymphoid nature by histopathology and was distinct from glial tumors by immunophenotyping (3).

Its diagnosis and management are a controversial topic in neuro-oncology owing to its complexity and limited number of controlled studies. Since it has a particular gene expression and genomic profile (4,5,6) its management also differs from that of other primary cancers and NHL. Historically also PCNSL has been considered to be associated with a significant worse prognosis than systemic lymphomas of the same histology. Historically also, despite multimodality treatment approach, improvement in chemotherapy regimens and tumour being highly chemo-radio sensitive (7,8) patient still have dismal prognosis and remission is of short duration.

In early 1970s it was a rare neoplasm comprising < 1% of intracranial tumors (ICT) (9,10,11) but later it was noticed that the incidence increased > 10-fold (12). Approximately there were 2.5 cases per 10 million population in 1973 and 30 cases per 10 million in 1992 (13). Hence in 1990s, PCNSL comprised nearly 7% of all primary brain tumors (14). This change in the frequency was considered due to the acquired immunodeficiency syndrome(AIDS) epidemic and thus this disease was called as MALIGNANCY DEFINING AIDS". However, with the use of HAART, the following next 5 years, a decrease in the incidence was reported.

At the same time an equal concern was the rising incidence among immunocompetent individuals. In India, although few studies have been published (3,11,15,16,17), in most a rising trend has been reported more commonly among immunocompetent patients which remains unexplained. Out study was aimed to assess the trend of incidence among the immunocompetent patients at our institute.

Material And Methods

This study was carried out at Apollo Cancer Institute (ACI), Chennai a tertiary care centre. All histopathologically proven cases of primary CNS lymphoma from January 2012 to May 2018 were included in the study. Immunodeficiency-associated lymphomas were excluded by HIV serology report. No other cause for immunocompromised state such as post-transplant state, history to suggest immunodeficiency states or long-term steroids usage was identified in any other patients. Complete clinical details were obtained from patient's records including clinical presentation, laboratory IHC findings etc. CSF findings were recorded whenever available. Possibility of systemic lymphoma was ruled out by obtaining details pertaining to lymphadenopathy, PET CT and bone marrow study. The total number of intracranial tumours (ICT) and gliomas diagnosed during the same period were also obtained to evaluate the relative incidence. Statistical analysis was performed using statistical software package SPSS version 20: categorical variable – chi square test, continuous variable – one-way ANOVA. P value of < 0.05 was considered statistically significant to refute the Null hypothesis.

Informed consent was obtained from all patients at the time of surgical procedure. Most patient (37 cases) underwent chemotherapy i.e. high dose MTX dose protocol or intensive chemo-immunotherapy (MTX, ritumixab, cytarabine) followed by whole brain radiation & focal boost later.

Results

Total 57 cases were reported as primary CNS lymphoma among which only 2 were retroviral positive and One was HBs Ag positive. A gradual increase in the number of cases every year was noticed. In 2012 incidence was 10.5 % and in 2017 it increases to 24.5% and in 2018 within 6 months incidence was 14% as shown in Figure 1. However, a parallel increase in the incidence in overall other CNS tumour especially Glioma (p=0.001) was also noticed during the same period (Figure 2). The general characteristics of the patient population are given in Table 1. The age of the patients ranged from 18-76 years, with mean age at diagnosis as 51.7 years. Males outnumbered females (37:20) with mean age in male as 52.95 and in female as 49.5yrs (p=0.016). The mean duration of symptoms before histological diagnosis was 1month but it ranged from 3 days to 2 years. The commonest presentation was focal neurological deficits followed by headache and vomiting. Other presenting symptoms included seizures, visual and speech disturbances, personality changes and gait disturbances. B-symptoms which includes fever, night sweats and weight loss were very uncommon in our series, and only one patient had B-symptoms at presentation

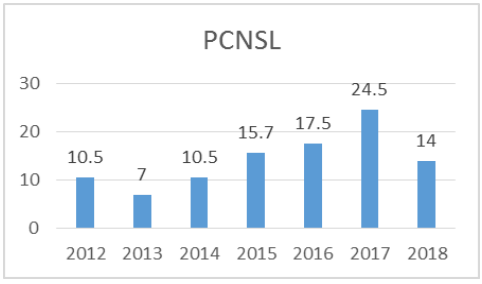

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Figure1. Year wise distribution of cases with incidence

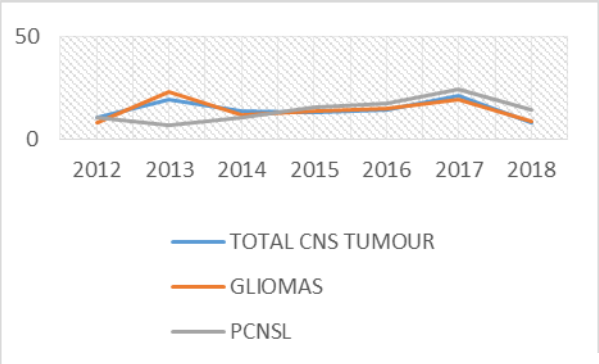

Figure 2. Trend of CNS tumours

The majority of the lesions were located in the supratentorial region with the frontal and temporal regions being the sites most commonly involved. The spine was involved in 3 cases (Figure 3) and there were 2 cases where orbit was involved including one case with both spine and orbit being involved.

The tumours were multifocal in 43.9% (n=24) cases. In most of the patients MRI was done at our institute but in few patients in whom imaging was done elsewhere, MRI findings were reconfirmed by our neuro-radiologists. Almost 90% of the tumors were larger than 1 cm, all were hypointense on T1W, and iso- to hyperintense on T2 W images with most tumors homogeneously contrast enhancing. Most of the lesions were associated with perilesional edema in FLAIR sequences. Borders were ill-defined in 80% (Figure 4) and sharply circumscribed (Figure 5) in few of the cases. More than two thirds of the lesions produced only a moderate or absent mass effect (51% and 15%, respectively). Only two cases were accompanied by hydrocephalus for which one underwent VP shunt and in other EVD was placed. None of the lesions had any evidence of bleed or calcification. In a few cases diffusion study was done, almost all were showing diffusion restriction. MRS was done in three patients only, all showing Choline peak.

Preoperative diagnosis of lymphoma was made in most of the patients, but in few, glioblastoma, meningioma, and metastasis were the presurgical diagnosis. In one case abscess was suspected due to the ring enhancing features near periventricular region. One case was initially diagnosed and treated as tuberculoma but as serial MRI sequences showed progression of the disease with new lesions stereotactic biopsy was done which revealed PCNSL. There was 1 case which was treated as multiple sclerosis for which patient was on long duration steroids. Initially there was improvement in the symptoms and imaging showed resolution of the symptoms, however few months later as repeat MRI revealed new lesions with typical radiological characteristics of lymphoma, PCNSL was suspected and patient was then evaluated and treated in the same direction.

All the patients were assessed for evidence of a systemic lymphoma. Most of the patients had a bone marrow evaluation which were normal. PET CT was done in 45 cases which did not revealed any other systemic involvement.

Mostly Stereotactic biopsy were performed (n= 24, 43.1%) to confirm the diagnosis as lesions were in eloquent areas like thalamic, basal ganglia, splenium lesions or in cases with confirmed lymphoma diagnosis. Craniotomy and excision of the lesion (gross total/ near total/ partial excision/ debulking) was done in 17 patients, mostly when a single accessible location of lesion causing mass effect was present. Craniotomy and open biopsy were mostly used in patients with cerebellar involvement. For orbital lesions diagnostic vitrectomy was done and for spinal lesions excision was done.

47 specimens were analyzed and reported at our pathology laboratory. All cases were Diffuse large B cell lymphomas showing features of NHL in which tumour cells were disposed in a diffuse sheet pattern or dispersed pattern. The cells were large having vesicular nucleus, 1-3 conspicuous nucleoli and moderate amount

of pale to eosinophilic cytoplasm. Perivascular arrangement of the tumour cells was observed in the majority of the cases (Figure 7). All cases showed a very high proliferative activity with Ki67 indexes of 70–90%.

In all cases Immunohistochemistry showed majority of cell with CD 20 cytoplasmic positivity (Figure 8,9), except one case which was T cell lymphoma with strongly CD 3 and negative CD 20 markers. EBV was negative in all cases except one case, which was histologically a diffuse large B cell lymphoma, a 71-year-old female neither immunocompromised nor immunosuppressed, but showed focal positivity for EBV. GFAP was done in few cases to rule out High grade glioma.

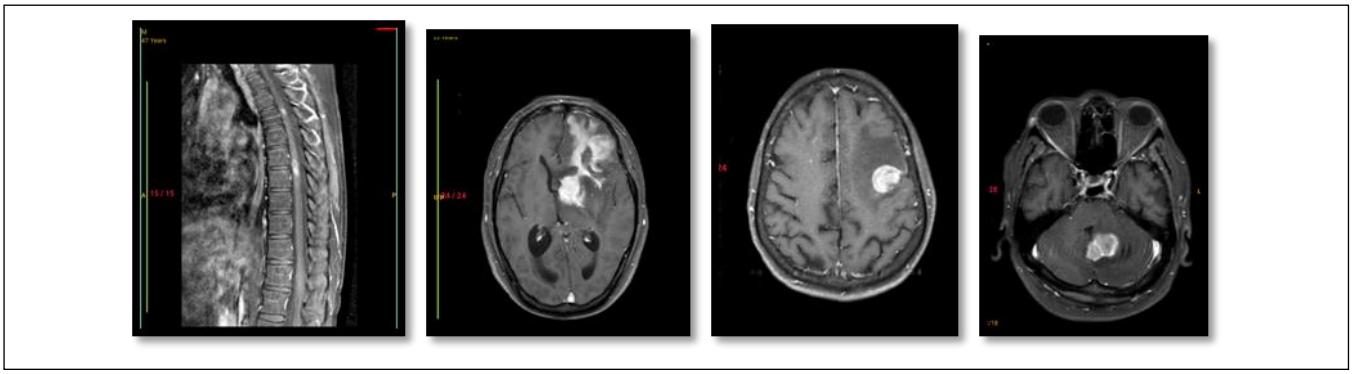

Figure 3. PCNSL involving spine

Figure 4. Heterogeneously enhancing ill-defined periventricular lesion

Figure 5. Heterogeneously enhancing well defined frontal lesion with perilesional oedema

Figure 6. PCNSL involving cerebellar

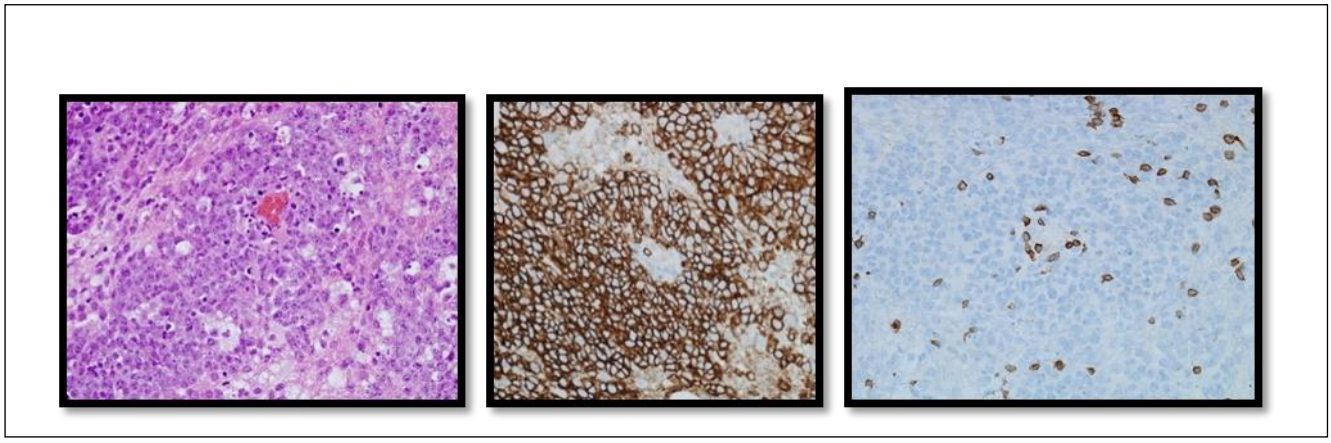

Figure 7: Photomicrograph showing neoplastic lymphoid cells around a vessel (H&EX10).

Figure 8: Photomicrograph showing tumour cells with strong CD-20 positivity

Figure 9: Photomicrograph showing tumour cells with interspersed CD-3 positive cells

Table 1. Clinical features of PCNSL

Sex	
Male	37
female	20
Age (years)	
Mean	51.7
Median	54
Female Mean age	49.
Male Mean age	52.95
Age distribution	Percent
<=20 years	5.3
21 to 30 years	1.8
31 to 40 years	12.3
41 to 50 years	10.5
51 to 60 years	50.9
61 to 70 years	14.0
71 to 80 years	5.3
Symptoms	Percent
LIMBS WEAKNESS	43.9
HEADACHE	38.6
SPEECH DYSFUNCTION	17.5
VOMITING	14
ALTERED SENSORIUM	12.3
BEHAVIOURAL DISTURBBANCE	12.3
VISION DISTURBBANCE	12.3
SEIZURES	12.3
MEMORY DISTURBBANCE	10.5
BACK ACHE	3.5

Region	Percent
MULTIFOCAL	43.9
SINGLE	42.1
ORBIT	3.5
SPINE	5.3
SPINE+PARENCHYMA	3.5
SPINE+ORBIT	1.8
FRONTAL	15.8
TEMPORAL	8.8
PARIETAL	5.3
GANGLIOCAPSULAR	7.0
THALAMIC	3.5
PERIVENTRICULAR+LOBAR	7.0
POSTERIOR FOSSA	10.5
CORPUSCALLOSUM	7.0
OTHERS	35.1
Surgical Intervention	Percent
STEREOTACTIC BIOPSY	42.1
CRANIOTOMY AND GROSS TOTAL EXCISION	10.5
CRANIOTOMY AND NEAR TOTAL EXCISION	8.8
CRANIOTOMY AND PARTIAL EXCISION / DEBULKING	15.8
CRANIOTOMY AND OPEN BIOPSY	10.5
VITRECTOMY	3.5
SPINE SURGERY	3.5
NIL SURGICAL INTERVENTION	5.3

Discussion

Our study was aimed to evaluate the clinicopathological profile of patients diagnosed as PCNSL, to determine the incidence of PCNSL at our institute, and whether the increase in the incidence is significant when compared to other intracranial tumours. Also, to compare the trend occurring in other parts of India and other countries.

Initial studies from western countries have reported an increased incidence of PCNSL in both immunocompromised and immunocompetent patients (13,1418,19,20). Later few reports suggested that the annual incidence of PCNSL appeared to be stabilizing or in fact its slightly declining. A large-case study in Japan has reported that PCNSL accounted for 2.4% of all ICT (21,22). Previous studies published from India (Table 1) indicates that there was no significant increase in the incidence of PCNSL.

In India where number of HIV positive patients are high, PCNSL is more common in immunocompromised group; it is also noted to be in the majority in the immunocompetent group too. The possible explanation for this could be that AIDS patients die earlier in India due to opportunistic infections. Though other lymphomas, including those at extra nodal sites seem to occur in India in patients with AIDS, PCNSLs are still infrequently reported (3,16).

In our study, over the last 5 years out of 2459 ICT, 57 cases were diagnosed as PCNSL and 1212 cases as glioma. A gradual progressive increase in number of PCNSL cases each year was noticed, but simultaneously a parallel rise was also noticed in number of overall ICT and glioma cases. Thus, in our study as well there is no statistically significant increase in the PCNSL cases. The reason in this increase in the number of ICT cases involving PCNSL, could be an increasing patient referral or an improved investigative modality, greater clinical and neuropathological awareness, availability of better immunohistochemistry technique.

In our study, the mean age at diagnosis was 51.7 years. which is a decade earlier than the west, similar to other Indian studies (Table 1). Slight male predominance was observed, which is similar to that reported by other studies (15,16). In most of the cases ie. in 42.1% stereotactic biopsy was performed. The histopathological diagnosis revealed that all cases except one, were diffuse large B-cell lymphomas (DLBCL), expressing B-cell markers such as CD20, CD19, and CD79a with predominantly a non-germinal centre B-cell-like (non-GCB) DLBCL subtype with a CD10- BCL6+ MUM1+ pattern. Only one case was T cell type. All cases showed a very high proliferative activity with Ki67 indexes of 70–90%. Epstein-Barr Virus (EBV) early RNA transcripts (EBER) was absent in all cases of immuno-competent patients except one.

Table 2. Indian Scenario: Previous studies published from India

	Powari et al. PGIMER	Sarkar et al. AIIMS	NIMHANS	Paul el al. NIMS (Hyderabad)	Paschira el al. GCRI (Gujarat)	Rudresha et al. Kidwai Memorial Institute of Oncology, Bengaluru	Present study
Study duration years	15(1985–1999)	24 (1983-2003)	18(1986-2003)	19 (1988 – 2006)	13(1997 - 2009)	6(2010-2016)	5 1/2 (2012-2018)
Total PCNSL	40	116	70	56	66	26	57
Median/ mean age	-	44.4 (mean)	39.5 (mean)	42 (median)	46(median)	42.5 (median)	54 (median)
Commonest site	Parietal	Frontal	Frontal	Frontal	Frontal	Cerebral hemishphere	Frontal
Immuocompromised state	2(0.5%)	1(0.86%)	1 (1.43%)	1(1.79%)	0	0	2
Cases underwent IHC	31	106		56	51	20	42
B cell positive	90.3%	99.1%		-	100%	100%	One T cell rest all B cell positive
Inference	no significant increase in the incidence of PCNSL	multicentric hospital based study did not reveal any increase in incidence of PCNSL cases in India over the past 24 years		no significant increase in the incidence of PCNSL	no significant increase in the incidence of PCNSL		no significant increase in the incidence of PCNSL

Conclusion

In lymphomas, PCNSL exhibits a unique pattern of manifestation and requires specific treatment. The incidence of PCNSL is increasing in a population older than 60 years, without clinically overt immunosuppression. In India, it appears to present a decade earlier. With rare exceptions, histopathologic diagnosis is mandatory in planning appropriate treatment. The role of a neurosurgeon in PCNSL is primarily to obtain tissue for confirmation of biopsy, that usually entails a Stereotactic needle biopsy as most lesions are deep seated. Cyto-reductive surgery is reserved for a large single lesion(s) producing mass effect. The mainstay of the treatment is a HD-MTX-based polychemotherapy but radiotherapy also has its role. Hence, it solicits an intense cooperation among various specialists: neurosurgery, neurology, ophthalmologists, haemato-oncology and radio-oncology. Further Molecular studies and genetic analysis is needed in understanding pathogenesis especially in immunocompetent population. Also, a multicentric registry and co-operative prospective study may throw more light on this topic.

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Postoperative Rise In Serum Sodium Level, An Indicator Of Diabetes Insipidus After Pituitary Adenoma Surgery

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Abstract

Objective: To study the efficacy of post-operative rise in serum sodium level as indicator of diabetes insipidus after pituitary adenoma

Methodology: The study is randomized controlled trial. It was conducted in Department of Neurosurgery and Biochemistry Punjab Institute/Ameeruddin Medical College from March 2016 to December 2017. Ethical approval was obtained from hospital Ethics Committee. Total no of 169 patients was enrolled for transspenoidal surgery of their pituitary adenoma. Sample size was calculated from the references study conducted by Schreckinger M et al (10). Non probability consecutive sampling technique was used to collect the sample size. Data was calculated from all consecutive sampling technique was used to collect the sample size. Data was calculated from all the patients regarding age, gender , duration of transspenoidal surgery, postoperative evidences of diabetes insipidus by measuring rise in serum sodium level > 145mEq. Mean and standard deviation was calculated for demographic variables like age and gender while frequency and percentage was calculated for outcome variables like type of diabetes insipidus and sensitivity and specificity of serum sodium > 145mEq test. Chi square test was applied and analysis was done using computer software SPSS versio 23. P value less than 0.05 was considered significant.

Results: Overall, 100% (n=169) patients were enrolled in this study, both genders. Gender distribution showed there were 68% (n=115) males and 32% (n=54) females. The mean age of the patients was 40.88+-4.95 years. Post-operative transient noted in 13.6% (n=23) patients. Serum sodium level (specific) observed in 92.9% (n=157) patients. While, > 145mEq sensitive was observed in 88.2% (n=149) patients. (Table1). The main outcome variable of this study was diabetes insipidus permanent, in our study, it was noted in 9.5% (n=16) patients. (Table 2). There was no association between diabetes insipidus permanent and effect modifiers. (Table 3)

Conclusion: From this study we conclude that level of sodium >145mEq is very sensitive and specific test which can be used to predict the outcome after pituitary adenoma surgery in the form of Diabetes Insipidus.

Keywords: Diabetes Insipidus, Pituitary Adenoma, Postoperative Sodium Level Increase transsphenoidal surgery, hypernatremia, hyponatremia, hypotonic polyuria, polydypsia .

Introduction

All over the world incidence of pituitary tumors is arguably the same (1). Harvey Cushing was the man to pioneer the technique of sublabial and transcranial approach of management in pituitary tumor surgery (2). Since then many evolution have taken place in this procedure. Now along with transsphenoidal surgery, many endoscopic ways to access the sella have been devised. Choice of the procedure is difficult as both endoscopic and transsphenoidal techniques have equal efficacy when it comes to treating the smaller sized tumors but in macro tumors endonasal approach has proved to be more beneficial.

Focus of study is diabetes insipidus which occurs postoperatively in pituitary adenoma surgery along with other hormonal and electrolyte abnormalities (3). Diabetes insipidus is a condition in which low level of ADH secreted by the posterior lobe of pituitary gland results in excessive water excretion and thus polyuria and if not managed properly by optimum fluid intake dehydration (4). One of the major findings in diabetes insipidus is low urine osmolality and high serum osmolality owing to increased serum sodium concentration. There are multiple factors which can predispose a patient to develop postoperative diabetes insipidus after transsphenoidal surgery like, male sex, young age, macro size of tumor, CSF leak and type of the tumor e.g. Rathke-Cleft cyst, craniopharyngiomas and adrenocorticotropic hormone secreting pituitary adenoma (5). Diabetes insipidus occurring postoperatively can be classified as, transient, permanent or triphasic (6). Transient type is the most

common, where prolonged polyuria occurs in only 2-10% (7). Transient diabetes insipidus is called so, because it resolves as soon as ADH secreting neurons recover their normal function. The triphasic type is very uncommon occurring in just 3.4% patients of transsphenoidal surgery. Usually what happens is, after 5-7 days of first phase of diabetes insipidus, it is followed by surge of ADH causing SIADH (syndrome of inappropriate secretion of antidiuretic hormone). This is caused by ADH release from degenerated posterior pituitary tumor or from remaing magnocellular neurons. The duration of second phase is variable, 2-14 days. When a patient after transsphenoidal surgery excretes large amount of urine, approximately >2.5ml\Kg body weight, diabetes insipidus should be considered as the diagnosis. But if there is history of excess fluid intake or intravenous administration during preoperative management or if postoperative polyuria is associated with continuous perioperative infusion of fluids, diabetes insipidus is less likely to be the cause of polyuria. Polyuria is associated with high serum sodium level in diabetes insipidus, if there is no rise in serum sodium level in polyuric patient fluid infusion must be slowed down and sodium level and urine output closely monitored. Confirmation of diagnosis can be done by measuring the high serum sodium level present in continued hypotonic polyuria.

Diabetes insipidus diagnosis is based on clinical as well as biochemical data. Clinical complaints regarding diabetes insipidus are, sudden onset of polydypsia and polyuria, in the time span of 24 to 48 hours postoperatively, patients usually craves for ice cold water (8). Urinalyis will show hypotonic urine with osmolality <200mOsm\kg H 2 O and specific gravity <1.005. Similarly high serum osmolality and hypernatremia is strongly indicative of diabetes insipidus. But patients with free access to fluid intake usually do not have hypernatremia or high serum osmolality due to intact thirst mechanism (9). So water deprivation test is ideal in such cases to detect hypernatremia and hyperosmolality of serum to confirm the diagnosis of diabetes insipidus.

Our study mainly focuses towards the use of serum sodium level in diagnosis of diabetes insipidus and to determine the sensitivity and specificity of this test in diagnosis. In previous literature multiple studies have tried to determine the predictors of diabetes insipidus in postoperative phase

of pituitary tumors surgery. Rationale of this study is to find out the importance of serum sodium level of >145mEq in diagnosing diabetes insipidus.

1.2. Materials and Methods:

The study is randomized control trail. It was conducted in Departments of Neurosurgery and Biochemistry from March 2016 to December 2017. Ethical approval was obtained from hospital Ethics Committee. Total no. of 169 patients was enrolled for transsphenoidal surgery of their pituitary adenoma. Informed consent was taken from the patients prior to surgery to include them in the study. Sample size was calculated from the reference study conducted by Schreckinger M et al (10). Non probability consecutive sampling technique was used to collect the sample size. Data was calculated from all the patients regarding age, gender, duration of transsphenoidal surgery, postoperative evidence of diabetes insipidus by measuring rise in serum sodium level <145mEq. Procedure was performed under general anesthesia, by well experienced neurosurgeon and the person conducting the research collected data from each patient postoperatively. The preoperative workup for patients undergoing transsphenoidal resection of the pituitary includes a thorough history of sinus disease (e.g., hyposmia, epistaxis, nasal polyps, nasal discharge, and sinusitis) and past nasal and sinus surgical treatment. Active or untreated chronic sphenoid sinusitis is a contraindication to performing the transsphenoidal approach to the pituitary. CT scan and MRI were advised preoperatively to diagnose the pituitary adenoma and identify the location of the tumor. In order to diagnose diabetes insipidus, postoperative complaints of polyuria and polydypsia, along with serum ADH level, urine and plasma osmolality were recorded. Serum ADH level was considered as gold standard for diagnosing postoperative diabetes insipidus. In certain cases water deprivation was also used where diagnosis was in doubt. All data collected was taken in the form of a Performa. Mean and standard deviation was calculated for demographic variables like age and gender while frequency and percentage was calculated for outcome variables like type of diabetes insipidus and sensitivity and specificity of serum sodium >145mEq test. Chi square test was applied and analysis was done using computer software SPSS version 23. P value less than 0.05 was considered significant.

1.3. Results

Overall, 100% (n=169) patients were enrolled in this study, both genders. Gender distribution showed there were 68% (n=115) males and 32% (n=54) females. The mean age of the patients was 40.88±4.95 years. Post-operative transient noted in 13.6% (n=23) patients. Serum sodium level.

(specific) observed in 92.9% (n=157) patients. While, > 145 mEq sensitive was observed in 88.2% (n=149) patients. (Table. 1). The main outcome variable of this study was diabetes insipidus permanent, in our study, it was noted in 9.5% (n=16) patients. (Table. 2). There was no association between diabetes insipidus permanent and effect modifiers. (Table. 3).

Table. 1

Demographic and baseline characteristics of the patients

Variable	Frequency	Precentage
Gender	M=115, F=54	M=68% F=32%
Post-Operative Transient	n=23	13.6%
Serum Sodium level Specific	n=157	92.9%
>145mEq sensitive	n=149	88.2%
	Mean±S.D	
Age(years)	0.88±4.95	

Table. 2

Distribution of Diabetes Insipidus Permanent

Diabetes Insipidus Permanent	Frequency	Percentage
Yes	16	9.5
No	153	90.5

Total	169	100.0

Table. 3

Association of Diabetes Insipidus Permanent with effect modifiers

Variable		Diabetes Insipidus Permanent		Total	Chi-Square P-value
		Yes	No		
Gender	Male	2	52	54	0.079
	Female	14	101	115	
Total		16	153	169	
Post-Operative Transient	Yes	1	22	23	0.367
	No	15	131	146	
Total		16	153	169	
Serum Sodium Level Specific	Yes	15	142	157	0.889
	No	1	11	12	

1.4. Discussion:

Majority of the patients undergoing transsphenoidal adenomectomy suffer from endocrine and other homeostatic abnormalities including water and electrolyte disturbances, which usually are transient. Many researches have shown that Diabetes insipidus is much more common complication when compared to hyponatremia caused by syndrome of inappropriate antidiuretic hormone secretion. Studies have shown that diabetes insipidus after pituitary surgery often occurs on first postoperative day and disappears usually within 10 days after surgery (11). In another study about outcomes of transsphenoidal surgery, cerebrospinal fluid leak was a more common complication with incidence of 2.7% while diabetes insipidus lasting less than a year postoperatively had incidence of 1.6% and more than year in 0.4% of the cases (12). Similarly incidence of diabetes insipidus in similar studies about outcomes of transsphenoidal surgery for Cushing syndrome were reported about 15% and other fluid and electrolyte abnormalities occurring in 12.5% of cases while neurological abnormalities had incident of 5.6% (13, 14). While determining the prevalence patterns and predictors of postoperative polyuria,

Hensen et all illustrated that after selective transsphenoidal surgery disturbances in osmoregulation can result in polyuria and polydypsia, which can be detected with the help of perturbations of serum sodium level, thus suggesting high prevalence of this finding in polyuric patients after transsphenoidal surgery for Cushing syndrome (15). In a study correlation between sign and symptoms and a specific finding were discussed, and suggested that diabetes insipidus was significantly associated with increased (P=0.001 and 0.002) thirst while hyponatremia was correlated with decreased thirst (p=0.003). Hypernatremia and increased serum osmolality had considerable association with diabetes insipidus suggesting its presence and severity (p=0.023). Diabetes insipidus and hyponatremia had no correlation with urine sodium excretion and electrolyte free water clearance though (16). Neurosurgeries such as pituitary adenoma surgery, subarachnoid hemorrhage surgery and traumatic brain injury surgery can cause diabetes insipidus acutely. As discussed earlier, onset of diabetes is one to three days after insult during neurosurgery and it manifests as polyuria, polydypsia and hypotonic urine (17). In neurosurgery patients, multiple factors are involved which can result in development of hypernatremia, for instance, diminished consciousness level, cerebral edema, sedation which is achieved for airway management or all of these combined. This is because, presence of these factors impair the sense of thirst or patient's perception regarding fluid ingestion. Therefore daily plasma sodium concentrations and urine output must be monitored on daily basis as patients are vulnerable to develop hypernatremia (18, 19).

1.5. Conclusion:

From this study we conclude that level of sodium >145mEq is very sensitive and specific test which can be used to predict the outcome after pituitary adenoma surgery in the form of Diabetes Insipidus.

1.6. Conflict of Interest:

There was no conflict of interest regarding this study.

1.7. *Funding Source*:

No extra funding source was utilized.

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Post Traumatic Hydrocephalus In Severe Head Injury – Risk Factors

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Abstract

Posttraumatic hydrocephalus (PTH) is a frequent and serious complication that follows a traumatic brain injury (TBI). Its incidence varies greatly from study to study, largely based on different criteria for its diagnosis. The purpose of this study is to identify the risk factors like age, admission Glasgow Coma Scale (GCS), decompressive craniectomy (DC) and findings in initial Computed tomography (CT) scan like Subarachnoid hemorrhage (SAH), Intraventricular hemorrhage (IVH) and skull base fracture which may predispose for the development of hydrocephalus in traumatic severe head injury patients.

This is a single center prospective observational study in which patients with age >=14 and GCS <=8 are followed with regular CT scan for a period of 4 months during January 2013 to January 2016 admitted in our hospital. A total of 32 post traumatic hydrocephalus cases have been identified among 489 cases included in the study resulting in the incidence of 6.54 %. Mean duration of presentation was 48.76 +/-33.26 days. 82% of patients in hydrocephalus group had SAH while 52% in non hydrocephalus group had SAH in initial scan (P=0.001). Decompressive craniectomy was done in 69% patients with hydrocephalus while only 32% of non hydrocephalus group underwent DC (P=0.00001). Other parameters namely age, sex, GCS, IVH and skull base fractures were not significantly associated with development of hydrocephalus.

To conclude decompressive craniectomy and SAH significantly increases the probability of development of post traumatic hydrocephalus while other factors like IVH, base of skull fracture, age and admission GCS do not increase the development of hydrocephalus. Early cranioplasty may prevent the development of hydrocephalus is to be studied.

Keywords: Hydrocephalus, Glasgow Coma Scale, Decompressive Craniectomy, Computed tomography, subarachnoid hemorrhage, Intraventricular hemorrhage, Skull base fractures.

Introduction

Posttraumatic hydrocephalus (PTH) is a frequent and serious complication that follows a traumatic brain injury (TBI). Its incidence varies greatly from study to study, largely based on different criteria for its diagnosis. It could greatly impact morbidity following a TBI and could result in increased mortality if it is not recognized and treated.

The pathogenesis of hydrocephalus after traumatic brain injury is either due to obstruction to CSF flow in the ventricle leading to obstructive hydrocephalus or due to blockage of arachnoid granulation resulting in communicating hydrocephalus by the blood. Risk factors for PTH are yet to be fully identified, as early diagnosis and treatment will reduce the morbidity and mortality.

Decompressive craniectomy done to treat raised intracranial pressure after head injury has been associated with a significant incidence of hydrocephalus. As there was conflicting evidence about the role of subarachnoid hemorrhage, intraventricular hemorrhage, skull base fracture, severity of injury, age and duration of coma in the development of PTH, we performed prospective study to identify whether these factors will predispose for the development of hydrocephalus.

We analyzed all severe head injury patients with regular CT scans to identify the incidence and risk factors for post traumatic hydrocephalus.

Aims and Objectives

1) To assess the incidence of post traumatic hydrocephalus in severe head injury.
2) Role of age, admission GCS, craniotomy and decompressive craniectomy in the development of hydrocephalus.
3) Role of subarachnoid hemorrhage, intra ventricular hemorrhage and skull base fracture in the development of hydrocephalus.

Materials and Methods

We did a prospective observational study of 709 severe head injury patients who presented to our hospital during January 2013 to January 2016.

Four hundred eighty nine patients were included in the study. The severity of injury was defined as duration of coma of at least 6 hours and a Glasgow Coma Scale (GCS) total score of 8 or less in the acute phase. Post Traumatic Hydrocephalus was defined as Evans ratio >0.3, accompanying transependymal edema, the presence of either clinical worsening or failure to make neurological improvement over time.

Post Traumatic Hydrocephalus was defined as the presence on any of the control CT scans of both of the following criteria: 1) Evans ratio >0.3 (the greatest width of the frontal horns divided by the largest biparietal distance between the inner tables of the skull) and 2) Gudeman CT criteriaas. Gudeman CT criteria include enlarged anterior horns of lateral ventricles and enlarged temporal horns and third ventricle in the presence of normal or absent sulci with periventricular translucency.

All severe head injury patients were examined by neurosurgeon in emergency department. Patients with age >=14, GCS <=8 are included in the study. Patients were excluded from the analysis if they were known to have had neurologic deficits before the trauma; those who were expired, lost follow up and CSF analysis suggestive of infection.

All the patients were regularly examined from the time of admission for added neurological deficits and CT brain was done whenever required. Also CT brain was taken for all the patients at the time of admission, 14, 30 and 60 days irrespective of clinical condition even when patient shows good clinical improvement.

The factors like age, sex, admission GCS, initial CT findings like SAH, IVH, Skull base fracture and whether craniotomy or decompressive craniectomy are compared between hydrocephalus and non hydrocephalus groups.

An informed consent is obtained from all the patient attendees. The information collected regarding all the cases were recorded in a master chart. The Statistical analysis was performed on a computer by STATA11.1 (College station, TX USA). The continuous variables were expressed as Mean and Standard deviation. Categorical variables were expressed as frequency and percentage. Independent t-test was used to find the significance between different groups. Chi- square test and fisher's exact test was used to find out association between the categorical variables. A probability value of less than 0.05 was considered statistically significant ($P<0.05$).

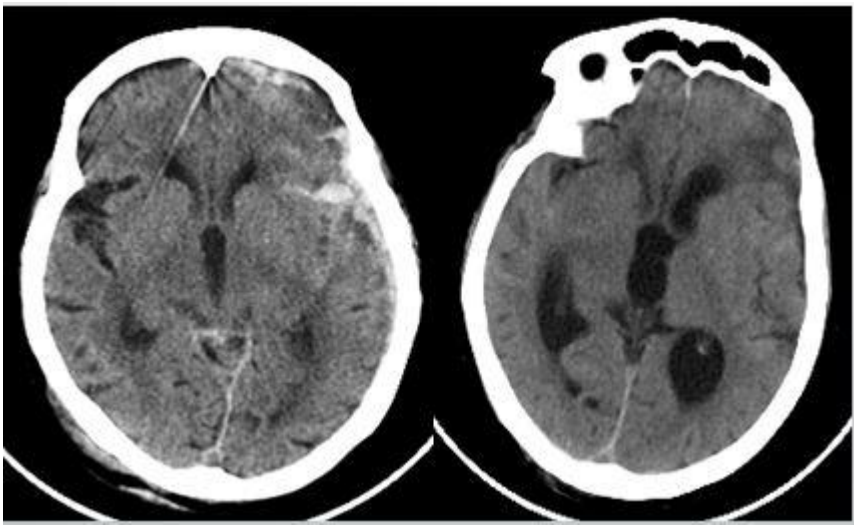


Fig 1: 46 years male who was managed conservatively, Plain CT brain axial section at admission (left) and 24 days CT brain showing hydrocephalus(right)

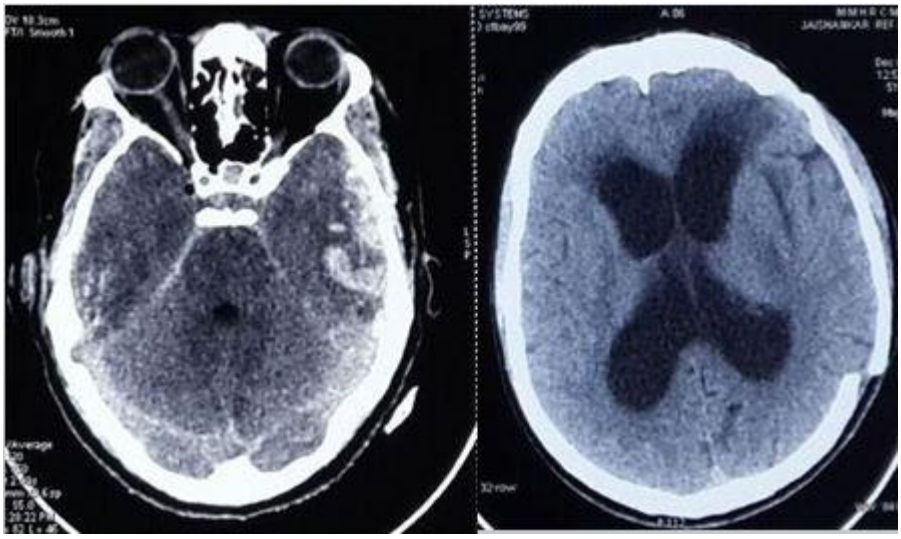


Fig 2: 37 years male who underwent craniotomy, CT brain plain axial section at admission (left) and Ct brain done on day 45 showing hydrocephalus (right)

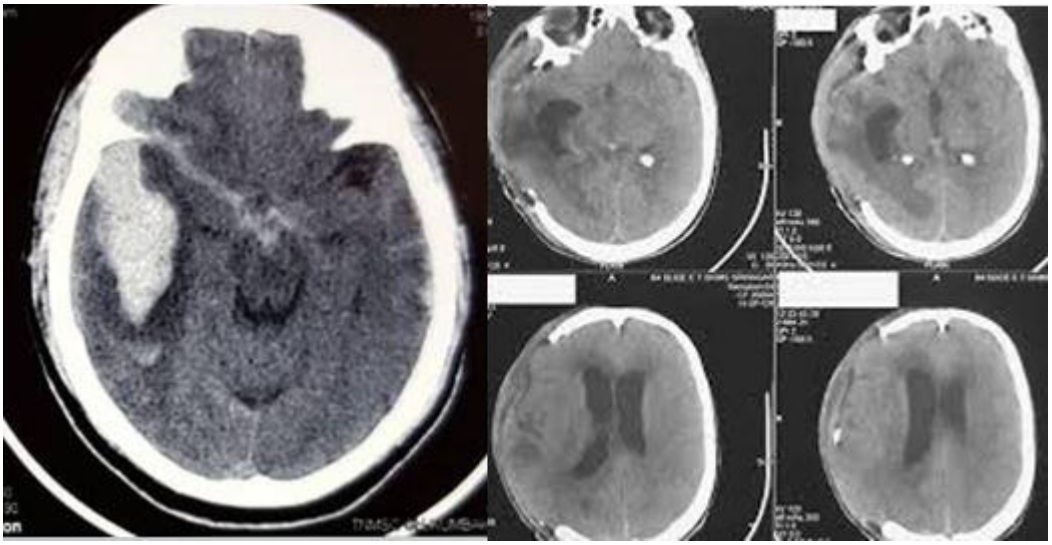


Fig 3: 64 years male who underwent decompressive hemicraniectomy, CT brain plain axial section at the time of admission (left) and CT brain done on day 50 showing hydrocephalus (right)

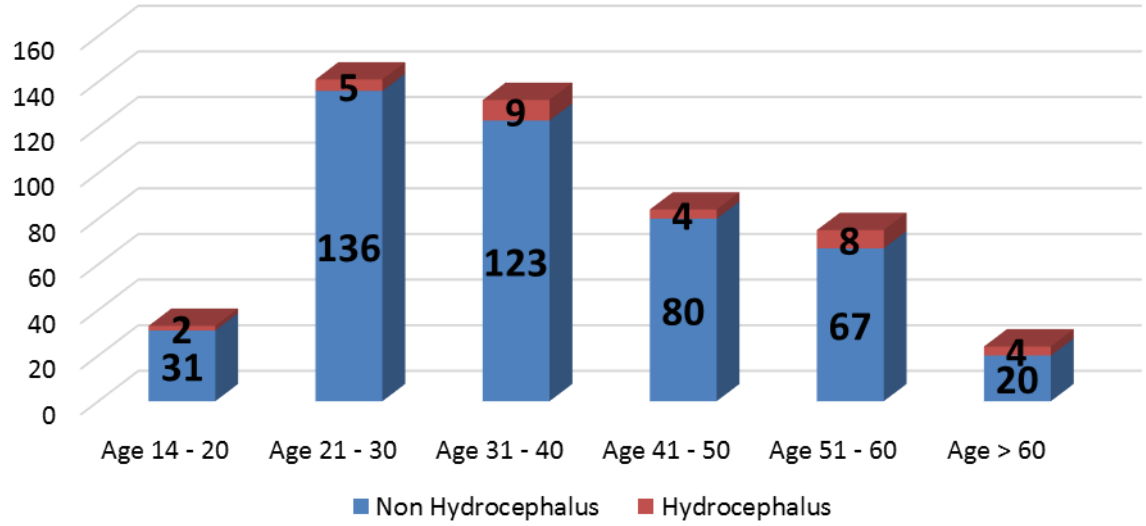
Results

Out of 709 patients who were admitted and managed for severe head injury in our institute, 489 patients met the inclusion criteria and were included for the analysis. Parameters included in the analysis were age, sex, Glasgow coma scale at admission, subarachnoid hemorrhage, intraventricular hemorrhage, skull base fractures and Decompressive craniectomy. The results were as follows.

1.1. Age

The age group ranges from 20 years to 65 years in hydrocephalus group and 15 years to 66 years in non hydrocephalus group. The mean age and standard deviation in hydrocephalus group is 41.21±13.37 and in non hydrocephalus group is 36.74±12.51. The unpaired t- test did not differ significantly (P=0.27).

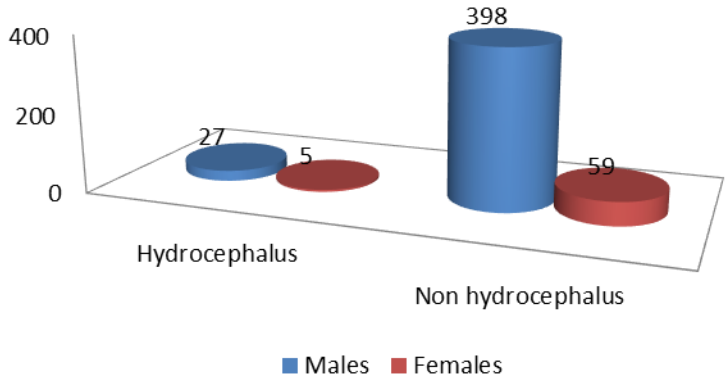
Out of 32 patients who developed hydrocephalus, 17 patients are from younger age, 4 from middle aged and 10 from older age group. There is no influence of age on development of hydrocephalus as p-value is found to be 0.26 which is not statistically significant.(Graph 1).



Graph 1: Age distribution in Hydrocephalus and Non Hydrocephalus groups (Age on X axis, n value on Y axis)

1.2. Sex

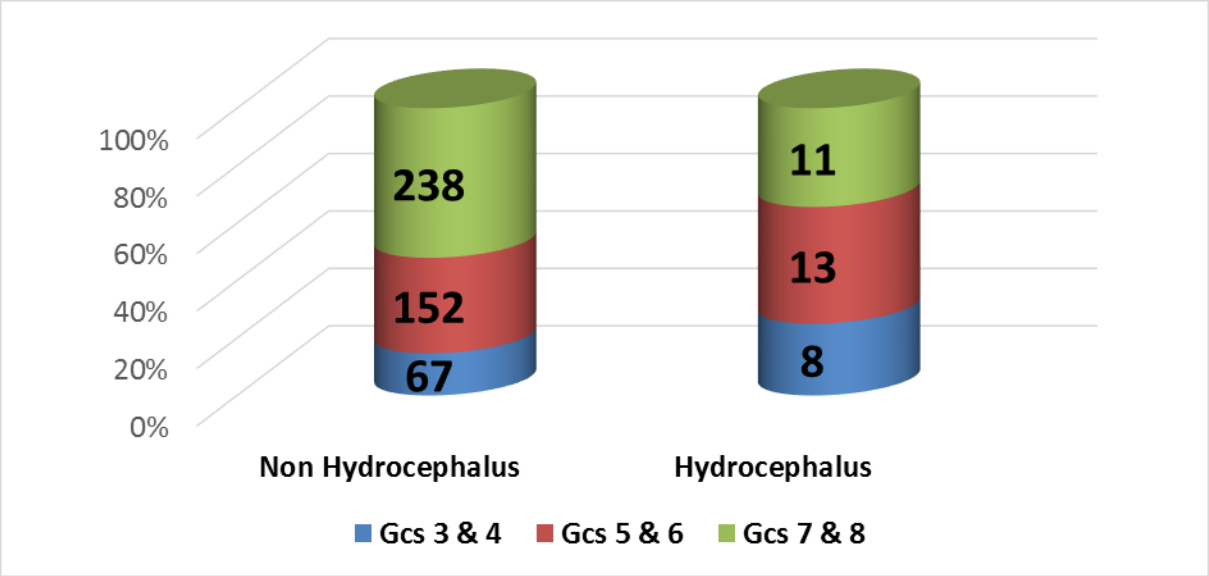
Out of 489 patients, 425 (86.9%) were males and 64 (13.1%) were females. Out of 32 patients who developed post traumatic hydrocephalus, 27 were males and 5 were females with P- value 0.65 which is not statistically significant. Hence there is no influence of Sex on development of post traumatic hydrocephalus (Graph 2).



Graph 2: Sex distribution in hydrocephalus and Non hydrocephalus groups

1.3. Glasgow Coma Scale at admission

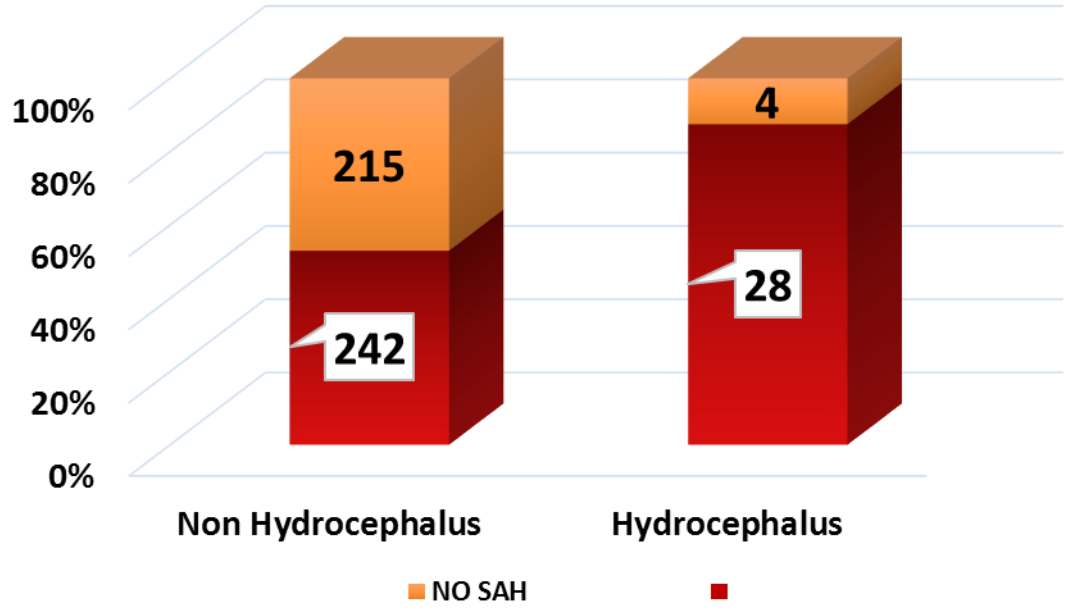
Among the severe head injury patients, GCS score of 7, 8 constitutes 55%, 5, 6 constitutes 32 % and 3, 4 constitutes 14 %. Most of the patients with GCS 3, 4 were excluded from the study due to death and lost follow-up.Out of 32 patients who developed hydrocephalus, GCS 7,8 constitutes 44 % and 5,6 constitutes 38 %. GCS does not seem to influence the development of post traumatic hydrocephalus as p value is 0.44 (Graph 3).



Graph 3:

1.4. Subarachnoid Hemorrhage

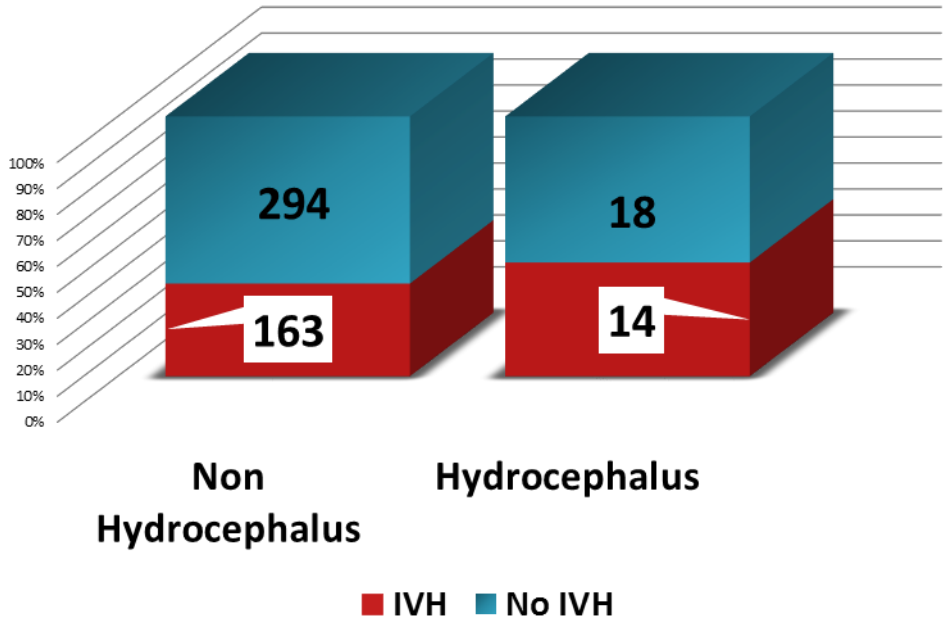
261 patients out of 489 had subarachnoid hemorrhage in our study with hemispheric region is the most common location. 26 patients out of 32 had subarachnoid hemorrhage in various locations like cerebral hemispheres, sylvian fissure, and basal cisterns. Subarachnoid hemorrhage greatly influences the development of hydrocephalus in head injury patients as Fisher exact test showed significant difference (P=0.0008). (Graph 4)



Graph 4:

1.5. Intraventricular Hemorrhage

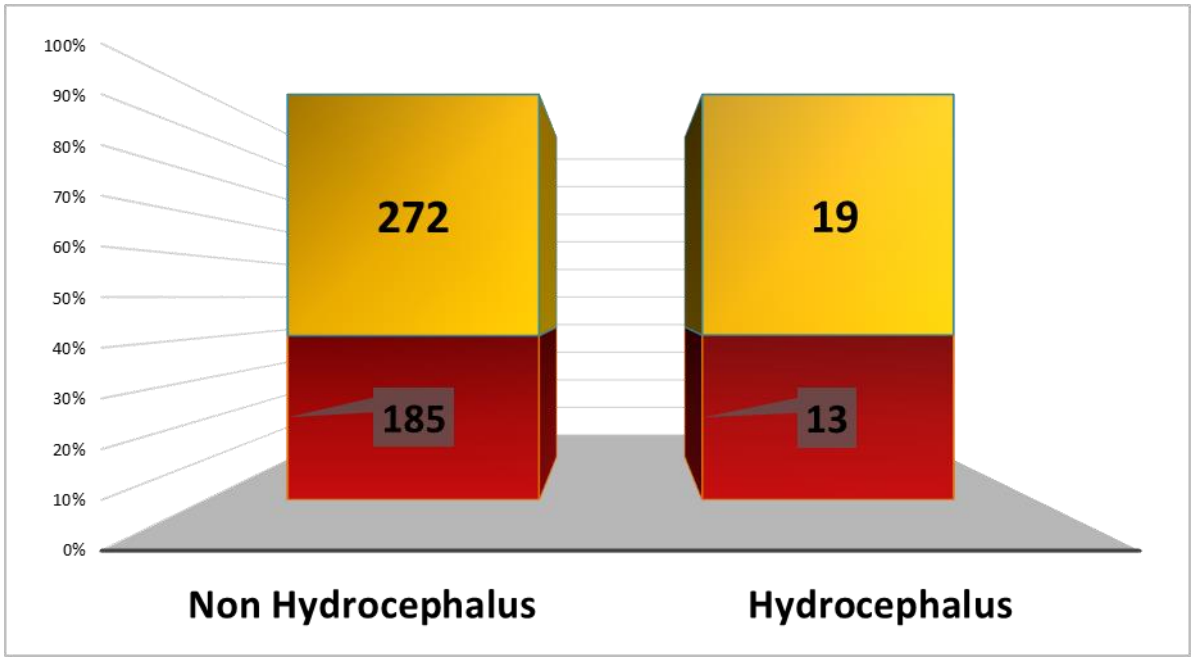
Only 152 patients had intraventricular hemorrhage in our study constituting less than 1/3 of total severe head injury. Only 14 patients in hydrocephalus and 138 patients in non hydrocephalus group had intra ventricular hemorrhage in our study. As P- value was 0.116 in our study, intra ventricular hemorrhage does not seem increase the risk of hydrocephalus in head injury (Graph 5).



Graph 5: Relation between Intraventricular hemorrhage and Post traumatic hydrocephalus

1.6. Skull base fractures

194 patients had base of skull fracture in our study in various locations extending from anterior to posterior cranial fossa.50% of patients in hydrocephalus group had skull base fracture while it constitutes only 39% in non hydrocephalus group. Most common location was middle cranial fossa in our study. Fisher exact test showed no significant difference between two groups (p=0.262) (Graph 6).

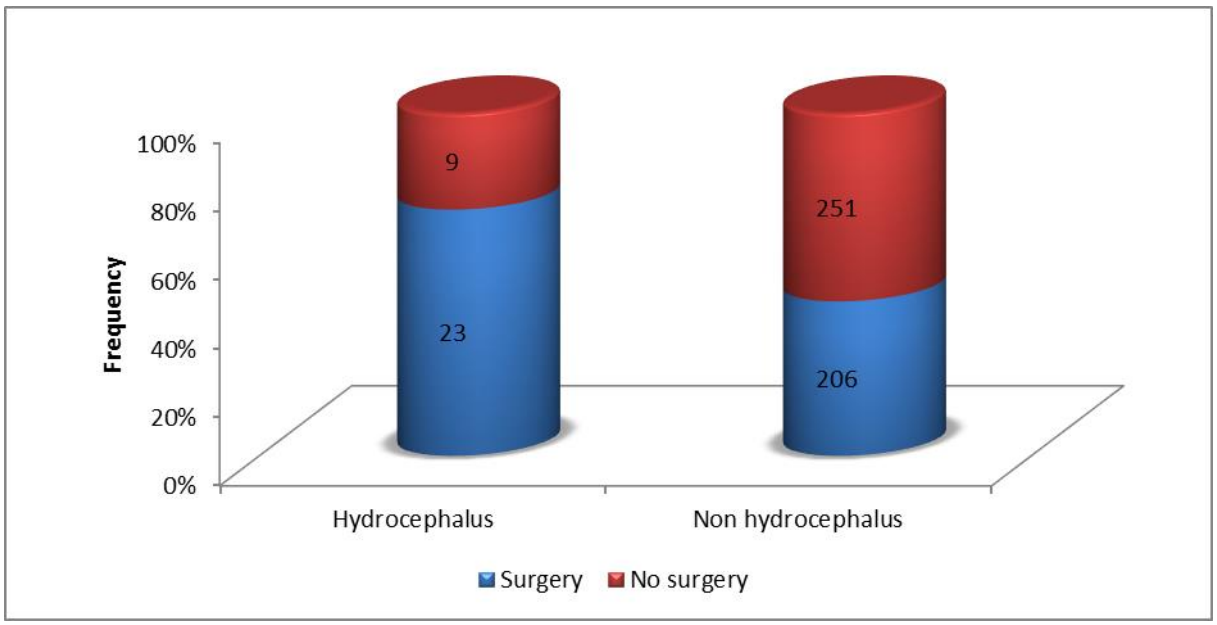


Graph 6: Graph depicting relation between skull base fractures and post traumatic hydrocephalus
Skull base fractures No skull base fractures

1.7. Decompressive craniectomy

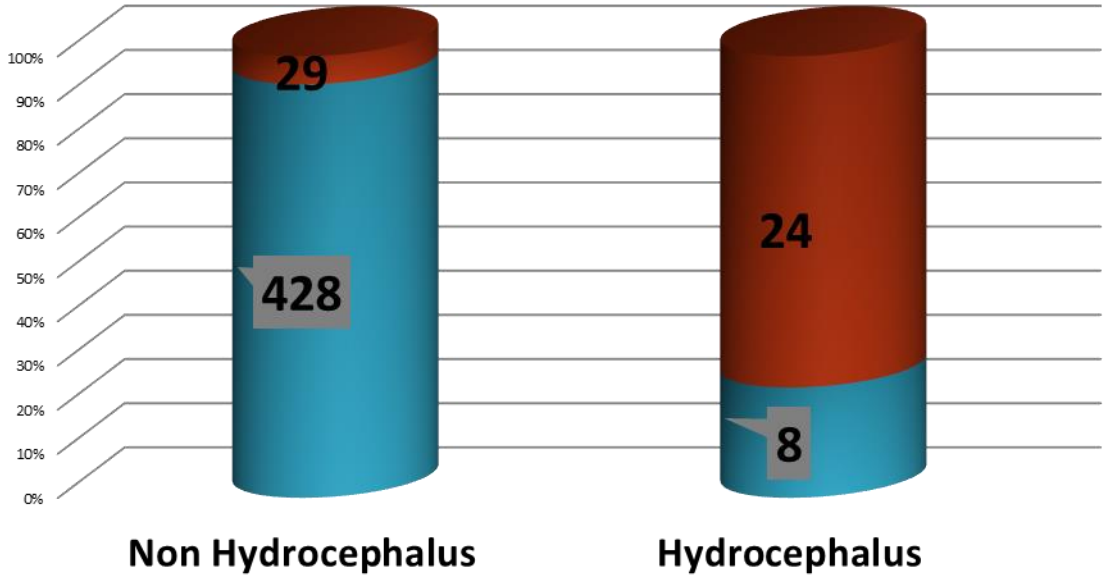
Total of 229 surgeries were performed which include both craniotomy and decompressive craniectomy out of 489 severe head injury patients constituting 47%. The most common indication was unilateral hemispheric

subdural hemorrhage. 23 patients in hydrocephalus group and 206 patients in non hydrocephalus group underwent surgery which includes both craniotomy and decompressive craniectomy. The difference was significant by Fisher exact test (p=0.005) which indicates that surgery itself increases the risk of post traumatic hydrocephalus (Graph 7).



Graph 7: Graph depicting Relation between surgery and development of hydrocephalus

Out of 489 patients, 61 patients underwent decompressive craniectomy. Unilateral frontotemperoparietal decompression was done for all the patients. 22 patients in hydrocephalus group and 39 patients in non hydrocephalus group underwent decompression in our study. The p-value was 0.0001 as calculated by Fisher exact test which is highly significant. Decompressive craniectomy definitely increases the risk of developing hydrocephalus (Graph 8).



Graph 8: Relation between decompressive craniectomy and hydrocephalus

No decompressive craniectomy Decompressive craniectomy

Discussion

In this prospective study which occurred over the course of 4 years in our hospital, we observed 489 cases of severe head injury. Daily neurological examination was performed on all the patients and CT brain was done whenever there were new neurological deficits or patient fails to improve over time. On following for 4 months, 32 patients developed hydrocephalus. The initial CT findings and other factors like age, admission GCS, surgery and decompression are compared between hydrocephalus and non hydrocephalus groups.

Incidence of PTH in world literature is quite variable, ranging from 0.7 to 29 %[1,2,3,4]. Kishore et al found that only 13.7 % of patients with ventriculomegaly had PTH[3]. In the present study, 32 cases out of 489 cases of severe head injury admitted at our center developed PTH. Thus the incidence was 6.54 % in severe head injuries.

PTH commonly occurs in first year post trauma and has been described as early as within 7 hours of injury[1,6,7]. In our series 1 patient was diagnosed on 14th post-trauma day and 1 as late as 190th day. The mean duration of presentation was 56.46 days with standard deviation of 41.59 (mean±SD) (56.46±41.59).

The age in hydrocephalus group ranged from 20 – 65 years with mean age and standard deviation of 41.21±13.37. The maximum number of patients belongs to younger age group (20-40 years) constituting 53% of patients with hydrocephalus. The age does not seem to increase the risk of PTH in our study (p=0.27). The sex distribution was not uniform with maximum number of patients belongs to males constituting 87% of cases in hydrocephalus group.

The retrospective study conducted by Byung-Rae Cho, MD also showed similar results that age and sex had no relation with post traumatic hydrocephalus[8].

The maximum number of patients falls into GCS score of 7, 8 constituting 55% of all cases. Out of 32 patients who developed hydrocephalus, 44% were from GCS scores of 7, 8, 38% were from 5, 6 and 3, 4 constitutes only 18%. The GCS among severe head injury patients was not considered as a risk factor for post traumatic hydrocephalus in our study as Fisher exact test does not show any significant difference between two groups. The same result was seen in retrospective study done by Byung-Rae Cho, MD[8].

Subarachnoid hemorrhage (SAH) has been cited as the most important pathology leading to development of PTH[1,9,10,11,12]. Obliteration of subarachnoid spaces with fibrous thickening of lepto-meninges particularly in sulci of the convexity and base of brain as a result of SAH has been suggested[13]. 54% of patients had subarachnoid hemorrhage in our study on admission CT brain. In hydrocephalus group, 82% of patients had subarachnoid hemorrhage and in non hydrocephalus group, only 52% had subarachnoid hemorrhage. SAH definitely increases the risk of developing hydrocephalus in our study (p=0.001). The study done by Anthony Marmarou showed SAH influences the post traumatic hydrocephalus[14].

Intra ventricular hemorrhage usually results in acute obstructive hydrocephalus but some studies showed that it increases the risk of hydrocephalus after acute phase causing communicating hydrocephalus. Retrospective cohort study done by Mohd Aidil Mohd Nor showed intraventricular hemorrhage is associated with increased risk of hydrocephalus[15].

31% of patients with severe head injury had intraventricular hemorrhage in our study. IVH constitutes 44% in hydrocephalus group and 31% in non hydrocephalus group. When fisher exact test was applied, there was no statistical significance between IVH and post traumatic hydrocephalus (0.116). The same result was seen in retrospective study done by Byung-Rae Cho, MD. Study performed by Areal Kaen et al. also showed no association between IVH and hydrocephalus[8,16]..

Retrospective cohort study done by Mohd Aidil Mohd Nor showed base of skull fracture increases the risk of post traumatic hydrocephalus probably by altering CSF circulation at the base of brain[15]. In our study skull base fracture was seen in 50% of patients in hydrocephalus group and 39% of patients in non hydrocephalus group. There was no association between skull base fracture and hydrocephalus in our study (p=0.262). Multivariate analysis done by Areal Kaen et al. showed no association between skull base fracture and hydrocephalus[16].

Surgery was performed in 47% of severe head injury patients in our study. 72% of patients in hydrocephalus group and 45% in non hydrocephalus group underwent surgery. We found that surgery increases the chances of developing hydrocephalus (P=0.005) in our study. Though there were many studies stating that decompressive craniectomy increases the risk of hydrocephalus but no studies are there to show any surgery will increase the risk of hydrocephalus.

Decompressive craniectomy (DC) has been found to be associated with development of PTH by altering CSF pressure dynamics, mechanical blockage around convexities or inflammation of arachnoid granulations by post-surgical debris. 9% of patients with severe head injury underwent decompressive craniectomy in our study. In hydrocephalus group decompression was done in 69% and in non hydrocephalus group 32% underwent decompression. Our study also showed similar results that DC definitely rises the risk of hydrocephalus in severe head injury (P=00001).Retrospective study done by Phuenpathom N also showed

similar result[16].Study done by Ariel Kaen and his colleagues found that the decompressive craniectomy significantly increases the risk of PTH and IHH predicts the development of hydrocephalus[16].Study done by Czosnyka at.al and Choi at. al on the influence of craniectomy on the CSF circulation identified large craniectomy with <25mm width at the sagittal sinus increases the risk of PTH[17,18].

Conclusion

In our study, we found that the incidence of post traumatic hydrocephalus was 6.54% in severe head injury. Risk factors like age, sex and admission GCS does not seems to increase the risk of post traumatic hydrocephalus. Subarachnoid hemorrhage is the only initial CT finding which increases the risk of post traumatic hydrocephalus whereas other findings like intra ventricular hemorrhage and skull base fracture does not seem to be the significant risk factors for post traumatic hydrocephalus. Surgery and decompressive craniectomy are two main factors which significantly increases the risk of post traumatic hydrocephalus.

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Production Of IDH1 R132H Recombinant Protein In Escherichia Coli As Therapeutic Candidate And Development Of Stable Transfected IDH1 R132H Malaysian Recurrent Glioblastoma Cell Line

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Abstract

Glioblastoma multiformes (GBMs) are the most malignant and aggressive primary adult brain tumors with a median survival of 15 months. Recurrent GBMs exhibit a higher malignancy and more resistance to medical treatments compared to the newly diagnosed GBMs which results in patient's death. Gliomas with IDH1 mutations were found to have better prognosis compared to IDH1 wildtype. The effect of IDH1 R132H mutation in recurrent GBMs remains far from elucidated. Therefore, stable transfected IDH1 R132H in Malaysian recurrent GBM cell line, USM-GI-06 is required. We performed cell line authentication and IDH1 gene screening on the USM-GI-06 cell line. IDH1 coding sequence was isolated from the cells, cloned into bacteria expression plasmid, mutated into IDH1 R132H and purify the IDH1 recombinant protein from *Escherichia coli (E.coli)*. The IDH1 R132H gene was transfected into the USM-GI-06 cells to create a stable transfected IDH1 R132H mutant cell line. We found that the USM-GI-06 cell line was unique, harbored IDH1 wildtype gene and suitable for transfection, thus it can be an alternative GBM model compared to commercially available cell lines. IDH1 R132H recombinant protein was successfully purified from the *E.coli* and can be used in the development of cancer vaccine and adoptive therapy in glioma. IDH1 R132H protein may exist different structural states in *E.coli* and GBM.

Keywords: Recurrent Glioblastoma, Escherichia coli, IDH1 R132H, protein expression, transfection

Introduction

Annually, about 20,000 people in the United State suffered from gliomas (Cohen et al. 2013). Gliomas are commonly found in adult central nervous system tumors, approximately 30% (Yamamichi et al. 2016). Gliomas are primary brain tumors classified into WHO grade I, II, III, and IV based on clinical criteria and histology (Shi et al. 2015). Grade IV gliomas, glioblastoma multiformes (GBMs) are the most frequent and most aggressive primary brain tumor in adults (Aum et al. 2014; Lau et al. 2014).

GBMs remain incurable even with the current surgical techniques, chemotherapy and radiotherapy treatments. The prognosis remains dismay as the median survival of GBM patients was approximately 15 months only (Liu et al. 2016). In addition, the recurrence rate of GBMs is about 90% (Weller et al. 2013). The recurrent GBMs were found to be more resistant to medical treatments and more aggressive compared to newly diagnosed GBMs (Lau et al. 2014).

IDH1 mutations were initially found in 12% of GBM patients (Parsons et al. 2008). Subsequent studies found that IDH1 mutations were highly restricted in gliomas (Bleeker et al. 2009). About 70% of diffuse astrocytomas and secondary GBMs harbored IDH1 mutations (Nobusawa et al. 2009). IDH1 mutations existed prior TP53 mutation and 1p/19q codeletion. The mutations were stable when progressed to a higher grade of gliomas (Dang et al. 2016). IDH1 mutated GBM patients have better overall survival and progression-free survival compared to IDH1 wildtype GBM patients (Liu et al. 2016). There are seven IDH1 mutations have been reported which were R132H, R132C, R132S, R132G, R132L, R132V and R132P (Agarwal et al. 2013). IDH1 R132H mutation was found in 92.7% of IDH1 mutated diffuse gliomas and the remaining IDH1 mutations were rare (Hartmann et al. 2009).

IDH1 enzyme catalyzes oxidative decarboxylation of isocitrate to alpha-ketoglutarate (α-KG) with production of NADPH. Mutant IDH1 inhibits the normal IDH1 enzymatic function resulting in a low level of α-KG. Mutant IDH1 exhibited novel enzymatic activity where α-ketoglutarate (α-KG) converted to D-2-hydroxyglutarate (D-2-HG) with oxidation of NADPH (Dang et al. 2009).

High frequency, stability and better prognosis of IDH1 R132H in gliomas have triggered the possibility of targeted glioma immunotherapy development. Therefore, IDH1 R132H antigen is required. Recurrent GBMs have limited standard care treatments and showed modest response to available treatments (van Linde et al. 2017). In addition, difficulty in establishing glioma cell line with endogenous IDH1 R132H mutation has imposed challenges in investigating the effects of IDH mutations in gliomas (Luchman et al. 2012). There was no study have been done to compare human IDH1 R132H gene expression in the prokaryotic *E.coli* and mammalian GBM cells.

Here, we authenticate the USM-GI-06 cell line and determine the IDH1 gene status. Full-length human IDH1 R132H coding sequence was cloned into pET-47b(+) plasmid and expressed in *E.coli* strain BL21(DE3). IDH1 R132H gene was transfected into the USM-GI-06 cell line established from a recurrent GBM patient in Hospital Universiti Sains Malaysia, Malaysia (Siti Zawani Mohd Ramli et al. 2011) to develop a new stable transfected IDH1 R132H mutant USM-GI-06 cell line. IDH1 R132H gene expression was compared in two different expression host system, prokaryotic *E.coli,* and mammalian GBM cell line.

Materials and Methods

Authentication and IDH1 gene screening of USM-GI-06 cell line

Cell culture and growth condition

USM-GI-06 was developed from a recurrent GBM patient in Hospital Universiti Sains Malaysia, Kelantan, Malaysia (Siti Zawani Mohd Ramli et al. 2011). USM-GI-06 cells were cultured in complete growth medium RPMI 1640 supplemented with 10% fetal bovine serum and 1% penicillin-streptomycin (GIBCO, USA). The cells were cultured at 37°C, 5% CO_2 humidified incubator.

Short Tandem Repeat profiling of USM-GI-06 cell line

Approximately $5x10^6$ culture cells were harvested for genomic DNA extraction using Exgene Cell SV kit (GeneAll, South Korea) according to the manufacturer's instructions. 50ng genomic DNA were used for STR profiling using AmpF/STR Identifiler Direct PCR Amplification kit and analyzed using GeneMapper ID version 3.2.1 software (Applied Biosystems, USA).

IDH1 gene analysis

PCR primers; 5'-AATGAGCTCTATATGCCATCACTG-3' (forward) and 5'-TTCATACCTTGCTTAATGGGTGT-3' (reverse) were used to amplify IDH1 gene (Agarwal et al. 2013) using Taq DNA polymerase (Thermo Fisher Scientific, USA) according to manufacturer instruction. Thermocycling conditions were 95°C for 5 minutes, followed by 35 cycles of 95°C for 30 seconds, annealing 55°C for 30 seconds, extension 72°C for 30 seconds, and 72°C for 5 minutes. The PCR product was sequenced by First BASE, Malaysia and aligned with IDH1 gene (NM_005896.2) from NCBI database using NCBI BLAST software.

Expression and purification of IDH1 R132H recombinant protein in Escherichia coli

Construction of pET-47b(+) IDH1 R132H plasmid

Approximately $1x10^7$ USM-GI-06 cells were harvested for total RNA extraction using RNeasy Mini kit (Qiagen, Germany) according to the manufacturer instructions. The integrity, concentration, and purity of extracted total RNA were determined. Forward (5'-ATGTCCAAAAAAATCAGTGGCGGT-3) and reverse (5'-TTAAAGTTTGGCCTGAGCTAGT-3') were designed to amplify IDH1 coding sequence via reverse-transcriptional PCR using OneTaq One-Step RT-PCR kit (New England Biolabs, USA) according to the manufacturer protocol. Thermocycling conditions were 48°C for 60 minutes, 94°C for 1 minute, followed by 40 cycles of 94°C for 15 seconds, annealing 52°C for 30 seconds, extension 68°C for 90 seconds, and 68°C for 5 minutes. The PCR product was cloned into pGEM-T vector system (Promega, USA) according to standard protocol. The plasmid was transformed into *E.coli* strain DH5α cells, grown on 100μg/ml ampicillin LB agar and incubated at 37°C for 16 hours. IDH1 wildtype gene in the pGEM-T plasmid and plain pET-47b(+) plasmid

were digested with NotI and SacII restriction enzymes and ligated using T4 DNA ligase (New England Biolabs, USA) according to standard procedures. The plasmid was transformed into *E.coli* strain DH5α cells and grown on 50µg/ml kanamycin LB agar.

IDH1 R132H was synthesized via site-directed mutagenesis PCR using QuikChange Lightning Multi Site-Directed Mutagenesis Kit (Agilent Technologies, USA) according to manufacturer's instructions with forward (5'-GTAAAACCTATCATCATAGGTCATCATGCTTATGGGGATCAATAC-3') and reverse (5'-GTATTGATCCCCATAAGCATGATGACCTATGATGATAGGTTTTAC-3') primers. The PCR product was transformed into *E.coli* strain XL10 Gold and cultured on 50µg/ml kanamycin LB agar. The plasmid with targeted point mutation (G395A) was designated as pET-47b(+) IDH1 R132H plasmid via sequencing.

Protein expression and purification of IDH1 R132H

pET-47b(+) recombinant plasmid was transformed into *E.coli* strain BL21(DE3) cells according to standard procedure. Overnight bacterial culture was added into fresh LB broth in ratio 1:100 and incubated at 25°C, 200 rpm until the OD_{600} was approximately 0.6-0.8. The culture was induced with 1mM IPTG final concentration and incubated for 16 hours. The bacteria pellet was collected and washed with 1x PBS. Urea lysis buffer was added, vortex vigorously for 5 minutes followed by sonication at 25% amplitude, 0.5-second pulse rate in 30 seconds duration for 5 times on ice. The cell lysate was made to 20mM imidazole final concentration, passed through the nickel-nitrilotriacetic acid agarose (NI-NTA) (Qiagen, Germany) followed by washing buffer and elution buffer. All of the flow-through were collected.

SDS-PAGE and Western assay

Approximately 5µg of purified IDH1 wildtype and IDH1 R132H recombinant proteins were subjected to 12% SDS-PAGE electrophoresis. The gel was electroblotted onto PVDF membrane at 13 Volts for 2 hours and blocked with 5% skim milk for 1 hour. Mouse monoclonal anti-Isocitrate Dehydrogenase 1-R132H clone HMab-1 (Milipore, USA) in 1:500 dilution and secondary goat anti-mouse IgG-HRP (Santa Cruz, USA) in 1:2000 dilution were used to detect IDH1 R132H protein.

Development of stable transfected IDH1 R132H mutant USM-GI-06 cell line

Construction of pEGFP-C1 IDH1 R132H plasmid

Forward (5'-TAAGCGCTCGAGATGTCCAAAAAAATCAGTGGCGGT-3') and reverse (5'-CGTCGTGGATCCTTAAAGTTTGGCCTGAGCTAGT-3') primers were designed to introduce restriction site XhoI and BamHI flanking IDH1 R132H gene by using KOD HOT Start DNA polymerase (Toyobo, Japan) and pET-47b(+) IDH1 R132H plasmid as template. Thermocycling conditions were 95°C for 2 minutes, followed by 35 cycles of 95°C for 20 seconds, annealing 50°C for 15 seconds, extension 70°C for 30 seconds, and 70°C for 5 minutes. PCR amplicon and pEGFP-C1 plasmid were digested using XhoI and BamHI restriction enzymes (New England Biolab, USA), followed by ligation and transformed into *E.coli* strain DH5α cells. The pEGFP-C1 IDH1 R132H plasmid was determined via sequencing.

Transfection of pEGFP-C1 IDH1 R132H plasmid into USM-GI-06 cells

50,000 USM-GI-06 cells were seeded per well in 24-well plate for 16 hours. 500ng plasmid was transfected into the cells using transfection reagent jetPRIME (Polyplus-transfection, France) according to standard protocol. After 6 hours of transfection, the transfection media was replaced with complete RPMI medium and incubated for 48 hours. The cells were maintained in selection medium containing complete RPMI medium and 100µg/ml G418 antibiotic (ThermoFisher Scientific, USA) for 17 days. 100µg/ml G418 antibiotic was determined from a kill curve assay. The survived cells were seeded single cell per well in 96-well plate. The cells were subsequently subcultured into 24-well plate, 6-well plate, and T25 flask respectively. Each batch of monoclonal cells was analyzed for gene expression via real-time PCR and western assay.

Confirmation of IDH1 R132H gene expression in transfected USM-GI-06 cells

1 x 10^7 of untransfected and transfected USM-GI-06 cells were lysed with 500µl of 300mM sucrose solution containing 1x protease inhibitor cocktail respectively. The cells were incubated at 4°C for 16 hours in a tube rotator. The cell lysate was centrifuged at 10,000g, 4°C for 10 minutes and the supernatant was collected. 20µg of the protein lysates were subjected to 10% SDS-PAGE and confirmed the IDH1 R132H gene expression using

primary antibody mouse anti-Isocitrate Dehydrogenase 1-R132H clone HMab-1 (Milipore,USA) as previously described. Rabbit polyclonal antibody, anti-Beta Actin (Abcam,UK) in 1:1000 dilution was used to detect housekeeping β-actin protein as a loading control.

Real-time PCR mixture was set up according to the Luna Universal One-Step RT-qPCR (New England Biolab, USA) manufacturer's protocol. Forward (5'-ACATGGTGGCCCAAGCTA-3') and reverse (5'-AGCAATGGGATTGGTGGA-3') were used to detect IDH1 gene (Rosiak et al. 2016) and beta actin were forward (5'-AGAGCTACGAGCTGCCTGAC-3') and reverse (5'-AGCACTGTGTTGGCGTACAG-3') (Song & Zuo 2014). The experiments were carried out using Applied Biosystems 7500 Real-Time PCR system (Applied Biosystem, USA) instrument in 3 independent biological replicates.

Statistical analysis

All experiments were performed in three biological replicates. Statistical analysis was performed using GraphPad Prism 6 (GraphPad Software). The data were analyzed using Student's t-test and expressed as mean ± SD (standard deviation). The level of significance is set at $P<0.05$.

Results and Discussion

A GBM cell line established from recurrent GBM patient in Kelantan, Malaysia (Siti Zawani Mohd Ramli et al. 2011) was named as USM-GI-06 cell line. STR profiling was performed for cell line authentication and confirmed that the cell line is unique compared to available glioma cell lines in American Type Culture Collection (ATCC) database (Tab.1). Hotspot mutation at codon 132 in IDH1 gene was amplified (Fig.1) and the electropherogram result showed that the nucleotides at codon 132 are CGT indicates that the cell line harbors IDH1 wildtype gene (Fig.2). As the prognosis of IDH1 wildtype GBM patients is poor and recurrent GBM showed modest response to current treatments, thus this cell line can be used as a GBM in-vitro model for various experimental testing.

Tab 1. Short Tandem Repeat profile of USM-GI-06 cell line

Genetic Locus	**USM-GI-06**
Amelogenin	X,X
D7S820	11
CSF1PO	10,11
TH01	8
D13S317	9
D16S539	12
vWA	15
TPOX	8
D5S818	12

USM-GI-06 cell line is not matched (>80%) with any cell line profiles in the ATCC STR database indicates that the recurrent GBM cell line is unique.

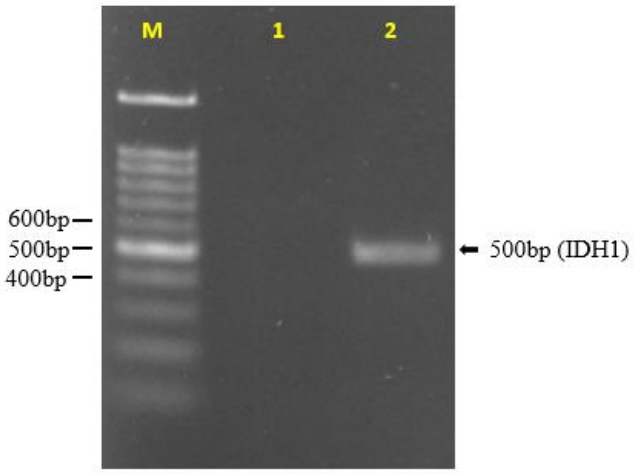

Fig 1. PCR amplification of IDH1 gene from USM-GI-06 cell line.

Lane M: 100bp DNA ladder, lane 1: Negative control, lane 2: 500bp of IDH1 amplicon

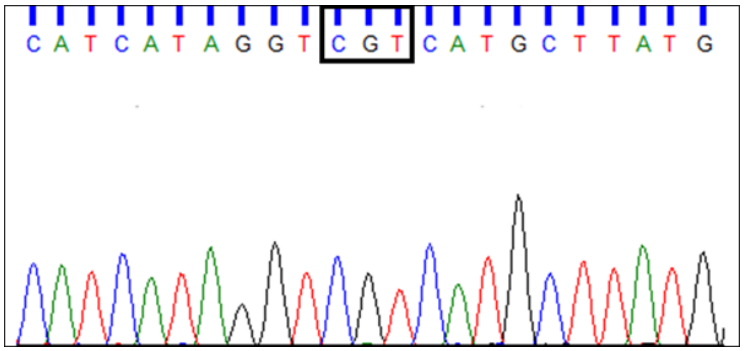

Fig 2. Electropherogram of IDH1 gene from USM-GI-06 cell line.

The box showed nucleotides (CGT) at codon 132 indicates that the cell line harbors IDH1 wildtype gene.

IDH1 wildtype gene was successfully mutated to IDH1 R132H (G395A) at codon 132 (Fig. 3). The molecular weight of IDH1 protein is 46.659kDa. Due to the hexahistidine residues at the N-terminus of IDH1 recombinant protein (1kDa), the expected molecular weight of IDH1 wildtype and IDH1 R132H recombinant protein was 47.659kDa. The purified IDH1 recombinant proteins migrated to approximately 48kDa size band in the gel which is close to the expected molecular weight as shown in Fig. 4A. We used hexahistidine tag as it is relatively small size and charge compared to other affinity tags such as Glutathione S-transferase (GST) and Maltose-binding protein (MBP) to minimize the effect of affinity tag on the protein structure and activity (Bornhorst & Falke 2000). In addition, purification of histidine-tagged recombinant protein using NI-NTA can be achieved faster within one day compared to non-histidine-tagged recombinant protein which required about three days (Trigoso et al. 2016).

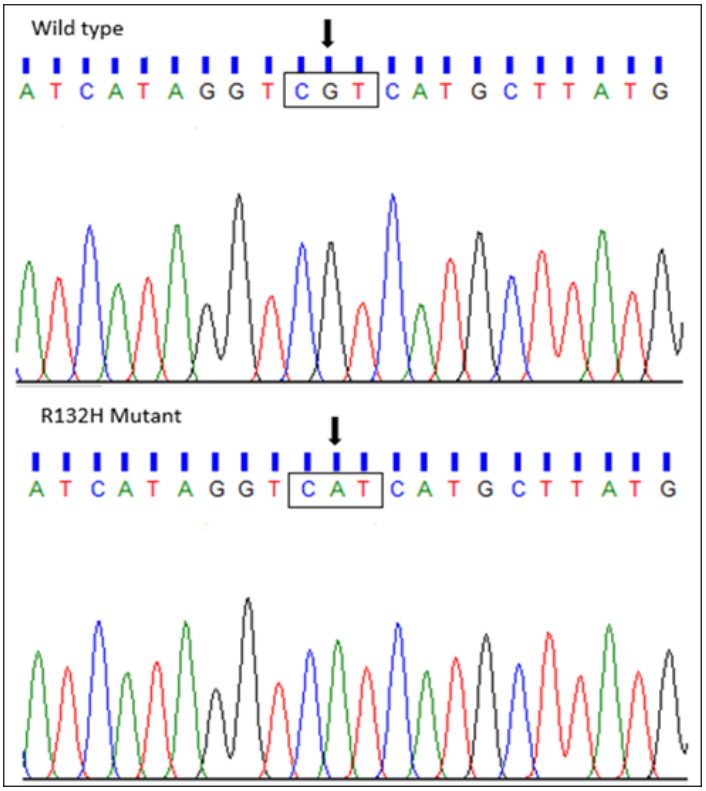

Fig 3. Electropherogram of IDH1 wildtype and IDH1 R132H gene.
The arrow indicates the point mutation site where CGT nucleotide mutated to CAT at the codon 132.

IDH1 R132H recombinant protein was successfully expressed in the *E.coli* (Fig. 4B). Purified human IDH1 R132H recombinant protein from the *E.coli* can be a potential candidate in adoptive T cell immunotherapy (ACT), cancer vaccine and immunocytokine developments. ACT has been performed in prostate cancer treatment targeting prostatic acid phosphatase (Lesterhuis et al. 2011). So far, there is no study using IDH1 R132H antigen in ACT to treat IDH1 R132H glioma yet. Fifteen mers of IDH1 R132H was found to elicit antitumor immunity against IDH1 R132H glioma in mice model (Schumacher et al. 2014) indicating that IDH1 R132H antigen is immunogenic. Gliomas were found to have immunosuppressive microenvironment (Kohanbash et al. 2017) therefore, immunocytokine can be used to deliver pro-inflammatory cytokines such as IL2, IL12 and tumor necrosis factor (TNF) targeting IDH1 R132H antigen in gliomas.

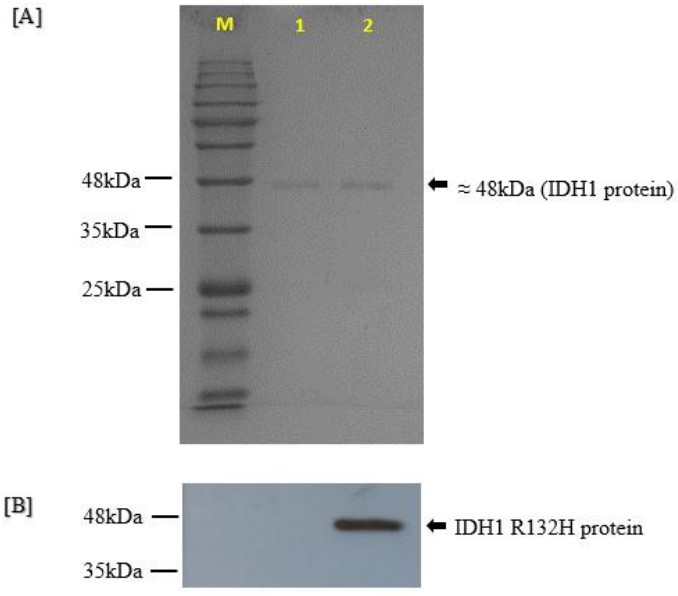

Fig 4. Confirmation of IDH1 R132H recombinant protein in *E.coli.*

[A]. Lane M: Bluelf Prestained protein marker, lane 1: 0.5µg of purified IDH1 wildtype protein, lane 2: 0.5µg of purified IDH1 R132H protein. [B].The band indicate IDH1 R132H mutant protein

We have successfully transfected and expressed IDH1 R132H gene in the USM-GI-06 cell line (Fig.5). Therefore, this cell line is suitable for gene transfection. We postulated that IDH1 R132H protein expressed by prokaryotic *E.coli* exists in monomeric state whereas, in mammalian GBM, it exists in dimeric state based on the molecular weight assumption. *E.coli* expressed a single IDH1 R132H polypeptide chain weighed 48kDa whereas transfected GBM cell line expressed IDH1 R132H which was more than 135kDa. The estimated molecular weight of a single polypeptide chain of IDH1 R132H tagged with green fluorescent protein (26.9kDa) was about 73.559kDa. Since the IDH1 enzyme exists in dimeric state, the expected molecular weight was approximately 147.318kDa which concordant to the actual position shown in the western assay.

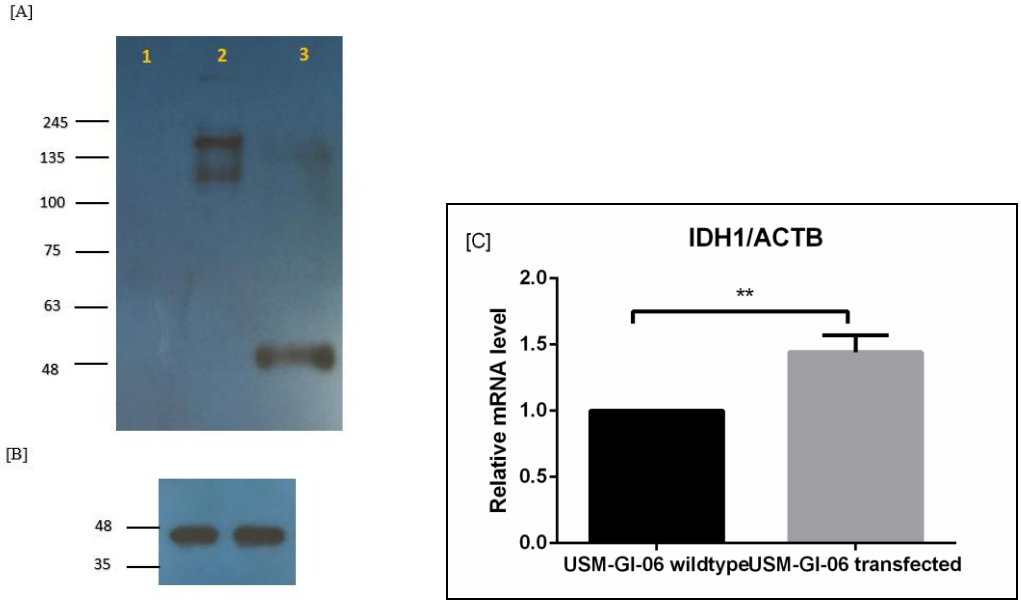

Fig 5. Confirmation of IDH1 R132H gene expression in stable transfected IDH1 R132H USM-GI-06 cells.

[A] Lane 1: Untransfected cell lysate, lane 2: Stable transfected IDH1 R132H cell lysate, lane 3: Purified IDH1 R132H recombinant protein from *E.coli*. [B] β-actin as loading control in both cell lysate. [C] Error bars are standard deviation (SD) from three replicates. Asterisk (*) indicates significance between column as (**) indicates (p<0.01) where p = 0.0037 (independent t test). The stable transfected USM-GI-06 cells showed a significant upregulation of the IDH1 gene expression by 1.442-fold (p<0.01) compared to parental cells.

Different IDH1 R132H molecular weight was possibly due to the post-translational modifications that exist in the mammalian cells and not *E.coli* (Sodoyer 2004). Post-translational modifications are known to regulate functional and structural properties of enzymes such as catalytic activity and oligomeric state (Prakasam et al. 2018). Thus, this may give insight about IDH1 R132H enzymatic activity and structural state in the different host system.

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Prognostic Factors In The Neurosurgical Treatment Of Cerebral Arteriovenous Malformations

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Abstract

Purpose

Arteriovenous Malformations (AVMs) of the brain are highly vascularized lesions representing a surgical challenge. This study aims to test whether certain clinical and paraclinical aspects of AVMs contribute to the general outcome of patients undergoing neurosurgical treatment.

Materials And Methods

A one-center one-surgeon retrospective study is performed in a 10-year interval, on 106 patients harboring symptomatic AVMs. Examined parameters are condensed into an original grading scale. Statistical analysis is performed using the "F test" and Pearson/Spearman coefficient to verify the causality between each of these parameters with the Glasgow Outcome Score (GOS).

Results

Patients' mean age is 37.26 years, with a standard deviation of 16.49 years and a 95% confidence interval of 37.26±3.34 years. Male-to-female ratio is 1.12. Linear inverse-proportional low-intensity relationships between GOS and age (r= -0.223, p = 0.021), presenting symptom (r= -0.287, p= 0.003), and venous drainage (r= -0.199, p= 0.041) are obtained. Linear inverse-proportional correlations of moderate intensity are observed between GOS and state of consciousness upon admission (r= -0.490, p= 0.000), and hemorrhage volume (r= -0.342, p= 0.000). No relationships between GOS and the other parameters studied are noticed.

Conclusion

The Spetzler-Martin grading scale remains a valid prognostic tool in the outcome of surgically treated cerebral AVMs. However, since resection of these lesions remains the only definitive curative option, new prognostic factors should be determined. Our study demonstrates that there is a correlation between patient outcome and neurological status upon admission, hemorrhage volume, as well as the presenting symptom and venous drainage of AVMs.

Keywords: Arteriovenous malformation, Consciousness, Hemorrhage, Outcome, Prognostic factor.

Introduction

Arteriovenous Malformations (AVMs) are non-neoplastic, highly vascularized lesions that arise within the central nervous system (CNS) [1–4]. They are comprised of one or more feeding arteries, one or more draining veins, and an interposing vascular nidus that replaces the normal local capillaries. Pathological studies show that there is no functioning neural tissue situated within these lesions [1,2]. These lesions are most frequently sporadic, however associations with genetic disorders, such as hereditary hemorrhagic telangiectasia have been documented [3–5]. They can be asymptomatic, or they can manifest through headache, epileptic seizures, or various degrees of loss of consciousness [1–7]. The most frequently used classification of AVMs is the Spetzler-Martin scale, employing the anatomical characteristics of these lesions, namely diameter, localization in respects to eloquent cerebral tissue, and depth of venous drainage [3,4,7]. These factors contribute to the resectability and other treatment options of these AVMs, the higher the grade, the more challenging the surgery becomes, and the postoperative outcome can worsen. However, according to our personal experience, we have confidence that the neurological status upon admission in a clinical facility also plays an important role in determining the outcome of AVM patients. Also, there is reason to consider that a hemorrhagic presentation can also lead to a poorer outcome, depending on the size and placement of the hemorrhage.

This study aims to test the extent to which clinical aspects of AVMs, such as neurological status upon admission, presenting symptom, presence of intracranial hemorrhage, presence of an associated aneurysm and surgical accessibility contribute to the general outcome of patients undergoing neurosurgical treatment of these lesions. Our aim is also to propose a statistical analysis on a single-center, single surgeon (represented by the third author) series, as well as to recommend a new classification method on the studied factors.

Material and Methods

A one-center one-surgeon retrospective study is performed in a 10-year interval, between January 2008 and December 2017. We evaluate a non-randomized cohort of 106 patients harboring symptomatic and pathologically verified AVMs, all of which are subjected to only neurosurgical treatment (endovascular therapy and radiosurgery excluded). Patient data are acquired from the integrated electronic database of the Cluj County Emergency Hospital (ATLASmed), the internal imagistic database of our department, patient files and the neurosurgical intervention registries. Preoperatively, all patients possessed either a contrast-enhanced computed tomography angiography (angio-CT) investigation or a magnetic resonance imaging (MRI) investigation with time-of-flight (TOF) sequences or contrast-enhanced angiography sequences to validate the imaging diagnostic and Spetzler-Martin grading. Postoperatively, our patients are investigated using a contrast-enhanced angio-CT scan or at minimum a native CT scan if the former is contraindicated. As is the protocol of our department, we only perform digital subtraction angiographies (DSA) under specific conditions since it is considered an invasive imagistic procedure with associated morbidity and mortality. Therefore, this imaging technique is not used to evaluate the patients postoperatively. Patients with restrictive comorbidities, contraindications for surgery, or having undergone other treatment modalities are not included in this study. All patients signed the informed consent and the study has been approved by the Ethical Committee of the "Iuliu Hatieganu" University of Medicine and Pharmacy.

The examined parameters are condensed into an original grading scale, each being assigned values in a numeric scale between 0 and 2, the value increasing according to severity (Table 1). The postoperative outcome of these patients is evaluated using the Glasgow Outcome Score (GOS) (Table 2). We used Microsoft® Excel® for Mac 2016 for the descriptive statistics, presenting value distribution graphs; mean, median, and standard deviation; confidence intervals; and minimal/maximal values and frequencies. With the help of Statsoft and SPSS applications, we then performed statistical analysis to establish the causality relationship between two variables (linear regression model, 'F test'), followed by the quantification of the relationship between two variables [bivariate analysis = Pearson coefficient (parametric test) / Spearman coefficient (nonparametric test for evenly/unevenly distributed value groups)] for each of these parameters and the GOS. We considered a p value of less than .05 as being statistically significant.

Table I: Designed Grading Scale

1. Consciousness	**0**	GCS 15-14
	1	GCS between 13 and 8
	2	Comatose
2. Presence of Intracranial Hemorrhage	**0**	No hemorrhage
	1	Hematoma volume < 30 mL
	2	Hematoma volume > 30 mL
3. Presence of Associated Aneurysm	**0**	No aneurysm
	1	1 unruptured aneurysm
	2	1 ruptured/≥2 aneurysms
4. Surgical Accessibility	**0**	Supratentorial superficial
	1	Supratentorial deep
	2	Posterior fossa
5. Venous drainage	**0**	Exclusively superficial
	1	Superficial and deep
	2	Exclusively deep
6. Presenting Clinical Feature	**0**	Headache
	1	Seizures (at least 1)
	2	Hemorrhage

Table II: Glasgow Outcome Scale

Glasgow Outcome Scale	
1	Death
2	Persistent Vegetative State – Minimal responsiveness
3	Severe Disability – Conscious, but disabled, depends on others for daily support
4	Moderate Disability – Disabled, but independent, able to work
5	Good Recovery – Able to resume normal life, ± minor deficits

Results

Patients' mean age is 37.26 years (the extremes are 10 months and 73 years respectively) with a standard deviation of 16.49 years and a 95% confidence interval of 37.26 ± 3.34 years. Male-to-female ratio was 1.12 (56 males, 50 females) (Fig. 1). Two incidence peaks are observed, the first corresponding to the third decade of life (26 cases, or 24.5%), and a second, smaller one, at the sixth decade (19 cases, or 17.9%) (Fig 2). There are 37 (34.9%) grade III AVMs, 30 (28.3%) grade IV AVMs, 27 (25.5%) grade II, 6 (5.7%) grade I and 6 (5.7%) grade V (Fig. 3). Concerning the presenting symptom, we considered only the most severe from the personal history of each patient. Out of all AVMs, 45 (42.46%) presented with hemorrhage and loss of consciousness, 34 (32.07%) with seizures, and 27 (25.47%) with headache (Fig. 4). 85 (80.19%) patients are discharged with a favorable outcome (GOS at least 4) and 21 (19.81%) with an unfavorable outcome (GOS 3 or less), out of which 12 (11.32%) were GOS 1. From the deceased patients, 5 (4.72%) were Spetzler-Martin grade III and 4 (3.77%) were Spetzler-Martin Grade IV. The distribution of Spetzler-Martin grades according to GOS on discharge is illustrated in Fig. 5.

Linear inverse-proportional low-intensity relationships between GOS and age (r= -0.223, p = 0.021), Spetzler-Martin grade (r = -0.296, p= 0.002), presenting symptom (r= -0.287, p= 0.003), and venous drainage (r= -0.199, p= 0.041) were obtained. Linear inverse-proportional correlations of moderate intensity are observed between GOS and state of consciousness upon admission (r= -0.490, p= 0.000), and hemorrhage volume (r= -0.342, p= 0.000). No additional relationships between GOS and the other parameters studied are remarked (Table III).

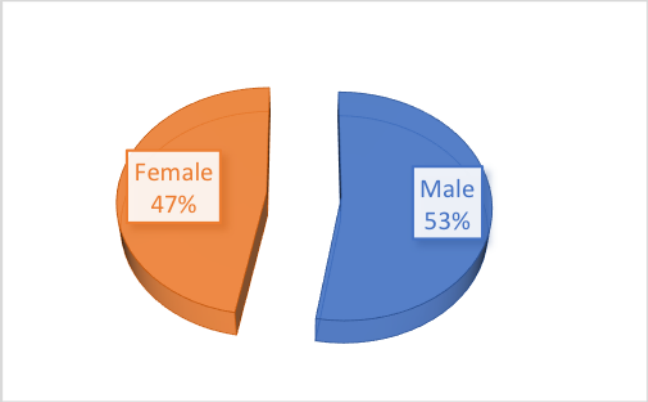

Figure 1: Gender distribution ratio.

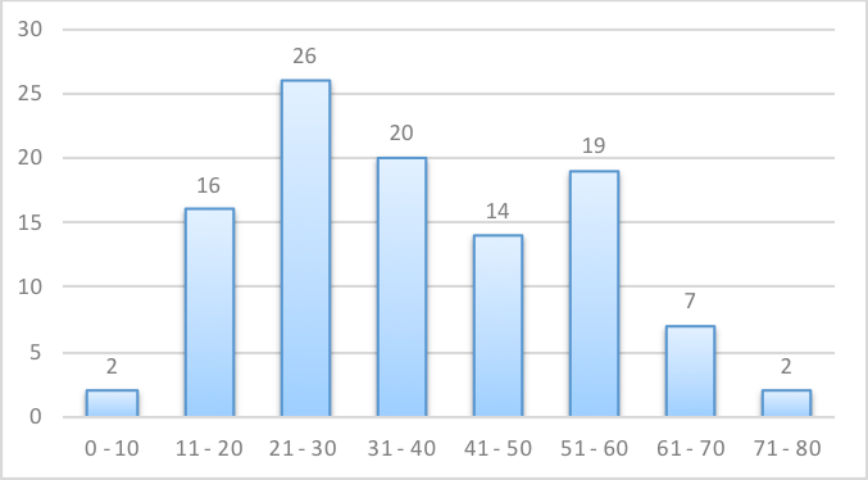

Figure 2: Distribution according to decade of life.

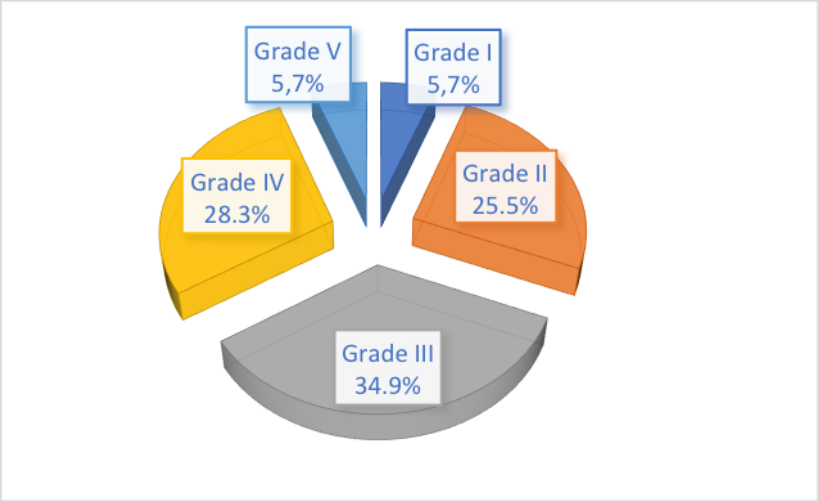

Figure 3: Distribution of AVMs on Spetzler-Martin scale.

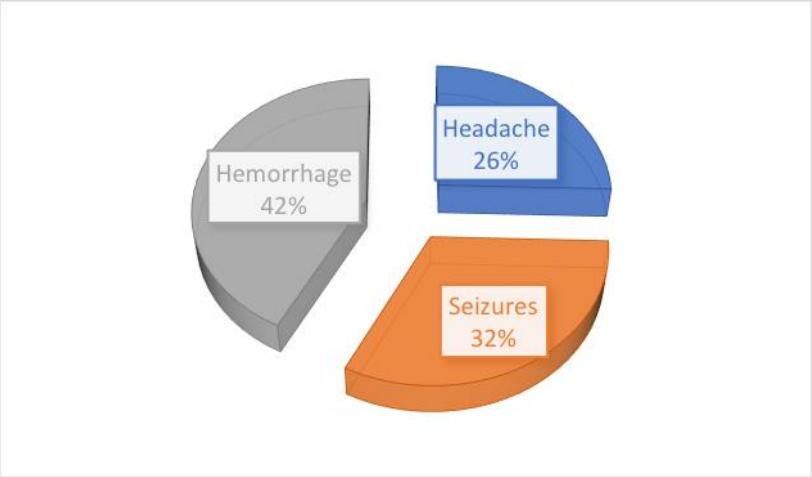

Figure 4: Distribution on presenting symptom.

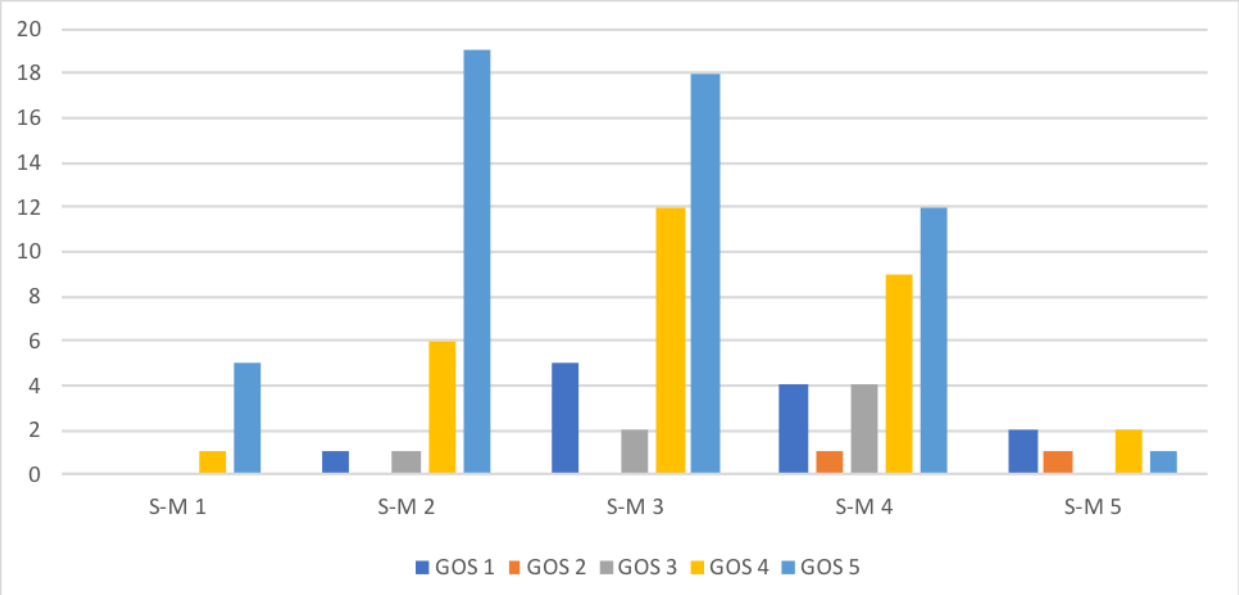

Figure 5: Distribution of Spetzler-Martin grades according to GOS on discharge.

		GOS	
Age	Pearson Correlation	-0.223(*)	Linear inverse-proportional low-intensity relationship
	Sig. (2-tailed)	0.021	P<0.05
	N	106	
Presenting Symptom	Pearson Correlation	-0.287(**)	Linear inverse-proportional low-intensity relationship
	Sig. (2-tailed)	0.003	P<0.01
	N	106	
Spetzler-Martin Grade	Pearson Correlation	-0.296(**)	Linear inverse-proportional low-intensity relationship
	Sig. (2-tailed)	0.002	P<0.01
	N	106	
Consciousness	Pearson Correlation	-.490(**)	Linear inverse-proportional moderate intensity relationship
	Sig. (2-tailed)	.000	P<0.01
	N	106	
		GOS	
Hemorrhage	Pearson Correlation	-.342(**)	Linear inverse-proportional moderate intensity relationship
	Sig. (2-tailed)	.000	P<0.01
	N	106	
Associated Aneurysm	Pearson Correlation	.004	
	Sig. (2-tailed)	.965	
	N	106	
Accessibility	Pearson Correlation	-.180	
	Sig. (2-tailed)	.064	
	N	106	
Drainage	Pearson Correlation	-.199(*)	Linear inverse-proportional low-intensity relationship

	Sig. (2-tailed)	.041	P<0.05
	N	106	

Table III: "F test" and Pearson/Spearman coefficient results.

Discussions

Our series demonstrates epidemiologic findings similar to other case series in the reported literature. The male-to-female ratio is close to 1, however gender distribution is not uniform within reported series, the majority of authors conveying a slightly higher incidence of AVMs in males, whereas others did so in female patients [3,4,6,8–12]. Other demographic discoveries, such as mean age and standard deviation, are in accordance with the data reported in the literature [6,8–18]. The mean age was 37.26 years, with a standard deviation of 16.49 years and a 95% confidence interval of 37.26 ± 3.34 years, which corresponds to the results of other similar studies. In literature, these numbers may vary widely, from a mean age of 27.9 [6] to 45 [19], however the consensus is that the majority of patients present within the second to fourth decade of life [3,12,18]. Our series include an extreme value, namely an infant of only 10 months, which could affect the standard deviation and confidence interval to a small extent.

Aside from these common discoveries, our series also possessed a secondary smaller incidence peak corresponding to patients in the 6th decade of life. To the extent of our knowledge, such a finding is not yet reported in the literature and may underscore the fact that the rate of symptomatic AVMs in middle-aged individuals is not negligible. As for the natural history of our patients, the majority (42.46%) present intracranial hemorrhage, followed by a history of epileptic seizures (32.07%) and headache (25.47%). Of note, despite the fact that all patients included in this study are fully documented and their symptoms logged, for the purpose of our statistical analysis we only took into account the most severe symptom in the personal history of each patient. Intracranial hemorrhage and subsequent deficits and alterations in neurological status preceded seizures in severity, whereas seizures are considered a worse symptom than headache. None of our patients are referred to our department with pure neurological deficit in absence of an intracranial hemorrhage or as a result of mass effect or hemodynamic disruptions such as arterial steal. These results are consistent with other patient-based studies that cite hemorrhage as the main presenting symptom and seizures as second [9–15, 17–20], only a few citing headache as more common than epilepsy [8].

As this observational study is designed only to assess the neurological outcome after neurosurgical removal of the AVM, all the patients included are subjected to the neurosurgical treatment of these lesions, without any adjuvant endovascular or radiosurgical therapies employed either before or after resection. Patients deemed inoperable because of the volume or accessibility of the lesion are not included. Patients with incidentally discovered asymptomatic AVMs or those who refused surgical intervention are also excluded from this study. It is also worth mentioning that some of the symptomatic patients who initially refused surgical resection and are maintained under observation returned after a variable period of time agreeing to undergo the intervention. In our series, the majority of patients have medium and medium-high grade AVMs (34.9% grade III, 28.3% grade IV and 25.5% grade II), while also including a few grade V (5.7%) and I (5.7%) lesions. All measurements are performed on the preoperative imaging investigations that the patients possess. In contrast, the majority of series in the reported literature exhibited a tendency for surgical treatment of lower grade lesions (grades I and II), whereas those of grade III or above are mostly treated multimodally with a combination of surgical, endovascular and radiosurgical therapy, or conservative treatment [9,13,21–23]. Despite the fact that our study does not take into account the cases managed conservatively, it shows that even higher-grade AVMs can be treated surgically with favorable results, in the hands of an experienced surgeon.

The reason why the mortality rate is as high as 11.32% is mainly because several of our patients are referred to our department in a critical condition, being either comatose or with a massive intracranial

hemorrhage due rupture of an AVM or an AVM-related aneurysm. Despite the lack of a consensus regarding the appropriate timing for surgery for critical patients [24,25], it is our doctrine to undergo surgery as soon as feasible in the presence of a rapid neurological deterioration. However, in spite of adequate technique, careful intraoperative hemostasis and proper postoperative treatment in intensive care units, some of them are unfortunately untreatable. Nevertheless, some of the patients admitted with a poor neurological status or with a substantial hemorrhage not only survive, but are discharged with a favorable outcome. This suggests that there is no absolute and definitive relationship between neurological status at onset or the presence and volume of hemorrhage and the outcome at discharge, the evolution of the patient depending on numerous additional and individual factors such as age, comorbidities and time between onset of symptoms and surgical intervention. Surgical technique and finesse are invaluable tools for the outcome of these patients, incomplete removal of the lesion or an inadequate hemostasis almost certainly leading to clinical deterioration, reintervention, neurological disability and eventually death.

The Spetzler-Martin grading scale remains a valid prognostic tool in the outcome of surgically treated cerebral AVMs [4,7,21,22,26]. However, as neurosurgical resection of these lesions remains the only definitive curative option, new prognostic factors should be determined. The GOS remains a simple and useful, albeit a biased method of determining neurological status upon discharge because of its relatively subjective method of assessment and category ambiguity. Therefore, a more precise score, such as the Modified Rankin Score, could hypothetically improve the accuracy of our results if employed in future analyses [27].

Our study further emphasizes that there is a strong correlation between neurological status upon admission and patient outcome [28,29]. Intracranial hemorrhage from an AVM and a large hemorrhage volume also resulted in poorer outcomes and there is increasing evidence that the morbidity and mortality caused by AVM rupture can be higher than previously estimated [19,30,31]. Other factors that were associated with a poor GOS upon discharge were advanced age, a high Spetzler-Martin grade, deep drainage and hemorrhage as the presenting symptom. Deep venous drainage is described in literature as an independent predictor for AVM rupture and poorer outcome [10,24,25]. AVMs possessing single draining veins are described as more prone to rupture [32]. However, our study did not account for the number of draining veins, focusing only on their depth in rapport with primary cerebral venous sinuses.

Aneurysms associated with AVMs are typically thought to increase morbidity due to their potential to cause more severe hemorrhages [10,17,19,24]. A possible reason why associated aneurysms did not behave as prognostic factors can be due to the small number of characteristic cases in our study. Another explanation may be due to the timely intervention in the treatment of these cases, not allowing the aneurysms to rupture and to cause deficit, or having treated the aneurysms in the appropriate time before permanent clinical deterioration could ensue. Deep situated AVMs and those residing in the posterior fossa have been shown more prone to rupture [6,10]. Our study did not obtain any significant correlation between the general location of the AVM (superficial supratentorial, deep supratentorial, and infratentorial) and the outcome at discharge. This may be due to a lack of specificity of the location, which we intend to ameliorate in a future study.

Notwithstanding the retrospective nature of this research, the absence of an observational control group, as well as the relative low number of cases included promising results, our study yielded promising results. The conclusions obtained are also in part based on our surgical experience, however there is still potential data to be extracted. We intend a continuation of this study in a prospective multicenter analysis, as well as the possible implementation of the designed grading system.

Conclusions

Our series respected the demographic data from similar studies. In our experience, even high-grade AVMs can be treated surgically alone with promising results. However, patients admitted in a poor neurological status or with massive intracranial hemorrhage can lead to higher complication and mortality rates, in spite of appropriate therapy. Our study demonstrates that age, neurological status on admission, Spetzler-Martin grades and AVM hemorrhage heavily impact neurological outcome, while other factors may be confirmed as prognostic

factors in future studies. By replacing the GOS with other postoperative neurological status scores such as the modified Rankin scale (mRS), we can obtain new and possibly more significant correlations in a future prospective research.

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Results Of A Contemporary Series Of Minimally Invasive Microsurgery For Glioblastoma: Extent Of Resection, Complications And Benefit Of Surgery

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Abstract

Purpose

Review results of resection of glioblastoma (GBM) using minimally invasive, fluorescence-guided (FGS) microsurgery.

Materials and Methods

Our Department keeps a prospective database since 2008. A review 2008-2016 found 177 cases with resection for newly diagnosed GBM. FGS with 5-ALA, navigation guidance and minimally invasive technique were used in all cases. High field intraoperative MRI (3T) was used in the last 20. Clinical and radiological data, including pre and postoperative tumor volume, complications, and size of the craniotomy were collected. Cox regression model was used to study influence of variables on survival.

Results

Mean age was 60.4 (28-82). Median OS was 17 months. Complete resection of enhancing tumor (CRET) was the objective of surgery in 144 (81%) and was achieved in 80% of those and in 65% of the whole series. Mean extent of resection (EOR) was 98%. Reasons for incomplete resection included missed rests in 11%, and neurophysiological monitoring warning in 9%. Neurological status at hospital discharge was unchanged from pre-operative in 61%, better in 25% and worse in 14%.

Mean surface of the craniotomy was 14 cm2. There were no 30 days mortality in the series. Variables independently associated with OS included: MGMT methylation ($p<0.001$), Age ($p=0.001$), KPS ($p=0.028$) and EOR ($p=0.002$). CRET significantly increased survival also in high risk subgroups of unmethylated MGMT, patients older than 70, and patients with KPS<80.

Conclusion

Maximum EOR improved survival for all the patients subgroups. Minimally invasive microsurgery allows efficacy with very low complication rates giving a good risk/benefit ratio.

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Keywords: Innovation, technology, research projects, etc.

Introduction

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Treatment of Glioblastoma remains and unsolved problem, where a proper treatment can increase survival, with very few long-term survivors. Maximal resection has shown association with longer survival in larger series with control of resection by MRI and multivariate analysis [1][2]. Best data available in recent years suggest the more extensive the resection, the longer survival, without any threshold [3]. However, as the resection is not going to be curative, it is fundamental to keep it safe, minimizing the damage and inconvenience to the patients. Safety of brain tumor resection should consider not only neurological deficit, but all kind of adverse events, like fistulas, bleeding, infection, wound pain, scar, deformity, deep vein thrombosis (DVT), anemia, as all are relevant to the patient quality of life.

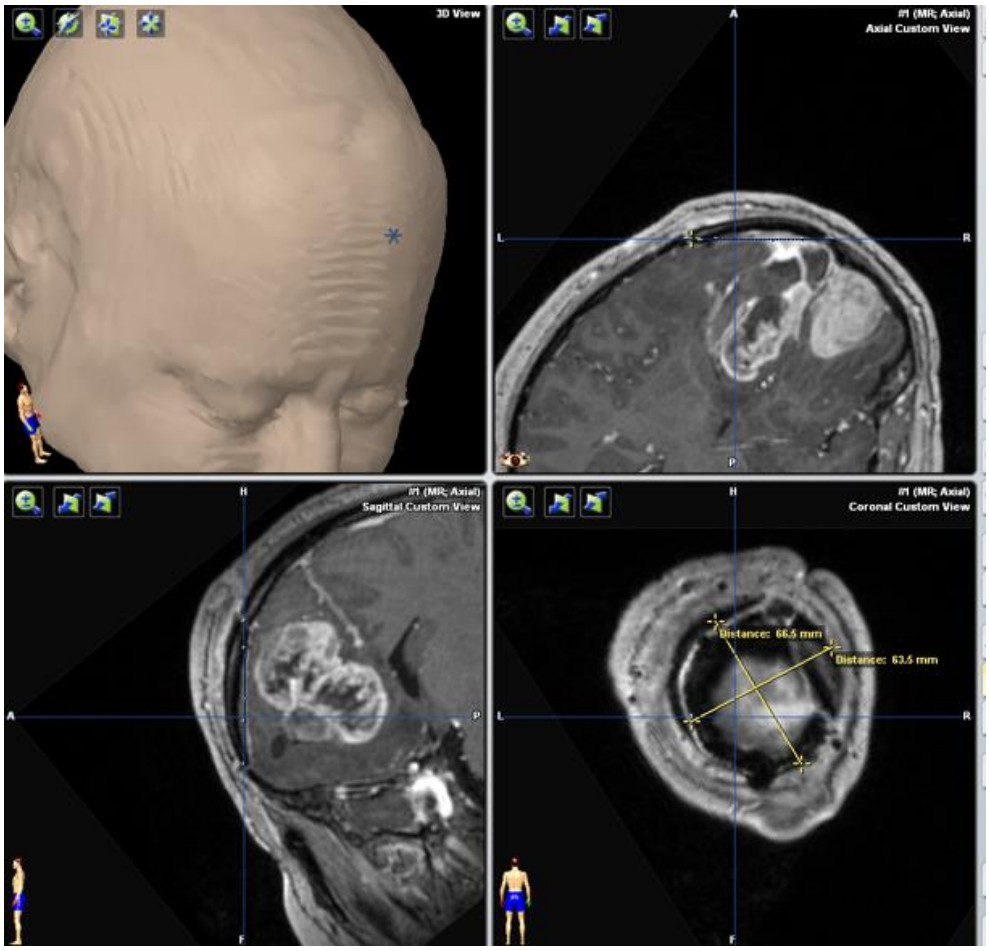
Modern surgical tools like fluorescence guided surgery, and intraoperative MRI allow the neurosurgeons to increase the resection with better identification of tumor in the surgical field while the more frequent use of neurophysiological monitoring, control the risk of neurological damage. We believe all this techniques can be combined also with a minimally invasive, key-hole concept surgery to provide best resection with minimal problems and fast recovery [4].

Material and Methods

Our neurosurgical Department keeps a prospective database for the patients operated on by gliomas. This database was searched to identify all the cases treated with surgery for newly diagnosed GBM since 2008 to 2016. Clinical data were retrieved from the electronical clinical system in our institution. The search found 177 cases were we had at least 30 days follow-up and these were included in the review. We included as newly diagnosed GBM, all the cases in whom we did a resection surgery before radiotherapy treatment, including a group of patients that have had biopsy or partial resection previously at a different institution.

FGS using 5 aminolevulinic acid (5-ALA, Medac), navigation guidance (Brainlab) , and microscope use (Pentero, Zeiss), were standard during the time of review. All the surgeries were performed or supervised by one of the two senior authors (RDV and STS). The use of minimally invasive technique was a trend during the years. It was not formally defined, rather, the surgical technique was evolving as we become more confident of the advantages of doing smaller craniotomies. Neurophisiological monitoring was used in selected cases, were we thought the tumor could be quite near eloquent areas. The monitoring was exclusively done in the border of the tumor, to assess resectability, search for the function distance from the tumor was not done.
High field intraoperative MRI (3T) become available in February 2016, and was used in the last 20 cases.
Clinical and radiological data, including pre and postoperative tumor volume, complications, and size of the craniotomy were collected. Cox regression model was used to study influence of variables on survival.
Craneotomy size was measured over the postoperative MRI T1 Gd volumetric sequence. To get a precise measurement, we imported the study into the Brainlab iplannet software, placed a plane tangent to the surface and measured the longest diameter and its perpendicular one. We applied the surface of the ellipse formula to that measurements.

Figure1



Results

Mean age of the patients was 60.4 (28-82). Mean tumor volume was 41 cc.
Neurophysiological monitoring was used in 44 cases (25%) . High field intraoperative MRI (3T) was used in the last 20 (11%).

Resection
Complete resection of enhancing tumor (CRET) was the objective of surgery *a priori* in 144 (81%) and was achieved in 80% of those and in 65% of the whole series.

Complete resection was not planned in some cases due to multicentric disease with small distant nodules or to diffuse invasion of eloquent areas.

Mean extent of resection in volume across the whole series, measured as percentage of preoperative volume resected (EOR) was 98%. Including only the cases with some residual disease, the mean size of residual tumor was 1.3cc
The reasons for incomplete resection were missed rests in 11%, and neurophysiological monitoring warning in 9%. The cases with iMRI had a higher percentage of complete resection when planned, 87% , and all the rest behind were due to neurophysiological monitoring warning, no formal comparison was made as the sample is very small..

Complications:

There was no 30 days mortality in the series.

Neurological status at hospital discharge was unchanged from pre-operative status in 61% of the cases, better in 25% and worse in 14%, at one month follow-up, only 7% were worse than preoperatively.

Non neurological complications were classified as complications from the approach or systemic complications, and were as follows:

- From the approach: Total 13 events (**7% of cases**):

  Reoperation due to bleeding: 1 (0,6%)
  Generalised seizures: 5 (3%)
  Tension resection cavities, needing CSF drainage: 2 (1%)
  Wound problems: 5 (3%) (3 of these have had a recent previous surgery at another center). Wound problems was subdivided in:
    CSF fistula: 2 (1%) (1 needed reoperation)
    CSF fistula + wound infection: 1 (0,6%)
    Wound infection: 2 (1%) (1 needed reoperation)

- Systemic complications : Total 14 events (**8% of cases**)

  Infection (Excluding wound or CNS infections): 11 (6%)
    Lung: 6 (3%)
    Urinary tract: 4 (2%)
    Unknown: 1 (0,6%)
  Hyponatremia 2 (1%)
  Confusional state: 1 (0,6%)
  Deep Vein Thrombosis: 1 (0,6%)
  Anemia needing Blood Transfusion: 1 (0.6%)

Craneotomy size:

In the series we found 125 craniotomies that have been planned the novo in our center, 52 patients had already craniotomies that have been planned in different centers for open biopsies or partial resection, and this modified the surgical planning. So for craniotomy size we analyzed only the 125 done de novo.

The Mean size of the craniotomies was 13,6 cm^2, Median size was 12,9 cm^2. We found 105 patients (84%) had a craniotomy smaller 20 cm^2 and 120 (96%) smaller than 25 cm^2 . Figure 2 show there was a weak correlation between craneiotomy size and tumor size.

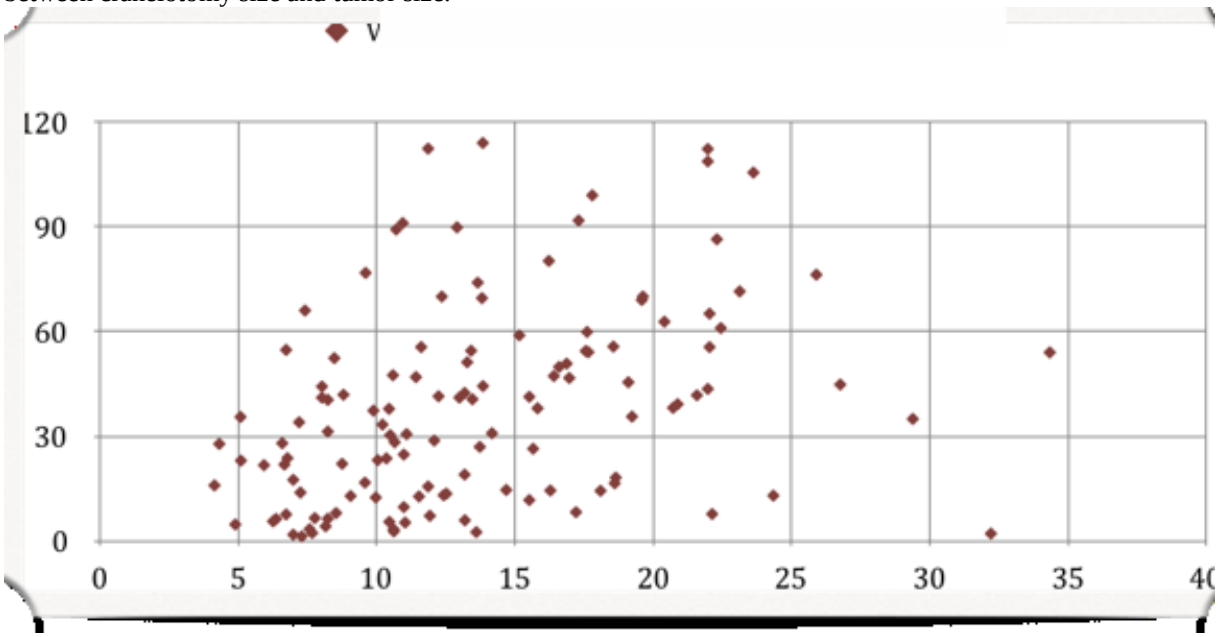
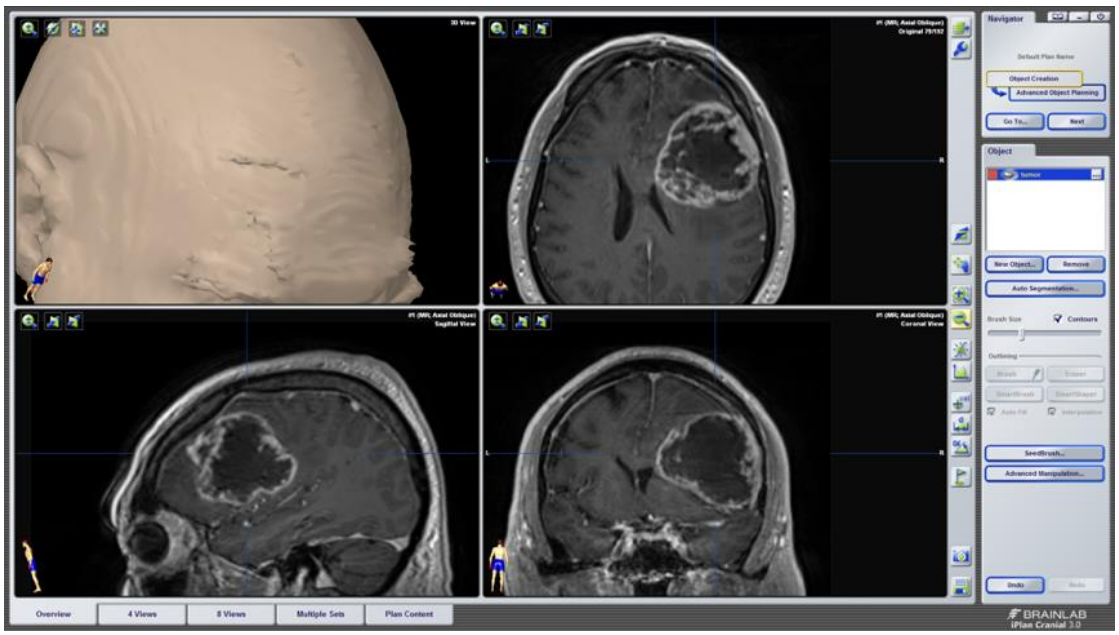
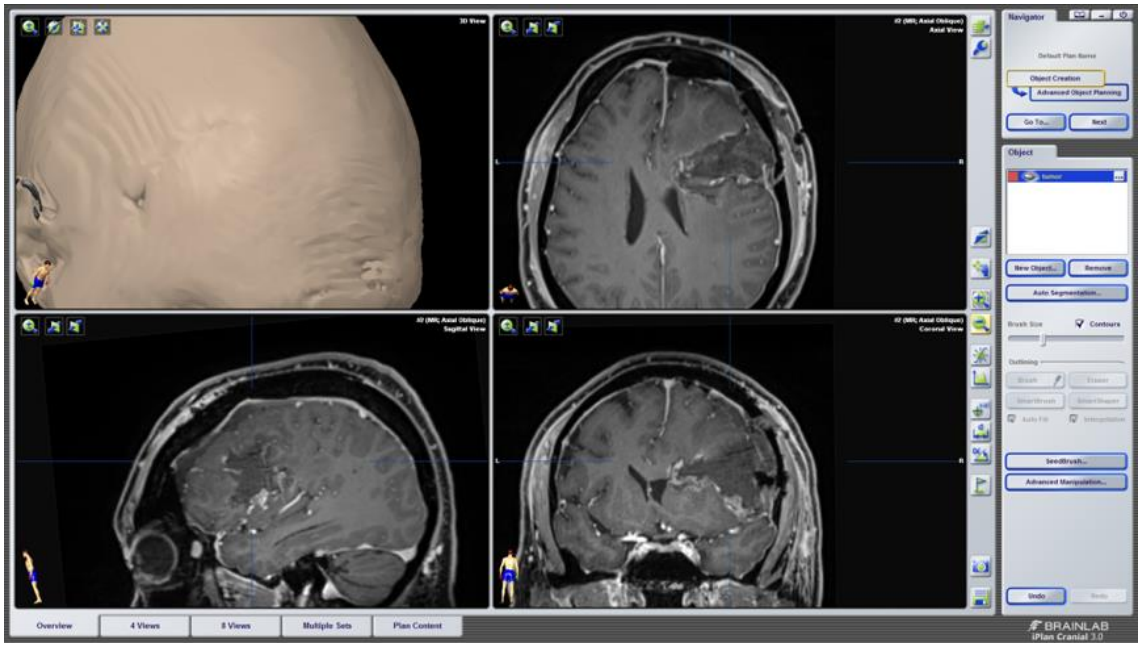


Figure 2. Each diamond represent a case, Y axis shows tumor volume in cc and , X axis craniotomy size in sq cm.

Figure 3 shows an example of a 108 cc tumor resected through an opening of 18 sq cm. the important part is not the total volume of the tumor, but its surface presentation.





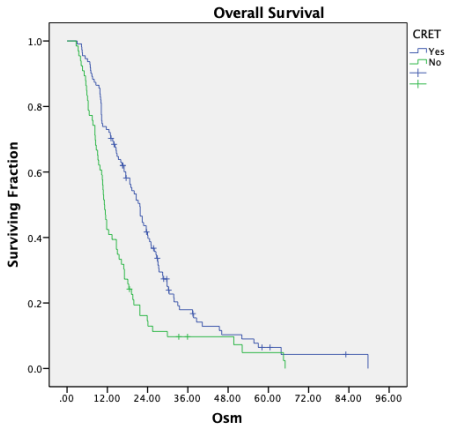
Survival

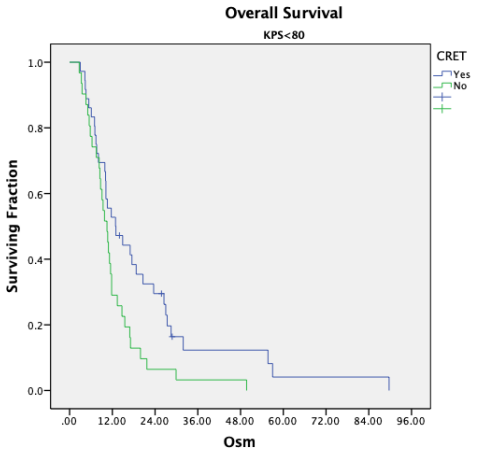
Median overall survival (OS) of the patient included was 17 months. Complete resection of enghancing tumor had a significant impact on survival, Log Rank p< 0.001. Figure 4.

Multivariate analysis found that the Variables independently associated with OS included:

MGMT methylation (p<0.001)
Age (p=0.001)
EOR (p=0.002)
KPS (p=0.028)

We performed a separate subgroup analysis of the impact of resection, and found that CRET significantly increased survival also in the high-risk subgroups of unmethylated MGMT, patients older than 70, and patients with KPS<80.





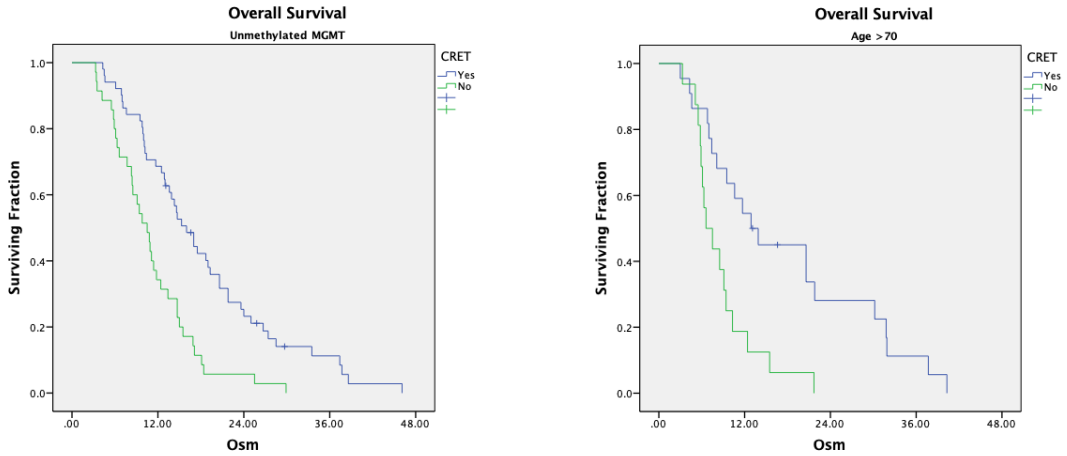


Figure 4: Kaplan Meier comparing effect of CRET in the total sample and for High-Risk subgroups, all differences were significant, by Log Rank p= 0.02 for patients with KPS < 80 and p= 0.002 for patients with Age > 70, and p <0.001 for MGMT unmethylated.

Discussion

It is well known an accepted now that maximum EOR improves survival in GBM. Our series is in agreement with much bigger ones, as should be expected. There is less data about the impact of resection in unfavorable subgroups. Still it is argued frequently that "bad cases" do not benefit from treatment in this disease, with the argument used for radiotherapy, chemotherapy or surgery.

We focus in unfavourable cases, as we had a good number of those, and found Getting CRET brings a benefit in survival also in the groups of worse prognosis, like unmethylated cases, older patients, or patients with lower KPS. In all these subgroups the expected survival is less and the benefit of surgery is smaller, but is present.

The key point to keep the benefit of surgery useful is keeping at a minimum all the complications. Surgery will be indicated if the total risk can be maintained at a very low level. Minimizing the total risk and complications of this patients is of paramount importance in all patients with glioblastoma, but even more so in the situation of bad subgroups.

The last issue in our work is the question of doing the minimally invasion possible. We do not have a comparator group with larger craniotomies, but it seems logical that many of the complications like epidural and subdural bleeding, and pain are related to the size of the opening,

Is obvious than modern imaging, modern navigation and modern surgical techniques, including microscope and endoscope allow to do excellent work through smaller opening but this issue seems not to have been systematically studied. To our knowledge there is not a reference in the literature as what should be the size of normal craniotomies. Our data can be a reference with the limitations of being single center, much more data would need to be collected to have a more general idea.

Conclusions

CRET increases OS even in the bad prognostic subgroups in GBM

Minimally invasive microsurgery with modern techniques can combine the efficacy of the resection with a very low complication rates giving a good risk/benefit ratio.

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Risk Factors Effecting Treatment Outcomes Of Acromegaly- 12 Years' Experience From A High-Volume Hospital.

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Abstract

Introduction:

Acromegaly is a rare and indolent disease with the estimated prevalence of 36-69 per million population worldwide and has 2-3 times higher mortality rates. It's an endocrinological disorder of the pituitary gland due to increased secretion of Growth Hormone(GH) and Insulin-like growth factor(IGF-1). We aim a) to study the demographic characteristics of the patient population and b) to identify the risk factors affecting the treatment outcomes, failure vs. remission.

Methods:

All patients who underwent Acromegaly treatment at the Aga Khan University from 2006-2018 were enrolled in the study. Data was collected retrospectively by reviewing patients' medical records. Chi-square and independent t-test was used for categorical and continuous variables, respectively. A p-value of <0.1 was considered significant.

Results:

We enrolled 53 patients (M:F=1.17:1), in total. Mean age and Body-mass Index was reported as 36.73years(SD 12.97years) and 28.36kg/m2(4.67kg/m2). Mean duration of symptoms was 26.64months(SD24.61months), whereas mean length of follow-up is reported to be 27.94months(SD31.2months). Risk analysis showed that tumor size >10mm, cavernous sinus extension and higher pre-operative levels of GH predicts factors associated with treatment failure. Receiver operating characteristic(ROC) curve indicated that a pre-operative GH levels of >5mcg/L has 95% sensitivity in predicting unfavorable outcome.

Conclusion:

We have described our 12 years' experience with the treatment outcomes of Acromegaly. We report that tumor size, cavernous sinus extension and pre-operative GH levels serve as useful predictor for adverse outcomes. Increase accessibility of different treatment modalities can play a pivotal role in increased rate of better outcomes.

Keywords: Acromegaly, treatment outcomes, risk factors.

Introduction

Acromegaly is a rare disease with the estimated prevalence of 36-69 per million population worldwide.(Daly, Petrossians, & Beckers, 2005; Găloiu & Poiană, 2015; Hoskuldsdottir, Fjalldal, & Sigurjonsdottir, 2015) It is an endocrinological disorder of the pituitary gland commonly due to abnormally increased secretion of Growth Hormone (GH). (Daly et al., 2005; Găloiu & Poiană, 2015) Increased amount of GH and Insulin like growth Factor I (IGF-I) causes metabolic and anatomic changes.(Giustina et al., 2014) Patients usually present with hypertension, diabetes mellitus and cardiovascular disease and sleep apnea. (Giustina et al., 2014; Hoskuldsdottir et al., 2015)
Acromegaly is associated with high morbidity and mortality, as great as 2-3 times than general population. Acromegaly has an indolent course, making it hard to diagnose. Average duration of symptoms prior to diagnosis can be 7-10 years and patients usually have advanced disease by the time of diagnosis.(Daly et al., 2005; Hoskuldsdottir et al., 2015) The treatment goals for acromegaly are: reduced GH level, IGF-I within

normal range, tumor shrinkage and controlled clinical symptoms. Due to complexity of the treatment, it is important to understand the risk factors effecting the treatment outcome i.e. remission vs. treatment failure.
Several studies have idetified the risk factors affecting the outcome including age, gender, pre-operative growth hormones level, pre-operative somatostatin treatment, endo-nasal surgical approach.(Anthony et al., 2015; Chen et al., 2017; Dagistanli et al., 2018; Lv et al., 2018; Park et al., 2017; Taghvaei, Sadrehosseini, Ardakani, Nakhjavani, & Zeinalizadeh, 2018; Zhang et al., 2015) A study done in South Korea identified premenopausal female has the highest rate of treatment failure and has identified the gender and the age as a risk factor.(Park et al., 2017) It is very important to understand the risk factors for the treatment failure and stratify the patient population, according so disease management can be tailored according to the needs.
A study done in a tertiary care hospital in Pakistan reported that among all patients presenting with pituitary lesions, including macro- and micro- adenoma, Acromegaly accounts for 16.7% and 14% respectively.(Chandna, Islam, Jabbar, Zuberi, & Haque, 2004) With this burden of the disease in our population, the risk factors affecting the treatment outcomes have not been studied. This study aims to highlight the basic demographic characteristics of the patient population. We aim to identify the associated factors increasing the risk of an unfavorable outcome, so that proportion of favorable outcome can be increased.

Methodology:

Total, 52 patients were enrolled, who underwent pituitary adenoma resection for Acromegaly between January 2006 and December 2018 at our high-volume tertiary care center. Data was collected retrospectively by reviewing charts, biochemical data and radiological images. Any patient whose medical records could not be found was excluded from the study.
Treatment outcomes were defined according to the Endocrinological Consensus 2018.(Melmed et al., 2018) A patient with post-operative growth hormones level of <1mcg/L was considered in remission. For the tumor size, tumor with maximum dimension of >10mm were considered macro-adenoma whereas those with less were categorized as micro-adenoma.
Data was recorded and analyzed using SPSS version 19. Frequencies and means were calculated for categorical and continuous variables, respectively. Chi-square was used to compare two categorical variables whereas t-test was used for the difference of means. Risk analysis was done on a total of 47 patients. Any patient with the missing data-point was excluded. However, analysis for endonasal endoscopic approach was done on 40 patients; since both endoscopic and microscopic approach were used for 6 patients 1 had a missing data-point. A p-value of <0.1 was considered significant.

Results:

A total of 52 patients (M:F=1.17:1) underwent adenomectomy for acromegaly. Mean age was found to be 36.73years (SD 12.97years). More than half of the patients were obese (BMI>27 kg/m2), with the mean BMI of 28.36 kg/m2 (SD 4.67 kg/m2). One-fourth of the patients had already developed Diabetes at the time of presentation whereas more than one-third complains of the high blood pressure. Most commonly reported presenting complains included headache (59.61), increased limb size (50%) and visual disturbances (46.15%). On average, patients were diagnosed with acromegaly after more than two years of development of symptoms. Only two patients reported the use of somatostatin.
Eight patients were reported to develop a neuro-related post-operative complications, which included Cerebospinal fluid (CSF) leak, transient Diabetes Insipidus (DI) and Occulomotor nerve palsy.
Review of radiological imaging revealed that 84% patient had a macroadenoma (>10mm) with supra-sellar extension being most common presentation (53.85%). In the post-operative follow-up imaging one-fifth of the patients had residual mass. (Table 1)
Risk analysis was done for various demographic, biochemical and radiological factors. (Table 2) We used Acromegaly Consensus 2018 to define remission and treatment failure, where pre-operative Growth Hormone (GH) level <1mcg/L was defined as remission.(Melmed et al., 2018) Remission was reported among 10 (20.41%) of the patient population. Risk analysis was performed on 47 patients (except for the surgical approach, where n=40). We identified significant results for pre-operative tumor size, cavernous sinus extension and for difference in pre- and post-operative levels of growth hormones. Our results showed that odds of having treatment failure with macroadenoma is 1.28 times higher than that of microadenoma. Also, cavernous sinus extension and higher level of growth hormones pre-operatively predicts poor outcome. (p-vaue 0.1)
The receiver operative characteristic curve (ROC) for pre-operative GH levels helps us identify the group patients who are higher risk of developing treatment failure. A cut-off of GH level greater than 5mcg/L shows sensitivity of 95% for predicting an unfavorable outcome. (Fig. 1)

Discussion:

We present our results of the treatment outcomes among patients with acromegaly undergoing the surgical resection at our center. The mean age of our study population was found to be 36.73 years (SD 12.97years), which depicts that our patient population is younger and because of the chronic nature of the disease it is important to have disease controlled in order to have an improved quality of life with higher level of functioning. Also 17% of our patients reported to have multiple co-morbids at the time of presentation which emphasize on the poor health status of our study population.

The mean duration of symptoms was found to be around 2 years which reinstate the indolent nature of the disease (Daly et al., 2005). Pre-operative use of Somatostatin analogue plays critical role in improving treatment outcomes. (reference of 2 studies) Nonetheless, it is an expensive treatment, which decreases the popularity of this effective modality despite of promising results. This can be reflected from our results where only 2 (3.85%) patients were reported to use it pre-operatively, which is why despite of protective effects of somatostatin analogue, reported in literature, we could not find any significant association between the intervention and improved outcome.(Dagistanli et al., 2018; Lv et al., 2018; Zhang et al., 2015) It is important to look into ways to improve the accessibility of the drug in our population. Radiosurgery has been reported as an excellent adjuvant therapy. It has shown improved cure rate when used with the surgical resection, especially for large tumors and the adenoma in location where access is challenging. (Gheorghiu, 2017; Naeem, Darbar, & Shamim, 2018; Trifiletti et al., 2018) Despite of the fact, only eight patients in our study received radiosurgery. The reasons could be it is recently introduced and is available in only one tertiary care center in the country. We hope to improve the coverage with the passage of timeand make it more readily available.

Younger age and female age has been identified as a risk factor for the treatment failure but no significant association can be shown in our study.(Chen et al., 2017) Comparison of endonasal endoscopic and microscopic surgical approach has been shown similar rate of remission.(Park et al., 2017) Our study did not show any significant difference between the two, either (p-value 0.5) However, another study done on 68 patients has shown better outcomes with the endonasal approach.(Taghvaei et al., 2018) The larger size of tumor and cavernous sinus extension, pre-operatively, reported to increase the risk of having a treatment failure, post-operatively. It is important to look for these markers while assessing the patient and devise a treatment plan accordingly.

It is very critical to do risk stratification of a patient pre-operatively in order to tailor the management accordingly. Of the risk factors studied, pre-operative Growth Hormone (GH) levels can serve a useful tool in identifying the patients at risk of developing treatment failure.(Anthony et al., 2015) The ROC curve (Fig. 1) describes the cut-off point that can be used to predict the outcome. A preoperative GH level of >5mcg/L predicts the poor outcome. This necessitates the need for using multimodal treatment for these patients.

We use a level of significance of <0.1 for our study. The level was higher as compared to the level of significance used in other studies. This does confer as a limitation to our study. However, this gives us fair idea about the risk factors. So that we can conduct further studies understanding the associated factors in greater detail. We studied various risk factors in the same study population and identified the predictors that can play role in improving the treatment outcomes, which, to the best of our knowledge, makes it the first risk analysis study from Pakistan. We also provide the results with long-term follow-up which becomes very important while dealing with the chronic disease.

Legend

Table 1: Demographic characteristics and treatment details of the patients with acromegaly.

S. No.	Parameters (N=52)	Mean (SD)/Frequency (%)
1	Age at the time of surgery (years)	36.73 (12.97)
2	M:F (Male-female ratio)	1.17:1
3	BMI (kg/m^2)	28.36 (4.67)

4	Co-morbids	
	Diabetes Mellitus	13 (25)
	Hypertension	20 (38.46)
	Dyslipidemia	5 (9.6)
	Ischemic Heart Disease (IHD)	0 (0)
	2 or more co-morbids	9 (17.31)
5	Presenting symptoms	
	Visual disturbance	24 (46.15)
	Weight gain	9 (17.31)
	Menstrual irregularity	8 (15.38)
	Coarse facial features	12 (23.08)
	Increased limb size	26 (50)
	Headache	31 (59.61)
	Change of voice	6 (11.54)
6	Duration of symptoms (in months)	26.64 (24.61)
7	Pre-operative treatment with somatostatin	2 (3.85)
8	Duration of surgery (in hours)	3.06 (1.32)
9	Surgical approach (n=51)	
	Endoscopic	19 (37.25)
	Microscopic	25 (49.02)
	Both	7 (13.72)
10	Post-operative complications	10 (19.23)
	Neuro-related complications	8 (15.38)
	Others	2 (3.85)
11	Post-surgery radiation(Cyberknife/gamma knife)	8 (15.38)

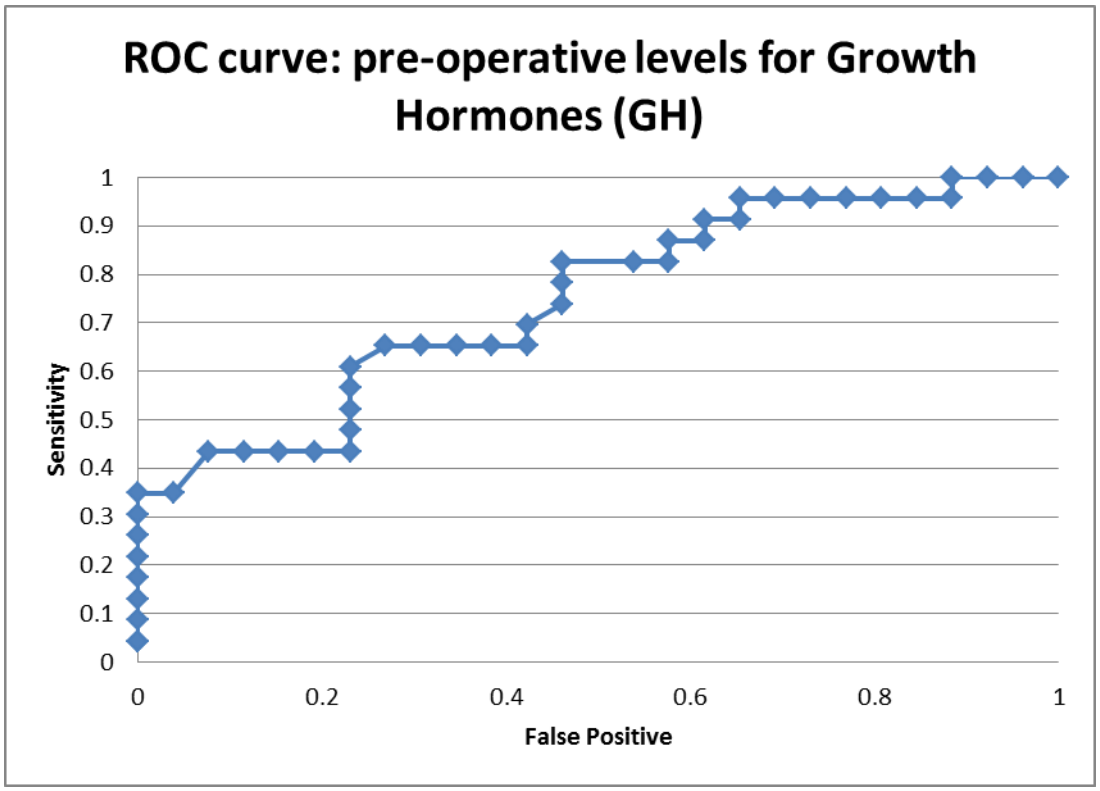
12	Blood loss (ml)	330.29 (243.84)
13	Pre-operative tumor size (n=50)	
	Micro (<10mm)	8 (16%)
	Macro (>10mm)	42 (84%)
14	Tumor extension on Pre-op MRI	
	Supra-sellar	28 (53.85)
	Para-sellar	13 (25)
	Infra-sellar	9 (17.31)
15	Residual mass on post-operative imaging (n=43)	9 (20.93)
16	Treatment outcome (n=49)	
	Remission	10 (20.41)
	Failure	39 (79.59)
17	Histopathology markers	
	CAM	24 (46.15)
	Synaptophysin	33 (63.46)
	Cytokeratin	11 (21.15)
	AE3	7 (13.46)
	GFAP	1 (1.92)
	Negative	19 (36.54)

Table 2: Risk factors associated with the treatment failure in acromegaly

S. no.	Risk factor (N=47)	Risk/Mean difference	95% Confidence interval	p-value
1	Age	2.01	-6.726-10.747	0.6
2	Male gender	0.364	0.81-1.361	0.177
3	Use of pre-op somatostatin	2.19	1.6-3	0.28
4	Post-operative Complications	1.071	0.18-6.19	0.9
5	Pre-operative tumor size <10mm	1.28	1.34-1.12	**0.1**

6	Cavernous Sinus extension on pre-operative imaging	3.063	0.68-13.74	**0.1**
7	Mean difference in pre-operative levels of Growth hormones	53.03	-17.68-123.73	**0.1**
8	Endonasal approach (n=40)	0.067	0.128-2.88	0.5

Figure 1: Reciever operating characteristic (ROC) curve for the pre-operative Growth Hormone levels (mcg/L) outcome (Failure or remission)



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Role Of Kinematic Magnetic Resonance Imaging For Evaluation Of Cervical Spondylotic Myeloradiculopathy: Diagnostic Accuracy And Surgical Planning

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Abstract

Objective: The dynamic part of cervical spondylotic myeloradiculopathy (CSM) is conventionally being evaluated using static magnetic resonance imaging (MRI), which does not address dynamic changes in flexion and extension of the cervical vertebral column. The objective of the study is to evaluate the utility of kinematic MRI imaging in diagnostic accuracy and surgical planning of evaluation of CSM.

Materials and methods: In a prospective study, 30 patients with CSM were evaluated with conventional standard MR cervical spine and kinematic MRI cervical spine with flexion and extension. Morphometric measurements were compared between neutral, flexion, and extension images.

Results: The cervical cord length and cervical canal length were significantly longer in flexion and significantly shorter in extension in all cervical cord sagittal lines. Flexion was associated with decrease in spinal cord compression in 40% of patients, whereas extension caused increase in compression (increase in the size of T2 hyperintensivity) in 75% of patients. Extension identified new subtle T2 hyperintensities. Interpretation of standard MRI findings and the clinical level of radiculopathy is poor, which improves when the neck is extended.

Conclusion: Our results suggest that integration of kinematic MRI with standard static MRI provides additional information in diagnostic accuracy and surgical planning.

Keywords: Cervical vertebrae, Magnetic resonance imaging, Spinal canal, Spondylosis.

Introduction

Cervical spondylotic myelopathy is one of the most common diseases of cervical spine that occurs during and after middle age.1-4 Cervical spondylosis is a chronic degenerative condition of the cervical spine that is caused by a combination of factors, such as vertebral disc protrusion, osteophyte formation, facet joint degeneration, and hypertrophy of the ligamentum flavum. Both mechanical and dynamic factors are reported to play a role in the pathophysiology of myelopathy[4, 5].

Conventionally, preoperative MRI of the cervical spine is done in neutral position only; however, CSM is a dynamic disease of lifestyle.[5] Kinematic MRI of the cervical spine in flexion and extension positions is not routine in evaluating CSM. Dynamic MRI studies[5,6] have been conducted in a few studies to see changes that occur in the spinal cord during flexion and extension of the cervical spine. However, there is lack of clear data of its utility.

The CSM is a progressive disease that requires immediate surgical intervention to minimize damage to the spinal cord and preserve its function. Surgical options include anterior cervical discectomy and fusion, posterior

laminectomy and decompression with or without instrumental stabilization. But the choice of surgery is mostly based on static MRI finding.

This study was conducted to assess the utility of kinematic MRI in CSM. The objective was to assess the morphometric measurements of the cervical spine in patients with CSM in the neutral, 30° flexion, and 30° extension positions and to assess its utility in diagnostic accuracy and surgical planning.

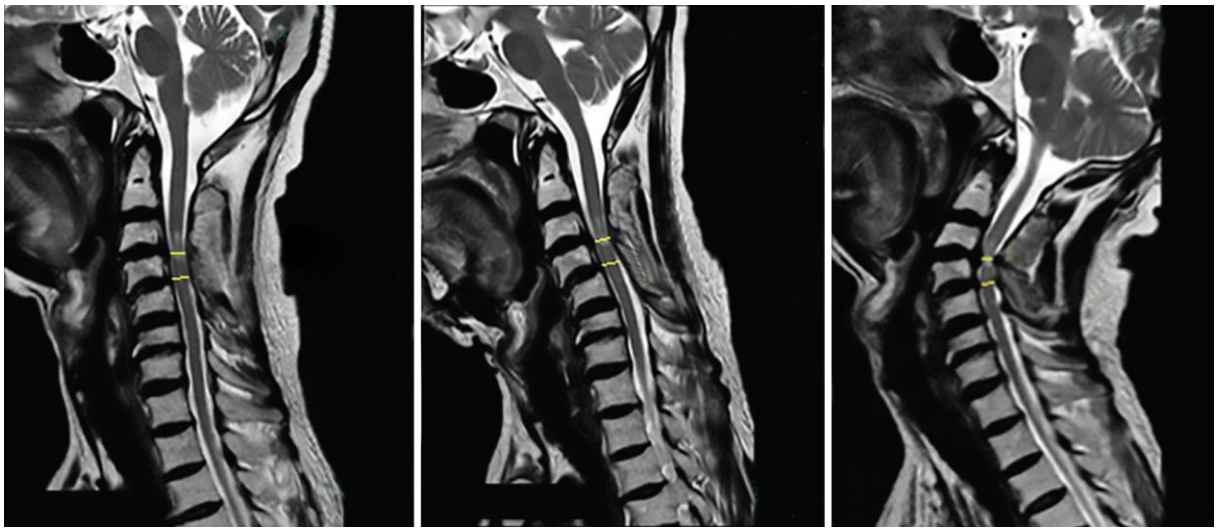
Materials and Methods

Following the approval of the Institutional Ethical Board, we conducted a prospective study of 32 patients diagnosed with CSM, during the period from July 2017 to December 2017. All patients met the criteria for CSM.[7,8] Thirty patients were included in the study in whom we could perform 30° neck flexion using a soft roll under occipital protuberance and 30° neck extension using a soft roll below shoulder. Two out of 32 patients were excluded who could not tolerate neck flexion or extension due to severe pain; 25 (83.33%) of the patients were male and 5 (16.66%) were female, with an average age of 65 years (42–82 years).

Inclusion Criteria
- A clinical and radiographic diagnosis of CSM
- Patients who could tolerate 30° flexion and extension of neck
- Age greater than 18 years
- Patients who signed informed consent form

Exclusion Criteria
- Patients younger than 18 years
- Patients with previous history of cervical spine surgery
- Patients refusing to participate or to sign the informed consent

All patients underwent an MRI of the cervical spine using the same apparatus (Magnetic Resonance 1.5T, Philips) supervised by primary authors who constantly monitored the patients in order to avoid the occurrence of neurological complications during neck flexion and extension. During the first step, the examination was conducted with the patients in the routine supine position with the neck in the neutral position (Fig. 1A). In the second step, a soft roll was positioned under the patient's occipital protuberance in order to achieve 30° neck flexion (Fig. 1B). In the third step, a soft roll was placed under the patient's shoulders to maintain 30° extension (Fig. 1C); T1 and T2 sagittal, axial, and coronal images were obtained in all positions.



Figs 1A to C: Cervical spine T2 sagittal MRI with manual morphometric measurement. (A) Neutral (C3–C4 = 0.68 cm, C4–C5 = 0.78 cm), (B) flexion (C3–C4 = 0.73 cm, C4–C5 = 0.88 cm), (C) extension (C3–C4 = 0.40 cm, C4–C5 = 0.60 cm)

All morphometric measurements were noted in the sagittal and axial T2-weighted MRI sequences of the neutral, flexion, and extension positions. The parameters studied were the anterior length of the spinal cord, the posterior length of the spinal cord, severity of cord compression with 300% magnification in sagittal T2-weighted MRI sequences.[9,10] All the images were analyzed by the primary author using standardized 300% magnification.

Anterior and posterior lengths of the spinal cord were calculated by measuring the distance between a straight line at the upper limit of the anterior and posterior arcs of C1 and a straight line along the lower border of body of C7 (Table 1).

Table 1: Details of manual morphometric measurement

ALSC	Anterior length of the spinal cord	Between C1 and C7 is a straight line crossing the spinal cord at the upper edge of the anterior arcs of C1 and a straight line passing along the lower terminal plate of C7
PLSC	Posterior length of the spinal cord	Between C1 and C7 is a straight line crossing the spinal cord at the upper edge of the posterior arcs of C1 and a straight line passing along the lower terminal plate of C7
DVC	Diameter of the vertebral canal	Shortest distance between the center of the posterior edge of the intervertebral disc of each segment and the anterior edge of the ligamentum flavum posteriorly
DSC	Diameter of the spinal cord	Shortest distance between the anterior and posterior edges of the spinal cord

Results

Two out of 32 patients were excluded who could not tolerate neck flexion or extension due to pain.

The average anterior length of spinal cord was significantly longer in flexion than in extension, and shorter in extension in all cervical cord sagittal lines ($p = 0.002$).

Flexion was associated with a decrease in spinal cord compression in 90% of patients, whereas extension caused an increase in compression in all patients. Extension identified new T2 hyperintensities, suggestive of increase in cord compression with neck extension.

In 5 (16.66%) patients, severe radiculopathy was present, but neutral MRI showed no cord compression, but extension MRI showed nerve root compression, which could explain the cause of radiculopathy; all these patients were treated conservatively with pharmacological drugs, regular physiotherapy, and regular follow-up. In 25 (76.66%) patients, extension MRI showed an increase in cord compression and out of these, 12 patients showed an increase in T2 hyperintensity signal changes. All these patients were treated with surgery—anterior cervical discectomy and fusion with polyetheretherketone cage. Two patients showed multiple- level cord compression with appearance of new T2 hyperintensities in extention as compared with neutral; these patients were treated with surgery—laminectomy, posterior decompression, and stabilization with instruments (Table 2).

Table 2: Summery of result

Findings (n = 30)	No	Percentage	Treatment Offered.
Radiculopathy was present, but neutral MRI showed no cord compression, but extension MRI showed mild compression	5	16.5	conservative
Increase in cord compression in extension MRI (Muhle grading/ manual morphometric measurement)	25	76.66	Anterior cervical discectomy and fusion
Increase in/ appearance of new T2 hyperintensities	12	40	Anterior cervical discectomy and fusion
Multiple-level cord compression	2	6.6	Posteriordecompression

Discussion

Our study findings show that CSM is a dynamic disease and the degree of cord compression varies with the position of the neck.

In all the patients in this study, the lengths of the spinal cord and severity of cervical cord compression were more in flexion than in neutral, and least in extension positions than neutral.

Extension of neck was associated with worsening of compression, prominence of T2 hyperintensity signals, and appearance of new T2 hyperintensity signals, which helped in planning the surgical strategy/approach— anterior *vs* posterior.

In some patients with radiculopathy, extension MRI helped in identification of nerve root compression, which could explain the cause of radiculopathy which could not be explained by conventional static MRI.

Our study has its limitations, such as the small number of patients evaluated, but the morphometric measurements can be reproduced in larger studies in future to investigate the role of kinematic MRI in evaluating patients with CSM.

CONCLUSION

Our results showed that kinematic MRI cervical spine primarily using flexion and extension of neck is very useful in diagnostic accuracy and surgical planning in CSM as compared with conventional static MRI.

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Surgical Management Of Orbital Tumour's: A Neurosurgical Perspective.

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Abstract

Introduction
Orbital tumors are rare and complex lesions, which require a multidisciplinary approach for diagnosis and management. They pose a great challenge for the neurosurgeons and ophthalmologists

Methods:
This is a retrospective study with analysis of data for 15 patients who underwent surgery for orbital tumors at our institution. Data available from 2007 to 2016 was collected and analysis was done. Clinical presentation, age, sex, imaging features, approaches planned, surgical reports, histopathological findings and follow up records were extracted for statistical analysis.

Results:
Most common presentation was exophthalmos (80%), visual disturbances (46.6%), diplopia (40%), retro-orbital or peri-orbital pain (20%). The most used surgical approach was FTOZ (33.3%) followed by lateral orbitotomy (20%). Histopathological findings showed that most of the orbital tumors were hemangiomatous tumors (33.3%) followed by neurofibromas (20%). Malignant tumors accounted for (33.3%). Total resection was achieved in 53.3% of cases. Recurrence was seen in 33.3% cases.

Conclusion:
Orbital tumors need a multidisciplinary approach. Early diagnosis, better imaging modalities correlated with good surgical skills provides good functional outcome. Surgical approach should be planned according to the location and extension of the tumor. Histopathology remains the mainstay of diagnosis in tumoral growth and for prognostication of the disease. This template will assist you in formatting your paper. Please, copy it on your computer and insert the text keeping the format and styles indicated. The various components of your paper (title, abstract, keywords, sections, text, etc.) are already defined on the style sheet, as illustrated by the portions given in this document.

Keywords: Proptosis, Orbital tumors, Surgical management, Histopathology

Abbreviations: FTOZ: fronto temporo orbito zygomatic osteotomy

Introduction

Orbital tumors are very rare tumors. Incidence of orbital tumors in neurosurgical practice is 3.5 to 4 %[1,2]. The orbital tumors can be divided into extraconal, intraconal and intra canalicular tumors[1]. These tumors include tumors of lacrimal gland, adipose tissue, fibrous tissue, muscle tissue, bone and cartilage, tumors of blood vessels and lymphatics, tumors of peripheral nerves and cranial nerves, tumors of optic nerve, tumors of dural meninges and arachnoid and metastasis from adjacent or distant site[1,2,3,4]. Orbital tumors present with visual disturbances as decreased vision and double vision, proptosis, periorbital and retro orbital pain, lacrimation, conjunctival edema and inflammation[3,4].

Many neoplastic conditions masquerade as or mimic other less aggressive inflammatory conditions and should be differentiated before definitive therapy is planned. Clinical examination and radiological investigations are not so helpful in preoperative diagnosis in all cases of orbital tumors. Until the histopathology is evident the actual diagnosis is still not confirmed by these pre-operative works up. All orbital lesions are subjected to histopathology for prognostication and for planning further management.

Many approaches are described for treating orbital tumors and in recent trend is towards endoscopic management of these tumors with less invasion and morbid technique compared to the open surgeries[5,6].

1.1. Aims and objectives:

To study the morphological and clinic pathological correlation of orbital tumors
To know the pattern of prevalence of orbital tumors in our institute
To help in formulating treatment strategy and surgical approaches
To study the outcome of orbital tumors

1.2. Material and methods:

We searched the database for all patients who underwent surgery for the treatment of orbital tumors at our institution between 2007 and 2016. Data from clinical notes, surgical reports, and radiological findings were obtained for the analysis. Tumor location, size and relation to neighboring anatomical structures were determined using preoperative computed tomography (CT) and magnetic resonance (MR) imaging. A cooperative team of neurosurgeons, an ophthalmologist and plastic surgeons participated in the treatment planning for each patient. The extent of the tumor resection was determined intra operatively and confirmed by follow-up MR images taken 3-6 months postoperatively. Morbidity, follow-up and outcome were analyzed from entries in the clinical notes and phone calls to the patients regarding their absence if not turn up for follow up.

1.3. Results:

Age and sex:
A total of 15 patients who underwent surgery for the treatment of orbital tumors were enrolled in the present study. There were 6 males and 9 females, and their ages ranged from 6 to 75 years (mean age of 40 years).

Table 1: Age wise distribution of orbital tumors

Age in years	Number	Percentage
0-9	2	13.33
10-19	3	20
20-29	1	6.66
30-39	2	13.33
40-49	1	6.66
50-59	2	13.33
60 and above	3	20

Presentation:
Right side predominant than left side (Rt: Lt=2:1). Exophthalmos present in 12 patients, visual disturbances in 7, diplopia in 6 and peri orbital and retro orbital pain in 3 patients. These were major symptomatic presentations.

Table 2: Common symptoms of orbital tumors

Symptoms	Number of patients	Frequency (%)
Exophthalmos	12	80
Visual disturbances	7	46.6
Diplopia	6	40
Pain	3	20
Lacrimation	3	20
Conjunctival edema	2	13.33
Inflammation	2	13.33

Site of involvement of orbital tumors:
Most of the tumors are primay intraorbital tumors. No tumor is extending into orbit from adjacent structures except for tuberculum sella meningioma's extending into optic canal and extending into orbit in 2 cases. One patient had medial and inferior orbital hemangioma extending into lesser orbital foramen into cheek. Most of the tumors are placed in middle and posterior third of orbit. Sites of involvement of orbit by the tumor included lateral orbit in 6, near orbital apex in 5, superior orbital in 3 and medial orbital in 1 patient. Majority of the tumors located in the posterior and middle third of the orbital space requiring extra orbital or transcranial approaches for surgery

Table 3: Site of involvement of tumor in orbit

Primary tumor involvement	Number	Percentage (%)
Lateral orbit	6	40
Medial orbit	1	6.6
Superior orbit	3	20
Near orbital apex	5	33.33

Surgical approach:
The surgical approaches used were transcranial/ extra orbital approaches in 15 patients. Lateral orbitotomy is the most common approach (6 cases) followed by FTOZ in 4 cases, frontoorbitotomy in 3 cases and fronto temporo orbitotomy in 2 cases.

Table 4: surgical approaches correlated with site of involvement

Surgical approach	Number	Percentage (%)	Site of lesion
Lateral orbitotomy	6	40	Lateral orbital tumor - 6
FTOZ	4	26.66	Tumor near orbital apex - 4
Fronto-orbital	3	20	Superior orbital tumors – 2 Medial orbital tumor -1
Fronto-temporo-orbital	2	13.33	Tumor near orbital apex -1 Superior orbital tumor -1

Amount of resection of tumor:
Near total, subtotal resection and biopsy were achieved in, 8, 5 and 2 patients, respectively. One patients with meningioma (FTOZ approach) experienced visual deterioration postoperatively. It was caused by the manipulation of optic nerve while drilling the optic canal roof. None of the patients died as a result of the surgical procedure.

Table 5: Amount of resection

Amount of resection	Number of cases	Percentage (%)
Near total	8	53.33
Subtotal	5	33.33
Biopsy	2	13.33

Histopathology of orbital tumors:
The underlying pathologies included cavernous hemangiomas in 3 patients, capillary hemangiomas in 2 patients, neurofibromas in 3 patients, meningiomas in 2 patients, sarcoma in 2 patients, metastasis in 1 patient, optic nerve glioma in 1 patient, lymphoma in 1 patient.

Table 6: Histological results

Tumor type	Number	Percentage (%)
Cavernous hemangioma	3	20
Capillary hemangioma	2	13.33
Neurofibroma	3	20
Meningioma	2	13.33
Sarcoma	2	13.33

Lymphoma	1	6.66
Metastasis	1	6.66

Outcome:

Patients with malignancy and subtotal resection for benign lesions were subjected to radiotherapy postoperatively. Follow up scans taken at 6 months post-operative period showed recurrence of tumor (metastasis from unknown origin) in one patient. One patient died at 6 months post op and did not turn up for follow up (sarcoma).

1.4. Discussion:

Orbital tumors are rare in neurosurgical practice. The histopathological characterstics of these tumors are critical to their biologic behaviour, line of management, outcome and prognosis. Orbital tumors can be developed either from structures located in the orbit or from the stuctures surrounding the orbit. Adjacent structures producing metastatic tumors into orbit include paranasal sinuses, nasal cavity, skin of fore head, eyelid and from parotid[2].

Operative approach for these tumors mainly depend on location, size, demarcation, extension, involved structures and histological type of the lesion. The least traumatic and easily accessible approach should be chosen. Procedures that can be performed will range from simple biopsy to near total or total resection depending on the histological variant[3,4,5]. Most appropriate surgical approach chosen for making complete excision possible. Approaches can be divided into trans orbital and extra orbital approaches. Most of the tumors present in anterior third of orbital space are approached through the trans orbital approaches and mostly dealt by ophtholmologists. Tumors of middle third and posterior third orbital space are approached by extra orbital or trans cranial approaches. Medially placed tumors are best approached by endoscopic techniquie by entering orbital space through lamina papyracea.

Table 7: Appropriate extra orbital surgical approach for tumors placed in middle and posterior third of orbit

Approach	Location of lesion
Inferior orbital approach or posterior inferior orbitotomy through Caldwell-Luc incision and maxillary sinus	Inferior and medial to optic nerve
Transcranial	
Fronto orbitotomy	Superior and medial (sometimes) to optic nerve
Fronto temporo orbitotomy	Tumors involving/ extending superior orbital fissure and optic nerve
FTOZ	Tumors involving /extending optic nerve or superior orbital fissure and extending into middle fossa

Table 8: Trans orbital approaches for tumors placed in anterior third of orbit

Approach	Site of lesion
Anterior orbitotomy (with or without removing orbital rim)	Superior
Lateral orbitotomy	Lateral
Medial orbitotomy	Medial and inferior
Combination of lateral and medial	Lateral and medial

In addition to the use of microscope, other more recent modalities, such as neuronavigation techniques, endoscopy, and stereotactic radiosurgery, have helped us in the surgical management of orbital tumors.

Our study :

A series of 15 orbital tumors in our study is based on clinical, radiological correlation and histopathological examination. Females are commonly affected than males. Median age group involved is 40 years. But less than 10 years and more than 60 years aged population are commonly involved than other groups. Right side eye is more involved than left side. In our study most of the tumors are primary intra orbital tumors with one case with tuberculum sella meningioma with intra canalicular extension and one case of metastasis.

Most of the tumors are present in middle and posterior third of orbit. Hence most surgical approaches are extra orbital requiring main role by a neurosurgeon. Most of the tumors are located in lateral orbital space requiring lateral orbitotomy in most of the cases. Six tumors were approahed through lateral orbitotomy. FTOZ is a good approach in which osteotomy can be done in single piece or two piece procedure. All FTOZ s are single piece osteotomies and this approach was the second most common approach we performed in 4 cases in our study.
Most of the tumors are benign in which vascular tumors are more common than others, followed by neurofibroma and meningioms. Malignant lesion are seen in five patients in which fibrous histiocytoma and rhabdomyosarcoma (sarcoma) in two patients, lymphoma in one, optic nerve glioma in one and metastasis in one patient. All the patients with incomplete resection or malignant lesions are subjected to radiotherapy. Recurrence was seen in one patient and one patient with sarcoma died within 6 months. Others were not having any recurrence and 6 months follow up scans showed no recurrence of the lesions.

1.5. Conclusion:

Orbit is an extremely difficult anatomical entity approached. Because of the technical advances in neurosurgery in the field of imaging, neuro navigation, endoscopy, microscope and stereotactic radiotherapy, management of orbital tumors became very least morbid as compared to years ago. Tumors in all locations of orbit as medial, lateral, superior and inferior can be accessed with less invasive and less morbid approaches. Complete removal of orbital tumor is made possible with these new advances. Tumors in medial and less accessible with small size can be subjected to stereotactic radiotherapy with good results. Histopathology of the tumor is the maintsay in further management and prognostication of the disease. Multi disciplinary approach with histopathological and good surgical skill correlation results in good outcome of the patient.

Images :

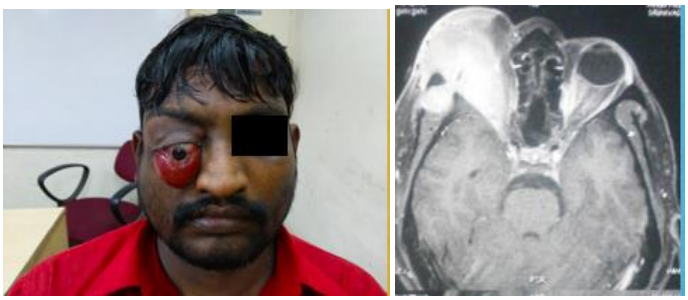

FIG 1a Pre operative

FIG 1b Post operative

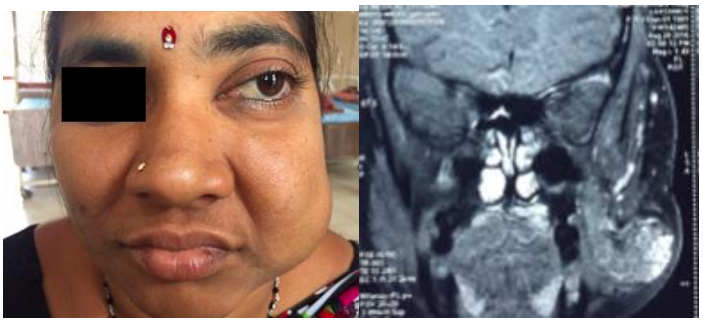

FIG 2a Pre-operative

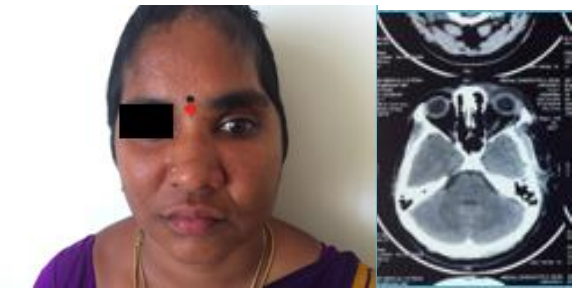

FIG 2b Post-operative

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Suturing In Endoscopic Endonasal Surgery: Pitfalls And Surgical Nuances.

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Abstract

Numerous skull base reconstruction techniques for prevention of postoperative CSF leakage are essential to improve the surgical results. Here, we report our algorithm for skull base reconstruction during EEA without initial lumbar drainage (LD) management, and discuss the associated outcomes and pitfalls.

Keywords: skull base reconstruction, endoscopic endonasal approach, CSF leakage, pituitary

Introduction

Various skull base reconstruction techniques have been developed in endoscopic endonasal approach (EEA) for skull base lesions to prevent postoperative cerebrospinal fluid (CSF) leakage [1]. This study was performed to evaluate the efficacy and pitfalls of our method of skull base reconstruction after EEA. Greater care with regard to postoperative CSF leakage is required in patients with prior EEA with radiotherapy and obesity. In such high-risk patients, postoperative late-LD and bed rest may be required to prevent postoperative CSF leakage. It is also important to restrict activities that result in increased intracranial pressure.

Materials and methods:

A total of 123 patients who underwent EEA (127 surgeries) between October 2014 and May 2017 were reviewed. Our algorithm for skull base reconstruction in EEA was categorized based on intraoperative CSF leakage graded as follows: Grade 0 was excluded from this study, Grade 1, dural suturing with abdominal fat graft or packing of gelatin sponge into the cavity; Grade 2, method for grade 1 with addition of mucosal flap or nasoseptal flap; Grade 3, duraplasty in fascia patchwork closure with nasoseptal flap. Bony reconstruction was not mandatory, and there was no postoperative bed rest or initial lumbar drainage (LD) insertion in any of the cases (Fig. 2 number 2).

・Endoscopic endonasal suturing technique.

Following total tumor removal, the optic chiasm, pituitary stalk, bilateral superior hypophysial artery can be seen. We can appreciate the large defect of the dura with high flow CSF leakage. The fascia lata graft is used as an inlay barrier. This suture techniques requires four hands. The surgeon do suturing two hands and the assistant maintain adequate tension. With a 6-0 prolene suture, retaining sutures are placed at different corners to hold the graft into place. Special instruments are necessary to overcome the challenging angles. Special care should be paid to avoid injuring the skeletonized ICA's and high skills are mandatory to avoid injury of the deep neural structures. In our experience, interrupted suture with ring culet technique or easy slip knot provides sufficient water tight closure. Intersuture distance should be equal as much as possible.

Here we can see eleven sutures can provide adequate water-tight closure (Fig. 2).

Results:

Postoperative CSF leakage after EEA was mostly (96.3%) prevented by our algorithm without postoperative initial LD or bed rest. On the other hand, reconstruction surgery was required for postoperative CSF leakage in two cases-one with prior multi-transsphenoidal surgery and radiotherapy and another patient with poor compliance due to communication difficulties. Both of the latter patients were obese.

Conclusion:

Endoscopic endonasal suturing technique for skull base reconstruction following EEA, can be considered as a modified algorithm to prevent postoperative CSF leakage

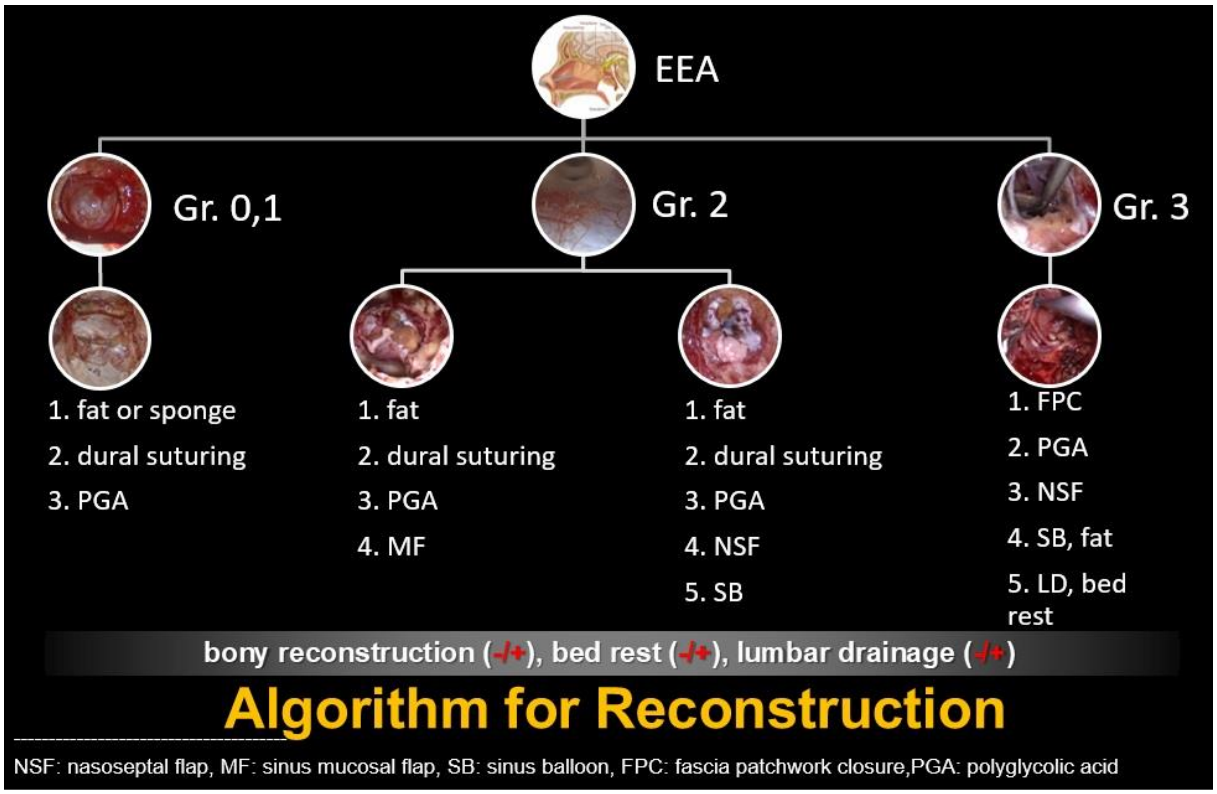

Figure 1: Algorithm for skull base reconstruction. Suturing technique is frequently applied.

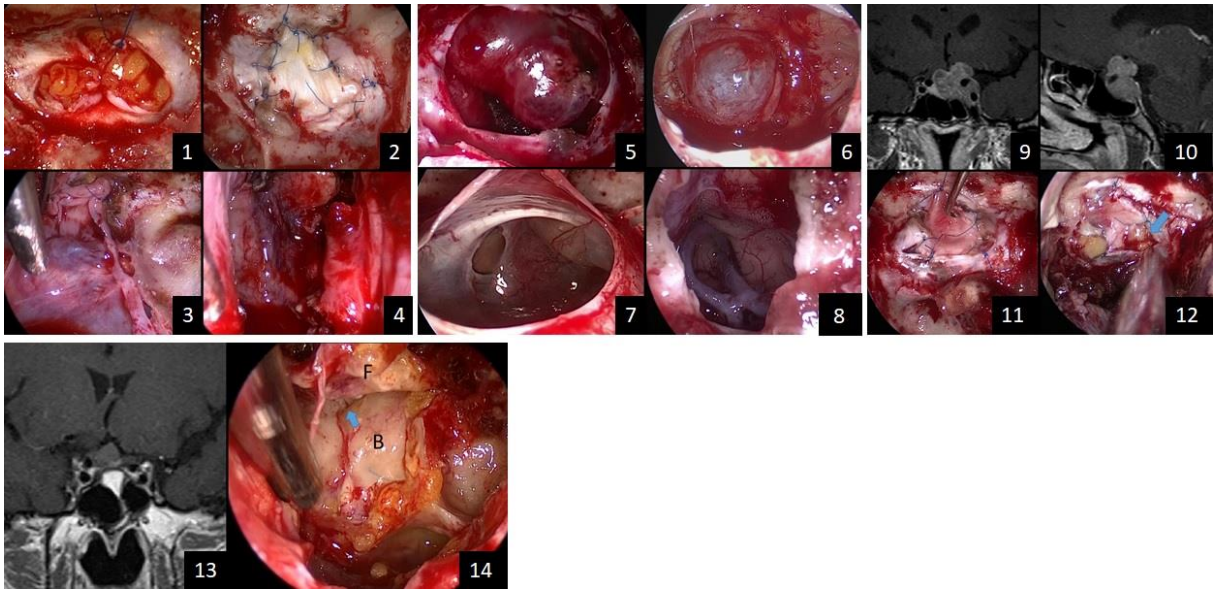

Figure 2: Intraoperative photograph showing skull base reconstruction in endoscopic endonasal surgery. The fat graft was packed into the cavity with anchoring dural sutures (1). Watertight duraplasty was achieved using the fascia patchwork closure technique (2). The mucosal flap from the posterior wall of the sphenoid sinus covered the sellar turcia (3). A pedicled nasoseptal flap was rotated to resurface the skull base defect at the end of the surgical procedure (4). Intraoperative photograph showing degree of CSF leakage. No leak was observed (5). Small leak was observed without obvious diaphragmatic defect (6). Moderate leak with small arachnoid defect was observed (7). High flow CSF leak was observed with large diaphragmatic and dural defect (8). Preoperative MRI showing an invasive pituitary tumor with optic chiasm compression (9,10). Intraoperative photograph showing duraplasty with fascia patchwork closure technique (11). Intraoperative photograph in repeat surgery showing leakage point (arrow) following peeling off the adhered NSF (12). Preoperative MRI showing a suprasellar tumor with optic chiasm compression (13). (14) Intraoperative photograph showing

the skull base following peeling off the fascia graft. Minor CSF leakage was identified (arrow). F: fascia graft, B: bony reconstruction

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The Correlation Of Optic Neural Sheath Diameter With Severity And Mortality In Patients With Non-Traumatic Intracranial Haemorrhage.

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Abstract

Purpose:
To study the optic neural sheath diameter in non-traumatic intracranial hemorrhage patient in order to identify if this bedside non-invasive ultrasonographic investigation may provide some guidance to subsequent clinical decisions. We evaluated the correlation between Optic neural sheath Diameter (ONSD), haemorrhage volume, Glasgow Coma Scale, and Intracerebral haemorrhage Score (ICH score).

Materials and Method:
This was a prospective single center, single operator, observational study carried out for 6 months from September 2017 till February 2018. Total of 50 patients were approached, out of which 5 were excluded due to ineligibility. ONSD was measured using standard technique as described in literature. The data was analysed using SPSS 24. Correlation between ONSD-haemorrhage volume, ONSD-GCS and ONSD-ICH Score were assessed using Pearson correlation.

Results:
The study included 45 patients (mean age: 59.9 ± 13.4 years old, 26(57.8%) Male), with the mean ONSD value 0.5919 ± 0.046 cm. The statistical assessment yielded positive correlation value of 0.303 (p-value = 0.043) between ONSD-Haemorrhage volume and correlation between ONSD-ICH was 0.372 (p-value = 0.012). Moreover, a negative correlation value of – 0.351 (p-value = 0.018) were shown between ONSD-GCS.

Conclusion:
Our study, indicate that as haemorrhage volume increases the ONSD increases as well. This correlation is similarly seen with increases in ICH score suggesting increase in mortality risk. ONSD is a non-invasive method to evaluate severity and mortality risk in patients with non traumatic intracranial haemorrhage.

Keywords: ONSD, GCS, ICH Score, mortality risk, Intracerebral haemorrhage, haemorrhagic stroke, Pearson correlation

Introduction

Non traumatic intracranial haemorrhage is defined as spontaneous bleeding within the cranium, layers covering the brain, in the brain parenchymal itself or into the ventricular system[1]. This includes primary intracerebral haemorrhage (intraparenchymal), subarachnoid haemorrhage, interventricular haemorrhage and subdural haemorrhage[1]. Primary intracerebral haemorrhage (PICH) is more common among Asian compared to other races [2]. In Malaysia, it is one of the leading cause of mortality and the most debilitating type of cerebrovascular event [2, 3, 6]. The proportion of Malaysians with PICH against all stroke types is about 25.2% which has a reported mortality rate about 32.5-43.9%[4, 5].

Numerous factors have been identified in contributing to the prognosis of patients with primary intracerebral haemorrhage [6]. These would include NCECT findings heralding increased intracranial pressure such as haemorrhage volume, midline shift, location of haemorrhage, pupil size and Glasgow Coma Scale (GCS) of the patient[6,7]. Left uncorrected, these on-going pathologies lead to brain herniation, precipitous fall in GCS and death. Interventions by Neurosurgeons are often directed at reducing the raised intracranial pressures which occur as a result of the PICH[5-7]. It is therefore vital initially to differentiate between PICH and other stroke types. However, to confirm bleeding, and to determine the resultant raised intracranial pressures requires non contrast enhanced computed tomography (NCECT) and other more invasive procedures eg ICP monitoring via intraventricular catheter[6-8]. This often requires movement of patients with stroke presentations to larger medical centers with such NCECT and Neurosurgery facilities.

Optic Neural Sheath Diameter (ONSD) measurement provides a valuable alternative in terms of evaluating intracranial pressure[9,11-13]. Previous study done in Malaysia by Raffiz and Abdullah (2017) showed that cut off point 5.205mm for ONSD has 95.8% sensitivity and 80.4% specificity in predicting raised intracranial pressure more than 20mmHg[9]. To date, there is no known study in Malaysia that has been done to show the relationship between optic neural sheath diameter and NCECT brain findings, Glasgow Coma Scale (GCS) and Intracerebral Haemorrhage (ICH) score.

This is a prospective observational study sought to elicit relationship between optic neural sheath diameter, NCECT brain findings, GCS and ICH score in patients with non-traumatic intracranial haemorrhage.

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Materials and Method

We conducted a prospective, single center, single operator, observational study on patients with PICH. The study was carried out over a six-month duration from September 2017 till February 2018 at Hospital Universiti Sains Malaysia (HUSM), Kelantan, Malaysia. The study protocol was reviewed and approved by USM Research Ethical Committee (JePEM).

We included all patients aged 18 and more with PICH as evidenced by NCECT done in HUSM. The onset of symptoms in this cohort of patients were less than 24 hours.

We excluded patients who presented with intracranial haemorrhage of traumatic origin, those who have been pre-treated with intracranial pressure lowering medications (such as mannitol, hyperosmolar saline solution;etc) and those with pre-existing ocular pathology. Patients with altered level of consciousness due to significant electrolyte imbalance, acute endocrine pathologies, acute ingestion of unknown substance, and other brain pathology with/without brain haemorrhage were excluded as well.

The Primary Investigator approached patient or their next of kin to obtain consent after assessing eligibility. A total of 50 patients were identified out of which 3 were deemed to be ineligible and 2 patients/next of kin declined to participate. The Study flow chart is as shown in Figure 1

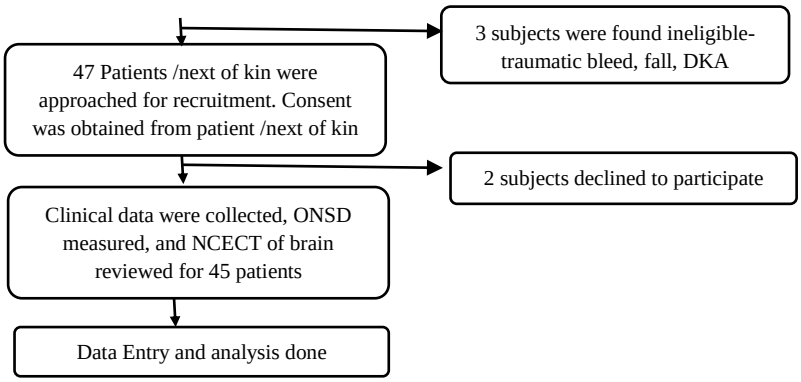

Figure 1. Study Flow Chart

Demographic details, clinical data, Glasgow Coma Scale scores and other relevant data were collected. Non Contrast Enhanced Computed Tomography of brain was reviewed after ONSD of both eyes were measured. Intraprenchymal haemorrhage volume was calculated via ABC/2 formula [7,10]. Formal report of the NCECT Brain report was also used to aid the data collection. ICH score was then be calculated for each patient.

SONOGRAHIC MEASUREMENT

Optic nerve is encompassed by connective tissue sheaths which are continuation of the layers covering the brain [11-13] .As a result, an increase in intracranial pressure would push the cerebrospinal fluid into the optic nerve sheath causing enlargement[11-13]. Utilizing this principle, sonographic measurement of optic nerve sheath is often used to evaluate intracranial pressure both in emergency department and critical care[9] . Furthermore, acquisition of skills to perform sonographic measurement of ONSD is not a tenuous process and this non-invasive procedure can easily be done at patients' bedside[9,15-16].

Sonographic measurement of ONSD was performed by a Primary Investigator who has completed WINFOCUS (Malaysia) Life Support- Basic Level 1 course using SAMSUNG Ultrasound machine with 7.5 MHz linear probe. The first 20 scans were done together with a credentialed master trainer as a validation test. ONSD was measured according to the standard technique as advocated in the literature [9, 11-13]. Patients were placed in supine position with head kept at 30-45 degree, ONSD was then measured in the axial view for both eyes[9, 11-13]. The probe was placed horizontally on the closed eyelid and cushioned by ultrasound gel covering the upper eyelid[9, 11-13]. After obtaining the optimal image, 3 readings were measured 3mm behind the papilla[9, 11-13](Figure 2). A total of 6 images for a patient were obtained and mean optic nerve sheath diameter were ascertained for each eye. Later, mean optic nerve sheath diameter for both eyes were calculated by averaging mean optic nerve sheath diameters of both right and left eyes. All the scans were performed by one Primary Investigator.

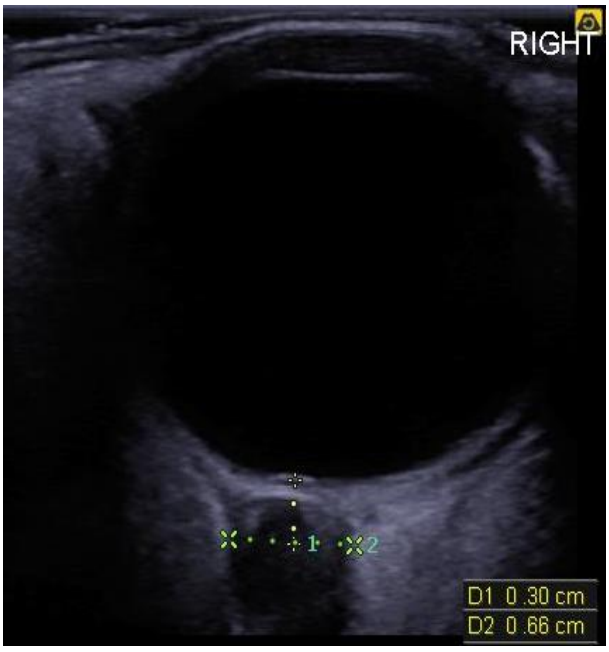

Figure 2: Right Optic nerve sheath measured at a depth of 3mm from behind the ocular globe.

The ocular scan was performed within 2 minutes for each eye (less than 5 minutes for both eyes).The sonographic clips were then saved and reviewed by credentialed master trainer. The primary investigator was blinded to both, the GCS Score and specific NCECT brain findings initially.

Data was then analyzed using SPSS. Basic descriptive statistical analysis was used to analyze the data and the values are represented in terms of percentages, mean, median, frequencies, minimum value, maximum value and standard deviations (SD). Pearson correlation coefficient and scatterplot were used to assess the strength of association between ONSD-Blood hemorrhage volume, ONSD- GCS score and ONSD- ICH score. 2-tail test with α value=0.05 was used to ascertain the significance.

Results

A total of 45 patients were recruited for this study and 270 sonograhic images of optic nerve sheath diameter were done, 3 images for each eye were measured and average reading of each eye was calculated. Table 1 below shows the demographic data obtained in this study where 57.8% of the sample consisted of men and the remaining were women. The mean age and mean haemorrhage volume of the patients in this sample were 59.4±13.4 years and 28.5± 30.0 cm^3. Median value for GCS and ICH Score in this study was shown to be 11 (4-15) and 2 (0-4) respectively. Out of 45 patients, 40 (88.9%) patients were known to have at least medical condition such as hypertension, cerebrovascular event, dyslipidemia, and ischemic heart disease.

Table 1. Demographic Data

	CLINICAL DEMOGRAPHICS	ICB(n=45) %
1.	*Age (years)	59.4 ± 13.4
2.	**Ethnicity- Malay Chinese Indian Others	43 (95.6%) 0 (0%) 1 (2.2%) 1 (2.2%)
3.	**Gender: Male	26 (57.8%)

	Female	19 (42.2%)

4.	** Co-morbidities : - Hypertension -non-compliance Antiplatelet/anticoagulant therapy Cerebrovascular event Dyslipidemia Ischemic Heart Disease	40 (88.9%) 36 (80%) 17 (37.8%) 16 (35.6%) 13 (28.9%) 6 (13.3%) 4 (8.1%)
5.	*Mean ONSD *Mean Haemorrhage volume ***GCS ***ICH Score	0.592 ± 0.046 cm 28.5 ± 30.0 cm^3 11 (4-15) 2 (0-4)

* = data represented by mean ± SD
** = data represented by frequency (percentage)
***= data represented by median (min-max)

As per Table 2 and Figure 3, ONSD-haemorrhage blood volume and ONSD-ICH Score was shown to have weak positive correlation of 0.302 (p-value = 0.0403 <0.05) and 0.372 (p-value = 0.012 <0.05) respectively. Similarly, a weak negative association was demonstrated between ONSD and GCS Score correlation of -0.351(p-value = 0.018 <0.05).

Table 2 Pearson Correlation of ONSD-Blood volume, ONSD-GCS and ONSD- ICH Score

ONSD-Blood volume	Pearson correlation Sig (2-tailed)	0.302* 0.043
ONSD-GCS Score	Pearson correlation Sig (2-tailed)	-0.351* 0.018
ONSD-ICH Score	Pearson correlation Sig (2-tailed)	0.372* 0.012

*Correlation is significant at the 0.05 level (2-tailed).

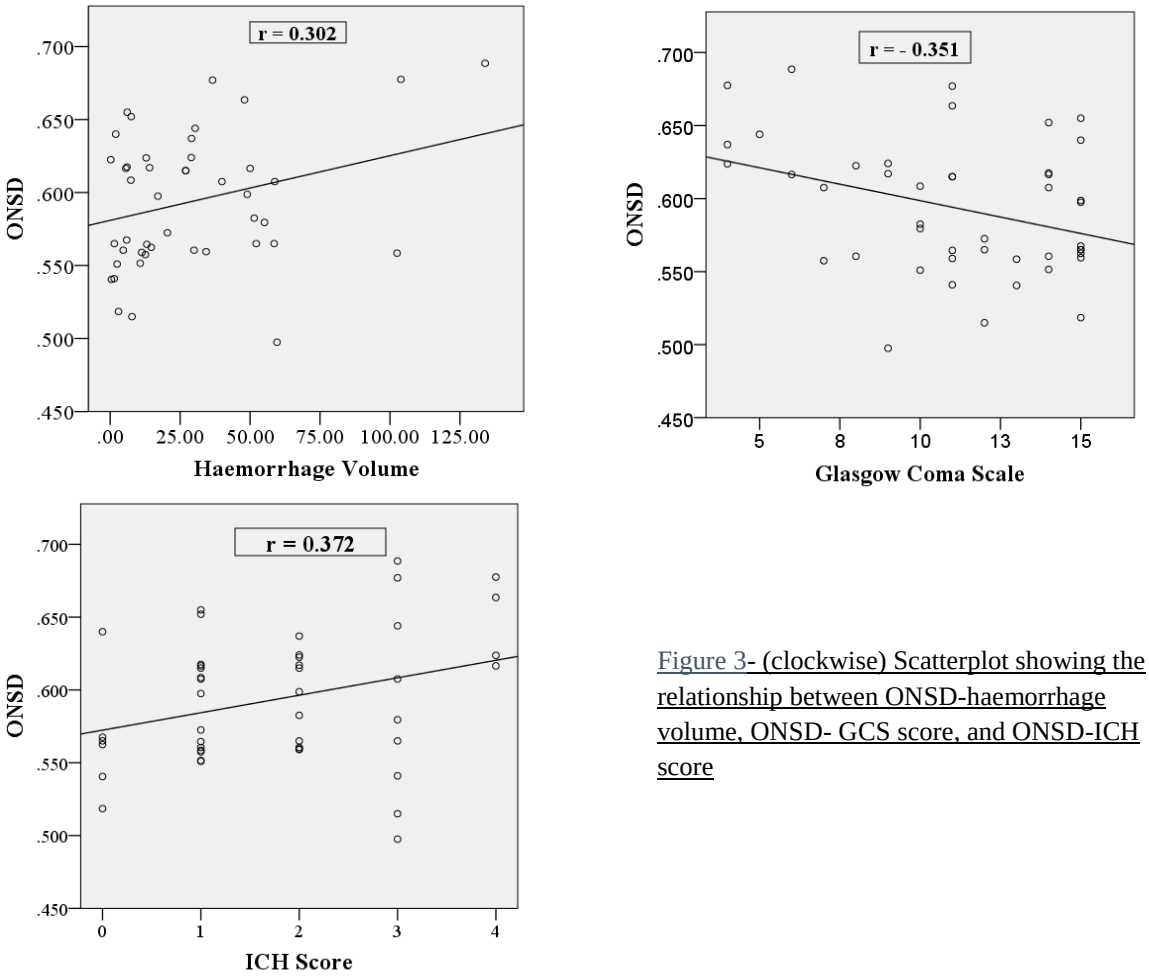

Figure 3- (clockwise) Scatterplot showing the relationship between ONSD-haemorrhage volume, ONSD- GCS score, and ONSD-ICH score

Interclass correlation between right eye and left eye ONSD was 0.994. Intraclass correlation between within 3 readings of right eye ONSD was shown to be 0.953 and left eyes was 0.970. This indicates a low variability.

Discussion

The mean age of patients recruited in this study was about 59.4 ± 13.4 which is in agreement with the mean age of acute haemorrhaghic stroke about 60.8 ± 13.1, recorded in Acute Stroke Registry (2010-2014)[2]. We found that hypertension was the most common comorbidity, at about 80% in PICH patients, which was consistent with the findings in Acute Stroke Registry (2010-2014)[2]. Ethnic distribution of PICH in this study showed that 95.6 % of the sample were Malays, this percentage is higher than the latest data obtained in Acute Stroke registry, approximately about 88.9%[2]. This is largely due to geographical distribution of patients, large proportion of patients were of Malay ethnicity as the sample subjects were recruited from Kelantan[14]. According to Department of Statistics of Malaysia (Sumber: Jabatan Perangkaan Malaysia 2017) 95.9 % of the population in Kelantan is made up of Malays and indigenous tribes as opposed to other states like Penang or Kuala Lumpur where the percentage ranges from 40-50%[14]. Therefore, ethnic distribution in this study is not a true representation of the entire Malaysian population.

Multiple studies have unveiled the capricious nature of the cut off value of ONSD in indicating increased intracranial pressure at a clinical significant level of more than 20 mmHg, but the evidence to support the correlation between ONSD and intracranial pressure is clear and almost indisputable[9, 15-16].

Our study unveiled that ONSD has a weak positive association with blood haemorrhage volume (r = 0.302). This finding is important and interesting because it reveals to us that the increase in intracranial pressure after PICH is not solely dependent on the initial haemorrhage volume[6-9]. Factors such as location of the bleed, perilesional

edema, cytotoxic edema, hydrocephalus, brain atrophy play an important part in the generation of elevated intracranial pressure state[6-9]. Many of these factors cannot be objectively and accurately quantified, resulting in the weak positive correlation result.

Furthermore, ONSD measurement usually indicates generalized increased intracranial pressure where the increased pressure is due to global swelling of the brain [11-13, 16]. The overall swelling in the brain increases the pressure in the skull vault and displaces the cerebrospinal fluid into potential spaces. This results in accumulation of cerebrospinal fluid in the optic nerve sheath increasing the width in the process[11-13,16]. An intraparenchymal bleeding at certain parts of the brain will only cause localized edema at that particular part of the brain which will not lead to generalized increase in intracranial pressure [16,17]. Therefore, the findings in this study agrees with previous study done by Jin Pyeong Yan et al who proposed that ONSD measurement is more suitable in for patients with larger amount of bleed[16].

It would seem naturally logical that a larger ONSD be linked to a lower GCS. This must be particularly true in large volume intracerebral haemorrhage which invariably results in widespread neurological function deficits. However, in smaller bleeds restricted to parts of the brain not linked to specific verbal or motor response, the association may be much less obvious. On the other hand, a small bleed at the brain stem or reticular activating system will not necessarily cause cerebral oedema but will cause rapid neurological deterioration [16, 17]. Therefore, in these cases GCS scoring does not reflect the increased intracranial pressure. Moreover, unless the bleeding occurs at critical areas of the brain such as infratentorial region or cerebellar, localized swelling would rapidly progress to cause brain herniation [16, 17]. As a consequence of this process the consciousness and neurological status of the patient will be impaired [16, 17].

The weak association between ICH score and ONSD was significant. This could be accounted by the fact that ICH Score is calculated by summing up points awarded for 5 categories such as GCS Score, region of bleed, volume of bleed, age and also extension of bleed into intraventricular region. The region of bleed and extension of bleed into intraventricular space would not have directly caused generalized increased intracranial pressure leading to ONSD dilatation. Furthermore, as we have discussed earlier, bleeding into critical region would greatly impact the mortality of the patient. Although, the relationship was weak but it was the strongest among the 3 correlations that was calculated. This further proves to us that a combination of clinical examination, radiological findings and ONSD might be a better tool in predicting mortality in this cohort of patients.

Despite the significance of our result, this study has its limitations. Foremost, the study is limited due to its small sample size and single center. Therefore, further research involving multi centers with larger sample should be carried out in future. Secondly, the ultrasound measurement in this study was done by a single primary physician eliminating the operator bias. Even though, sonographic measurement of ONSD is shown to have a good reproducibility (good inter observer variability), sonography measurement is operator dependent[18,19]. Large scale practice of ONSD measure by the multitude of the front liners may cause variation. Third limitations in this study was that we were unable to obtain actual measurement of increased intracranial pressure via intraventricular catheter. We strongly advocate for another study to evaluate the relationship between haemorrhage blood volume, intracranial pressure and ONSD with a larger group and done in multicenter setting.

Conclusion

An increased ONSD is linked to larger haemorrhage volumes and increased mortality risk (ICH scores). Further work is needed to determine specific cut-off ONSD levels together with other clinical parameters which may predict need for surgical interventions. At the moment, ONSD may be used as a non-invasive adjunct to evaluate severity and mortality risk in patients with PICH.

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The Use Of Magnetoencephalographic Brainwaves In Detecting Neurocognitive Impairments In Traumatic Brain Injury

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Abstract

Objectives: The purpose of this study was to investigate the potential of magnetoencephalography (MEG) as a tool for early detection of brainwave disruption in traumatic brain injury (TBI) patients and compare the MEG results to neuropsychological assessments.
Methods: Our study consisted of 12 TBI patients aged 14–26 who had a Glasgow Coma Scale (GCS) of 9–13 in the first 24 hours after a motor vehicle accident. According to the severity of their GCS score, and regardless of the type of brain injury, patients were then distributed into two groups, moderate TBI (GCS score 9–12) or mild TBI (GCS score of 13). Neuropsychological tests were given to patients before the MEG recording. MEG was used to measure the power of the different frequency bands delta, theta, alpha, beta, and gamma.
Results: The power of the beta frequency band was reduced and the theta/beta ratio was significantly increased in the moderate TBI group compared to the mild TBI group. Neuropsychological assessments results tended to support this finding but did not reach significance.
Conclusion: The MEG results suggest that moderate TBI patients have greater processing and attention deficits than mild TBI patients. We concluded that MEG plays an important role in objectively detecting brain wave changes after TBI, which has implications for the prediction of cognitive sequelae after TBI.
Keywords: Magnetoencephalography, neuropsychology tests, spectral analysis, traumatic brain injury, brainwaves

Introduction

Trauma cases contributed to 11.65% of visits to emergency departments at Malaysia Ministry of health general hospitals, of which about 80% involved head injury. Traumatic brain injury (TBI) may lead to a wide range of short- or long-term issues affecting cognitive and motor functions, sensation, and emotion (1, 2). TBI can cause brain connectivity disruption in widely disparate brain regions which may not necessarily correspond to the locations of focal lesions as shown using conventional neuroanatomical imaging such as Computer Tomography (CT) and Magnetic Resonance Imaging (MRI) (1). Another limitation of conventional neuroanatomical imaging is its inability to show functional abnormalities in patients with TBI(3, 4). We therefore sought to use brainwave data obtained via magnetoencephalography (MEG) as a tool to diagnose functional disturbances.There are few studies regarding the use of quantitative brainwave or electroencephalography (EEG), using spectral power analyses, for TBI (3,4). We chose to conduct spectral analysis using MEG, which is a non-invasive imaging technique that directly measures neuronal current brain activity in grey matter, with high temporal resolution (< 1 ms) and a spatial localization accuracy of 2–3 mm at the cortical level (5). Electrical conductivity differences between the brain, cerebrospinal fluid skull, and scalp interfere with the scalp EEG view of the brain's electrical activity but have minimal impact on MEG (6). A few studies have examined changes in the spectral power bands of TBI patients and have found that TBI patients have more prominent low-frequency amplitude waves, such as delta and theta bands (7, 8)and these injured neuronal tissues who generate the multifocal low-frequency neuronal magnetic signal that can be localized

directly using MEG instead of EEG . These changes are linked to cognitive and affective sequelae.Pioneering studies by Lewine et al(8)showed that MEG slow waves were 65% sensitive in detecting symptomatic concussions, whereas EEG was only 20–25% sensitive,and MRI was only 20% sensitive indetecting lesions in patients with mild or moderate TBI. In 2002, MEG achieved recognition as reimbursable clinical procedure by the American Medical Association, including recording and analysis of spontaneous brain magnetic activity for epileptic foci and of evoked magnetic fields (e.g. sensory, motor, language, visual cortex, etc.) under Current Procedure Terminology (CPT) (9).

We used the Glasgow Coma Scale (GCS) to indicate the severity of TBI among our sample subjects. GCS is a clinical tool designed to measure cognitive impairment. GCS scores of 3 to 8 are indicative of severe TBI, scores of 9 to 12 indicate moderate TBI, and scores of 13 to 15 indicate mild TBI. We then evaluated cognitive impairment in mild and moderate TBI patients using neuropsychological assessments, which are specialized task-oriented evaluations of human brain-behaviour relationships that incorporate patient history, presentation, and clinical findings. MEG data for all patients was then recorded.

Spectral analysis subdivides MEG results into several bands—the delta, theta, alpha, beta,

and gamma bands. We hypothesized that all bands could be affected by TBI, with consequences for cognitive impairment.The hippocampus is especially prone to injury in TBI, which will subsequently reduce hippocampal Theta activity, causing persistent learning and memory deficits. The hippocampus plays a vital role in a variety of memory tasks and is normally dominated by theta bands, which synchronize activity across distal brain regions for cognitive processing (10, 11). A pathological increase in theta bands is also seen in patients with Alzheimer's disease (12)which is characterized by a loss of cholinergic functions that is believed to be an important contributor to cognitive deficits. Cholinergic neuronal loss is found in several areas of the limbic system, such as the medial septal nucleus, which have major projections to the hippocampus (13). Thus, cholinergic dysfunction after TBI may also

contribute to learning, memory and attention deficits (14). Alpha band power reduction is related to post-traumatic stress disorder symptoms (15).Alpha rhythms also play roles in perceptual learning (16, 17), and attention is one of the key factors that can determine perceptual learning outcomes.The alpha band is also responsible for the synchronization of working memory (18). The functional role of the beta band, which originates in the sensorimotor cortex, is related to action-related language processing (19) Hirata et al(20) reported that increased beta from MEG signals from the inferior frontal gyrus and middle frontal gyrus during a word-reading test without phonation. A decrease in beta power is also seen in attention deficit disorder(21).The amygdala is a subcortical area involved in emotional processing and regulation. Numerous studies have shown that gamma band oscillations are observed in the amygdala during emotional memory and processing (22, 23)Gamma oscillation is also seen in the hippocampus (24) and in several areas of the neocortex (25), as well as in the thalamus (26). It is also thought to have a role in cognitive execution (27). Abnormal slow/delta-waves are not specific as it can also been found in neurological/psychiatric disorders such as epilepsy, brain tumors, Alzheimer's disease, and other organic brain disease. Other external factors such as neuroleptic, sedative,and hypnotic medications, as well as sleep deprivation may also contritube to increase slow waves. However , Huang et al study shown injured neurons due to TBI ,causing deafferentation from axonal injury to the associated white matter fiber tracts, which detected by diffusion tensor imaging as reduced fractional anisotropy(28).However, delta band activity also increases, mainly in the frontal lobes, during tasks such as mental calculations and semantic tasks(29).

We hypothesized that the combination of MEG data with neuropsychological assessments in the detection of potential neurological and cognitive deficits would yield clinically relevant data that would not be easily acquired via routine bedside neurological examination. Our results include analysis of patient MEG findings in relation to neuropsychological scores for memory, attention and language.

1.0METHODOLOGY

Materials and methods

1.1The subjects

This prospective study was approved by Universiti Sains Malaysia Kubang Kerian Human Ethical Committee (ref. HUSM/11/020/Jld.6). The study consisted patients of Malaysian population aged of 14–30 years old who received a GCS score of 9–13, were recruited from the emergency department of Hospital Universiti Sains Malaysia during the first 24 hours after injury. Inclusion criteria were: between 14 and 30 years of age; causes of head injury were clear (e.g. sustaining a force to the head); Glasgow Coma Scale from 9-13 (within 24 h of injury); Modified Marshall I-V on basis of CT scan findings, Every participant was able to tolerate enclosed space for MEG; Malay or English speaking, to comply with instructions to complete tasks during MEG and able to give informed consent . Exclusion criteria included ferrous metal inside the body or items that might interfere

with MEG data acquisition; presence of implanted medical devices; seizures or other neurological disorders, or active substance abuse; certain ongoing medications (anticonvulsants, benzodiazepines, and/or GABA antagonists) known to directly or significantly influence electroencephalographic (EEG) findings.

1.2 Neuropsychological assessments

All participants underwent cognitive-behavioural testing including the Wechsler Abbreviated Scale of Intelligence (WASI), Wechsler Memory Scales 1 (WMS1, Immediate), Wechsler Memory Scales 2 (WMS2, Delayed), Wechsler Memory Scales 3 (WMS3, Total), Benton Visual Retention Scale (BVRT), Rey Auditory Verbal Learning Test 1 (RAVLT1, Immediate Recall), Rey Auditory Verbal Learning Test 2 (RAVLT2, Delayed Recall), and Comprehensive Trail Making Test (CTMT). These assessments were carried out by a trained research associates .The results were scored, double scored, and reviewed by a licensed neuropsychologist to maintain reliability. All evaluations were administered in a single session in a quiet room, within 1 week of the MEG .

1.3 Sample groups

On the basis of clinical admission measures, the patients were placed into two different groups. Criteria for assignment to the Mild head injury group were GCS 13, post traumatic amnesia (PTA) less than 1 hour, and loss of counsciousness LOC less than 20 minutes. Criteria for the Moderate head injury group were GCS 9-12, PTA 1hour to 6days and LOC 1 hour to 24 hours. The sample size of this study calculated based on the previous study by Huang et al(1) published in Brain injury journal of Taylor &Francis in 2017. The calculated sample size for this study using software GPower 3.1.7 , tests - Means: Difference between two dependent means (matched pairs),analysis:A priori: Compute required sample size ,Input:Tail(s)=One,Effect size dz =0.95,α err prob=0.05, Power (1-β err prob)=0.90.Output: Noncentrality parameter δ=3.1507936, Critical t=1.8124611,Df=10,Total sample size=11,Actual power=0.9002194

1.4 MEG recordings

Our MEG recordings were performed in a magnetically shielded room using a whole-head Electa Neuromag 306 channel MEG system (Helsinki, Finland) in the Laboratory for MEG, Department of Neurosciences, Universiti Sains Malaysia. Prior to recording, four small coils were applied to the left and right side of each patient's forehead: to the left and right mastoid processes, for head position indicator and head digitization points on the nasion, and at left and right preauricular positions. The sampling rate was 1,000 Hz. Spontaneous MEG recording was conducted for 30 minutes for each TBI patients in two resting conditions, eyes closed and eyes open. A 1-minute sample of artefact- and noise-free magnetometer data was selected for the analysis of the total power in the delta (0.5–4 Hz), theta (4–7 Hz), alpha (8–13 Hz), beta (13–30 Hz), and gamma (30–50 Hz) bands using Fast Fourier Transform (fft-size-1024, fft-step 512, hanning type window). MEG brainwaves detection and localization is usually manually performed by MEG analysts. In our study,MEG data were recorded from TBI patients, who were all within 1 months of injury

1.5 Statistical methods

Band power from the MEG spontaneous data was compared between the two groups of TBI patients using non-parametric Man-Whitney U tests (SPSS version 22.0 for Windows) for each condition (eyes close and eyes open) from 15 brain regions (left anterior temporal, left posterior temporal, left frontal, left central, left parietal, midline fronto-polar, midline frontal, midline central, midline parietal, mid occipito-polar, right frontal, right central, right parietal, right anterior temporal, and right posterior temporal) . The significance level was set at $p < 0.05$.

2.0.Results

Twelve TBI patients with GCS scores ranging from 9 to 13 were recruited into our study: one patient each with a GCS score of 9, 10, and 12; three patients with a GCS score of 11; and six patients with a GCS score of 13. Their mean age was 18.4 (with a standard deviation of 4.1). There were three females and nine males, with a mixture of intracranial pathologies detected on neuroanatomical CT imaging. Demographic data is illustrated in Table 1. Resting state MEG data were recorded.

2.1 Neuropsychological test outcomes

The two groups were compared in terms of age, mean GCS score, and neuropsychological

test results. The two group, showed statistically significant difference happened in the power band spectral analysis (p = 0.002). Neuropsychological tests for memory, attention, and language failed to show statistically significant differences between the two groups. Table 2 illustrates those detailed parameters.

2.2 MEG spectral analysis during two resting state conditions

2.2 (a) Eyes-closed condition

Regarding spontaneous MEG power spectral analysis during the eyes-closed condition,there were no significant differences found in the delta, theta, alpha, and gamma frequency bands between the two groups of TBI patients in any of the 15 brain regions we examined. However, there was lower beta power in the midline and right parietal regions (Table 3), a higher theta/beta ratio in left anterior temporal and left central regions (Table 4), and a higher alpha/beta ratio in the left and right central brain regions (Table 5) in moderate TBI group compare to mild TBI group.

2.2(b) Eye open condition

During eyes-open condition, there were again no significant differences found in delta, theta, alpha, beta, and gamma frequency bands between the two groups. Although the difference in beta power between the two groups was significantly lower in the eyes-closed condition, this was not true for the eyes-open condition. Similarly, there was no significant difference in alpha/beta ratio between the two groups during the eyes-closed condition.
However, similar to the results in the eyes-open condition, during the eyes-closed condition a higher theta/beta ratio was observed in the left and right central brain regions of patients in the moderate TBI group as compared to those in the mild TBI group (Table 6). Table 7 summarises our MEG results.

3.0 Discussion

3.1 TBI

TBI causes damage to the white matter tracts of the brain via diffuse axonal injury or focal brain damage, resulting in contusion and intracranial haemorrhage. These kinds of injury result in neuronal degeneration and disrupted connectivity within and between brain areas, which leads to a loss or reduction of cognitive function (31)

3.2 Functions of the different bands

Spectral analysis subdivides MEG results into several bands—the delta, theta, alpha, beta, and gamma bands. We hypothesized that all bands could be affected by TBI, with consequences for cognitive impairment.
Ishihara et al (32) was the first who reported frontal midline theta rhythm that appears over medial frontal areas in the EEG of normal subjects when performing a broad range of cognitive tasks demanding mental concentration. Mild and moderate TBI in this study , due to midline and temporal polar zones are affected (33) facing distortion of theta/beta signal is detected mainly through a task of voluntary orienting of attention. The result of Theta/beta ratio decrease in mild head injury may signify the recovery of the cerebral function (34) or it can also meant the increase theta/beta ratio in moderate TBI group suffered more obvious attention deficit comparing to the mild TBI group .Egner and Grunzelier(35) summarized that enhanced beta power may increase activation in a noradrenergic vigilance and alertness network. The parietal and mid-central are linked to visual and cognitive aspects of visuo-motor transformation(36). In our study lower beta power is seen in midline and right parietal region which meant patient lack of attentiveness to proceed and execute a task .
Higher alpha/beta ratio in left and right central brain region is seen in our study . this is supported by previous study (37) which showed abnormal induced and evoked alpha activity due to poor working memory capacity .

3.3 Comparison of the eyes closed and eyes open results

The power of the brainwave bands change from childhood through adulthood. Up until the sixth decade of life, low-frequency bands such as delta and theta bands decrease over time, while high-frequency bands (particularly the beta band) increase significantly(38, 39). Our study therefore selected patients in the age group 14–30 to avoid age-related confounding variables. Resting-state MEG recordings are a crucial tool for studying intrinsic brain activity. MEG acts as a complementary tool to fMRI for analyses of cortical communication patterns as well as analysis of the fundamental differences in connectivity between healthy and diseased populations (40, 41). When a patient is relaxed with closed eyes, their brainwave activity is usually characterized by the posteriorly dominant alpha rhythm. Recent studies have established the existence of α-oscillations, which exert inhibitory effects on irrelevant or interfering processing and can thus improve behavioural performance (42, 43)
This supports our result that the eyes-close condition gave more reliable information than eyes-open condition.

3.4 Sensitivity of neuropsychological test versus MEG

Neuropsychological tests, which are used after TBI to assess various aspects of behaviour (e.g., social functioning, cognitive abilities, and psychiatric symptoms), typically show that some significant behavioural

impairment will be prolonged (44, 45). However, in our study, neuropsychological assessments were not able to detect significant differences between mild and moderate TBI patients even when MEG recordings showed significant changes in the frequency band activity of the two groups. This can be explained by the fact that MEG is an objective measurement while neuropsychology tests are subjective assessments.

4.0 Conclusions

MEG may aid in the prognostication and improve the management of TBI patients by analysing the power of patients' brainwave frequency bands. Patients with neurocognitive limitations should be given greater attention and provided with proper rehabilitation. However, the findings of our study need to be replicated with a larger sample in order to make clinical recommendations.

5.0 Limitation and Future Recommendation

Due to the high costs of MEG, the sample size has always been less in all MEG related researches. However with the significant results that obtained in this study,larger sample size is proposed in future and also patients who go through rehabilitation exercises to see the changes in the MEG .

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Table 1: Descriptive statistics of Traumatic Brain Injury (TBI) Patients with Injury Findings

TBI Subjects	Age (years)	Gender	GCS-Total	Injury
Patient 1	17.5	F	9	Traumatic SAH at left Sylvian, right Quadrigeminal Cistern
Patient 2	26	M	11	Right Temporoparietal SDH (less than 1cm) Small temporal contusion
Patient 3	21.11	M	12	Right temporal contusion and left temporoparietal EDH
Patient 4	15.11	M	13	Tentorial SDH
Patient 5	17.1	M	13	Right temporal contusion and right thin SDH
Patient 6	16.1	M	11	Left frontal contusion, left SDH, right occipital fracture
Patient 7	14.6	M	13	Right parieto-occipital EDH, 2.8cm midline shift
Patient 8	24.8	M	10	Right posterior parietal thin SDH
Patient 9	23	M	13	Left frontal EDH, vertex EDH, right temporoparietaoccipital contusion
Patient 10	16.1	F	11	Right SDH with underlying temporal contusion
Patient 11	15	M	13	Bilateral frontal EDH
Patient 12	14.9	F	13	Depressed frontal bone skull fracture

Table 2: Demographic and Neuropsychological Data of Mild (n=6) and Moderate (n=6) Traumatic Brain Injury Patients

	Severity	Mean	SD	Z-score	P-value
Age	Mild	16.62	3.25		
	Moderate	20.27	4.39	-1.925	0.054
***GCS**	Mild	13.00	0.00		
	Moderate	10.67	1.03	-3.102	***0.002****
WASI	Mild	76.33	10.61		
	Moderate	76.17	13.32	-0.321	0.748
WMS1	Mild	64.67	16.26		
	Moderate	61.17	12.25	-0.179	0.858
WMS2	Mild	65.00	17.54		
	Moderate	62.17	14.01	-0.191	0.849
WMS3	Mild	64.33	16.33		
	Moderate	60.33	13.06	-0.631	0.528
BVRTVM	Mild	6.67	2.50		
	Moderate	5.17	1.72	-0.819	0.413
RAVLT1	Mild	39.50	18.16		
	Moderate	37.50	11.15	-0.241	0.81
RAVLT2	Mild	7.83	4.12		
	Moderate	6.17	4.96	-0.405	0.686
CTMT	Mild	28.00	8.49		
	Moderate	21.17	4.12	-1.451	0.147

GCS – Glasgow Coma Scale (*Grouping variable), WASI – Wechsler Abbreviated Scale of Intelligence, WMS1 – Wechsler Memory Scales (Immediate), WMS2 – Wechsler Memory Scales (Delayed), WMS3 – Wechsler Memory Scales (Total), BVRT – Benton Visual Retention Scale, RAVLT1 – Rey Auditory Verbal Learning Test (Immediate Recall), RAVLT2 – Rey Auditory Verbal Learning Test (Delayed Recall), CTMT – Comprehensive Trail Making Test. *P value<.05 is significant shown in bold and italic

Table 3: MEG power spectral analysis for Beta frequency in eye close condition from Mild (n=6) and moderate (n=6) Traumatic Brain Injury patients. Lower beta power in midline and right parietal region is seen

Brain Region	Severity	Mean	SD	Z - score	P – value
Lt Ant Temporal	Mild	2.71	0.40		
	Moderate	2.65	0.34	-0.48	0.631
Lt Post Temporal	Mild	2.66	0.47		
	Moderate	2.54	0.19	-0.16	0.873
Left Frontal	Mild	2.31	0.21		
	Moderate	2.12	0.19	-1.601	0.109
Left Central	Mild	2.16	0.23		
	Moderate	2.01	0.26	-0.961	0.337
Left Parietal	Mild	1.91	0.29		
	Moderate	1.75	0.15	-1.281	0.2
Mid Fronto-polar	Mild	2.31	0.09		
	Moderate	2.15	0.21	-1.601	0.109
Midline Frontal	Mild	2.03	0.45		
	Moderate	1.86	0.32	-0.32	0.749
Midline Central	Mild	2.03	0.47		
	Moderate	1.86	0.31	-0.32	0.749
Midline Perietal	Mild	1.85	0.29		
	Moderate	1.59	0.06	-2.085	**0.037***
Mid Occipito-polar	Mild	2.08	0.24		
	Moderate	1.91	0.13	-1.761	0.078
Right Frontal	Mild	2.03	0.14		
	Moderate	1.96	0.29	-0.16	0.873
Right Central	Mild	2.07	0.14		
	Moderate	1.88	0.28	-0.961	0.337
Right Parietal	Mild	1.87	0.21		
	Moderate	1.55	0.11	-2.882	**0.004***
Rt Ant Temporal	Mild	2.30	0.08		
	Moderate	2.34	0.30	-0.32	0.749
Rt Post Temporal	Mild	2.48	0.19		
	Moderate	2.33	0.18	-1.281	0.2

SD – Standard Deviation, Lt – Left, Ant – Anterior, Post – Posterior, Mid – Mdline, Rt – Right,

*P value < .05 is significant shown in bold and italic

Table 4: Theta/Beta ratio from MEG power spectral analysis in eye close condition from Mild (n=6) and Moderate (n=6) Traumatic Brain Injury patients. Higher Theta/Beta ratio in left anterior temporal region

Lt Ant Temporal	Mild	0.95	0.04		
	Moderate	1.02	0.05	-2.082	**0.037***
Lt Post Temporal	Mild	0.96	0.05		
	Moderate	1.04	0.10	-1.761	0.078
Left Frontal	Mild	0.98	0.04		
	Moderate	1.05	0.10	-1.281	0.2
Left Central	Mild	0.96	0.04		
	Moderate	1.06	0.09	-2.082	**0.037***
Left Parietal	Mild	1.00	0.13		
	Moderate	1.11	0.16	-1.121	0.262
Mid Fronto-polar	Mild	0.99	0.08		
	Moderate	1.06	0.15	-0.801	0.423
Midline Frontal	Mild	0.98	0.09		
	Moderate	0.99	0.10	0	1
Midline Central	Mild	1.06	0.14		
	Moderate	1.10	0.11	-0.642	0.521
Midline Parietal	Mild	1.06	0.16		
	Moderate	1.16	0.24	-0.801	0.423
Mid Occipito-polar	Mild	1.02	0.06		
	Moderate	1.08	0.16	-0.16	0.873
Right Frontal	Mild	1.02	0.10		
	Moderate	1.11	0.18	-1.121	0.262
Right Central	Mild	0.97	0.07		
	Moderate	1.07	0.15	-1.441	0.15
Right Parietal	Mild	1.05	0.16		
	Moderate	1.19	0.24	-1.121	0.262
Rt Ant Temporal	Mild	1.01	0.08		
	Moderate	1.04	0.09	-0.801	0.423
Rt Post Temporal	Mild	1.00	0.08		
	Moderate	1.04	0.11	-0.801	0.423

Table 5: Alpha/Beta ratio from MEG power spectral analysis in eye close condition from Mild (n=6) and Moderate (n=6) Traumatic Brain Injury patients. Higher Alpha/Beta ratio in left and right Central brain region

Brain Region	Severity	Mean	SD	Z- score	P - value
Lt Ant Temporal	Mild	0.97	0.05		
	Moderate	1.00	0.03	-1.601	0.109
Lt Post Temporal	Mild	0.99	0.09		
	Moderate	1.09	0.12	-1.281	0.2
Left Frontal	Mild	0.95	0.06		
	Moderate	1.01	0.05	-1.761	0.078
Left Central	Mild	0.97	0.10		
	Moderate	1.11	0.06	-2.082	**0.037***
Left Parietal	Mild	1.04	0.11		
	Moderate	1.14	0.11	-1.281	0.2
Mid Fronto-polar	Mild	0.97	0.06		
	Moderate	1.01	0.09	-0.961	0.337
Midline Frontal	Mild	0.94	0.06		
	Moderate	0.98	0.09	-1.121	0.262
Midline Central	Mild	1.01	0.10		
	Moderate	1.09	0.06	-1.761	0.078
Midline Parietal	Mild	1.10	0.21		
	Moderate	1.24	0.09	-1.922	0.055
Mid Occipito-polar	Mild	1.12	0.13		
	Moderate	1.19	0.12	-0.801	0.423
Right Frontal	Mild	0.96	0.06		
	Moderate	1.05	0.10	-1.441	0.15
Right Central	Mild	0.99	0.10		
	Moderate	1.17	0.09	-2.402	**0.016***
Right Parietal	Mild	1.08	0.13		
	Moderate	1.23	0.07	-1.922	0.055
Rt Ant Temporal	Mild	0.98	0.06		
	Moderate	1.03	0.04	-1.281	0.2
Rt Post Temporal	Mild	1.02	0.12		
	Moderate	1.10	0.10	-1.281	0.2

SD – Standard Deviation, Lt – Left, Ant – Anterior, Post – Posterior, Mid – Midline, Rt – Right, *P value < .05 is significant shown in bold and italic

Table 6: Theta/Beta ratio from MEG power spectral analysis in eye open condition from Mild (n=6) and Moderate (n=6) Traumatic Brain Injury patients. High Theta/Beta ratio in the left and right central brain region is seen

Brain Region	Severity	Mean	SD	Z - score	P - value
Lt Ant Temporal	Mild	1.01	0.13		
	Moderate	1.04	0.09	-0.641	0.522
Lt Post Temporal	Mild	0.95	0.06		
	Moderate	1.07	0.16	-1.601	0.109
Left Frontal	Mild	0.98	0.12		
	Moderate	1.07	0.16	-0.961	0.337
Left Central	Mild	0.93	0.06		
	Moderate	1.07	0.11	-2.082	**0.037***
Left Parietal	Mild	0.95	0.09		
	Moderate	1.05	0.15	-1.281	0.2
Mid Fronto-polar	Mild	1.03	0.13		
	Moderate	1.08	0.15	-0.801	0.423
Midline Frontal	Mild	0.92	0.06		
	Moderate	0.99	0.09	-1.761	0.078
Midline Central	Mild	0.98	0.07		
	Moderate	1.12	0.16	-1.761	0.078
Midline Parietal	Mild	0.92	0.06		
	Moderate	1.06	0.22	-1.922	0.055
Mid Occipito-polar	Mild	0.88	0.05		
	Moderate	0.94	0.09	-1.601	0.109
Right Frontal	Mild	0.98	0.06		
	Moderate	1.09	0.14	-1.441	0.15
Right Central	Mild	0.92	0.05		
	Moderate	1.07	0.13	-2.242	**0.025***
Right Parietal	Mild	0.95	0.06		
	Moderate	1.10	0.22	-1.441	0.15
Rt Ant Temporal	Mild	1.05	0.06		
	Moderate	1.07	0.09	-0.32	0.749
Rt Post Temporal	Mild	0.93	0.05		
	Moderate	1.01	0.11	-1.441	0.15

Table 7: Summary of the results

	Eye Close		Eye Open	
	Mild	Moderate	Mild	Moderate
Beta Power	Increased	Decreased	No change	No change
Theta/Beta Ratio	Decreased	Increased	Decreased	Increased
Alpha/Beta Ratio	Decreased	Increased	No change	No change

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Watertight Robust Osteoconductive Barrier For Skull Base Reconstruction Following Expanded-Endoscopic Endonasal Approaches

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Abstract

Endoscopic skull base reconstruction (ESBR) following expanded-endoscopic endonasal approaches (EEA) in high-risk non-ideal endoscopic reconstructive candidates remains extremely challenging, and further innovations remain necessary. Herein, we introduce the watertight robust osteoconductive (WRO) barrier as an alternative durable option.

Keywords: skull base reconstruction, endoscopic endonasal approach, CSF leak, transsphenoidal surgery, watertight

Introduction

By concluding the experiences of endoscopic skull base experts1-7 based on a thorough survey of the English literature we were able to study the reconstructive knowledge gap. If there is an available watertight robust barrier that is enough to withstand postoperative adjunctive radiation and chemotherapy (avascular environment), applicable for irregular-deep-critical bone defects, efficiently evaluated with neuroimaging, simple in its technique, without donor site complications and can be considered as a good endoscopic reconstructive alternative, it will be a great advantage. We selected a well-known malleable osteoconductive-and-osteoinductive material, which became a robust barrier within a few minutes, that have good biocompatibility, superior bone regeneration and can survive avascular environment. Herein, we present the watertight robust osteoconductive barrier (WRO-barrier) for endoscopic skull base reconstruction (ESBR) as an alternative durable option and we will discuss its distinct qualities and limitations (Fig. 1,2).

Methods

Distinctively, we focused on ten clinical circumstances. A 3D-skull base-water system model was innovated to investigate the ESBR under realistic conditions. A large-irregular defect (31x89 mm) extending from the crista galli to the mid-clivus was achieved. Then, WRO-barrier was fashioned and its tolerance was evaluated under stressful settings, including an exceedingly high (55 cmH2O) pressure, with radiological assessment. Next, the whole WRO-barrier was drilled to examine its practical-safe removal (simulating redo-EEA) and the whole experiment was repeated. Finally, WRO-barrier was kept into place to value its 18-month long-term high-tolerance (Fig. 1,2).

Results

In all experiments WRO-barriers were satisfactorily fashioned to conform the geometry of the created defect under realistic circumstances via EEA, tolerated an exceedingly high pressure without evidence of leak even under stressful settings, resisted sudden-elevated pressure, and remained in its position to maintain long-term watertight seal (18 months), efficiently evaluated with neuroimaging and simply removed-and-reconstructed when redo-EEA is needed (Fig. 2).

Conclusion

WRO-barrier as an osteoconductive watertight robust design for endoscopic cranial base reconstruction can contribute in decreasing the CSF leak rate and can be considered as a promising alternative durable option for designated patients with complex/invasive skull base tumours that require aggressive removal (with large defect) and postoperative adjunctive chemo-radiotherapy (avascular environment). It tolerates an exceedingly high (55 cmH2O) pressure and remains in its position to maintain watertight seal even under stressful conditions. Besides, it can be simply removed and reconstructed when redo-surgery is needed.

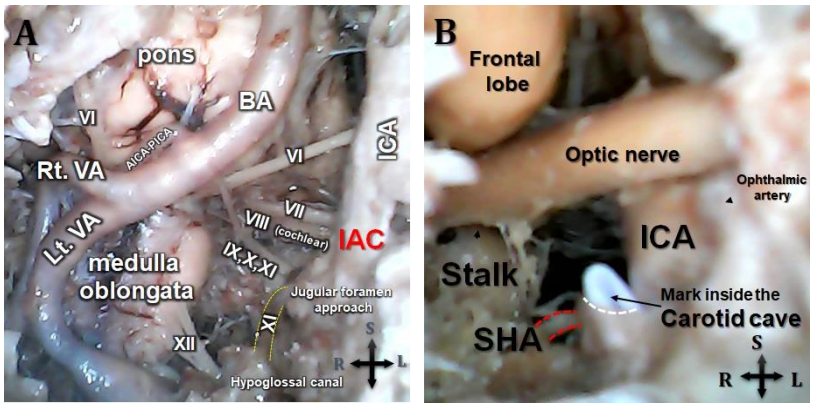

Figure 1

Figure 1: Endoscopic video-captured view following cadaveric dissection (by the lead author (A.N.)): (A): *An example of the daunting challenge of complex skull base defect following extensive drilling of the clivus and completing the left-sided sub-lacerum infrapetrous approach to the jugular foramen. The brainstem, cranial nerves from VI to XII, union of both vertebral arteries to form the basilar artery can be appreciated via endoscopic endonasal perspective.* ***(B):*** *Crtical anatomical structures around the left orbital apex: the carotid cave can be also identified to show the anatomy of the superior hypophyseal artery (SHA).* ***BA:*** *basilar artery;* ***Rt. VA:*** *right vertebral artery;* ***Lt. VA:*** *left vertebral artery;* ***AICA:*** *anterior inferior cerebellar artery;* ***PICA:*** *posterior inferior cerebellar artery;* ***ICA:*** *internal carotid artery;* ***VI:*** *6th cranial nerve;* ***VII:*** *7th cranial nerve;* ***VIII:*** *8th cranial nerve;* ***IX:*** *9th cranial nerve;* ***X:*** *10th cranial nerve;* ***XI:*** *11th cranial nerve;* ***XII:*** *12th cranial nerve;* ***S:*** *superior;* ***R:*** *right;* ***L:*** *left.*

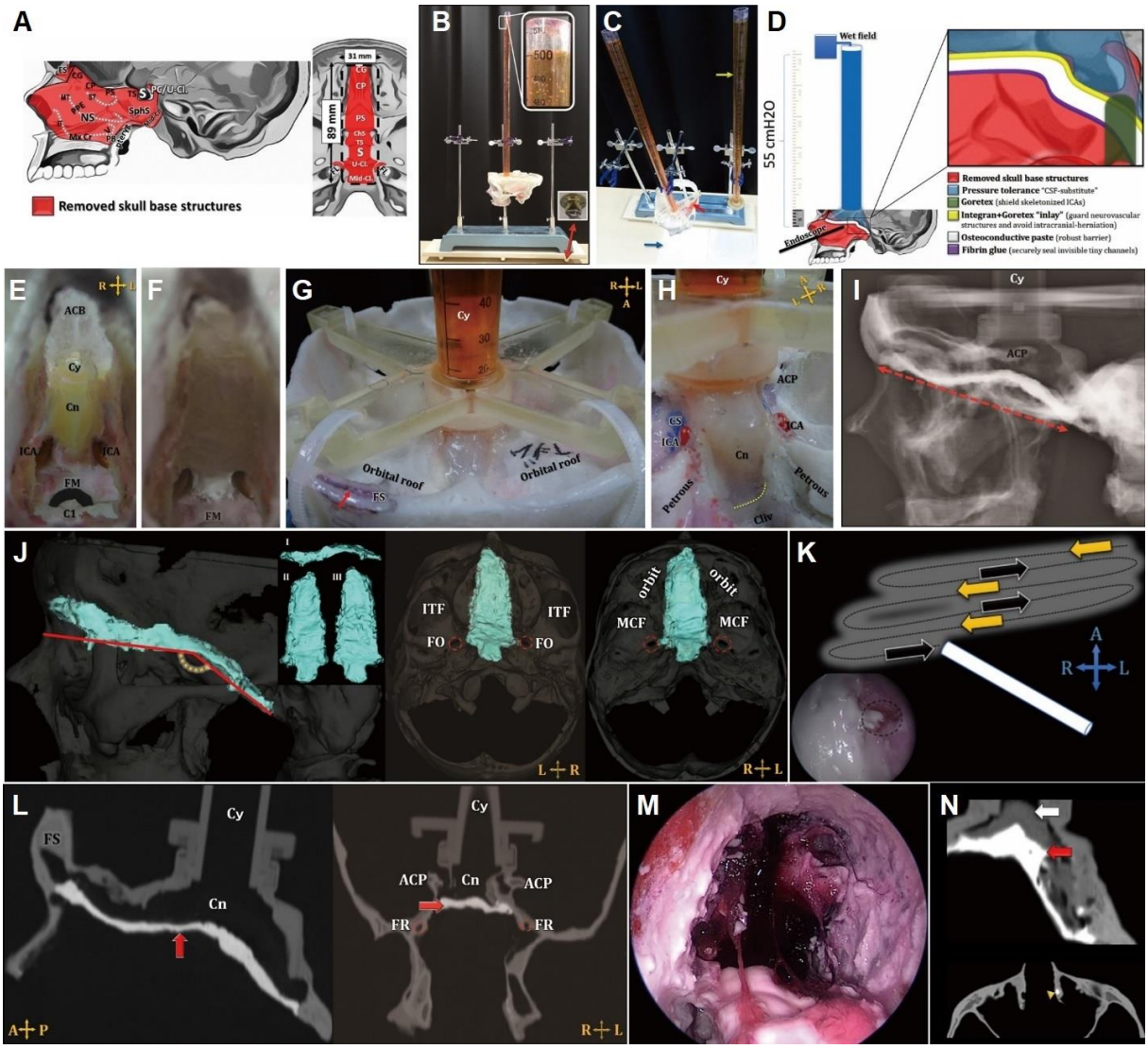

Figure 2

Figure 2: A: Extensive endoscopic drilling of the skull base *The 3D skull base model (sagittal "left" and axial "right" views) was used to create a 31x89 mm skull base defect (black-dotted line on axial view) extending from the crista galli (Draf III) to the mid-clivus via EEA. Extensive removal of all turbinates, nasal septum and the maxillary crest were completed for wide exposure, and careful partial skeletonization of the silicon representing the paraclival-ICAs were achieved.* ***FS:*** *frontal sinus (Draf III),* ***CG:*** *crista galli,* ***CP:*** *cribriform plate,* ***PS:*** *planum sphenoidale,* ***chS:*** *pre-chiasmatic sulcus,* ***TS:*** *tuberculum sellae,* ***S:*** *sella,* ***SphS:*** *sphenoid sinus,* ***PC/U-Cl:*** *posterior clinoid/ upper-clivus,* ***mid-cl:*** *mid-clivus,* ***FL:*** *foramen lacerum,* ***ST:*** *superior turbinate,* ***MT:*** *middle turbinate,* ***IT:*** *inferior turbinate,* ***PPE:*** *perpendicular plate of ethmoid,* ***NS:*** *nasal septum,* ***V:*** *vomer,* ***PB:*** *palatine bone,* ***Mx Cr:*** *maxillary crest,* ***pteryg:*** *pterygoids*. **B:** Skull base model showing that the WRO-barrier tolerated an exceedingly high (55 cmH_2O) pressure and remains in its position to maintain watertight seal even under stressful conditions. **D:** The constitution of WRO-barrier. **E,F:** Before and after creating the WRO-barrier to cover the large skull base defect (*pertinent anatomy from the endoscopic endonasal prospective*). **G, H:** Pertinent anatomy from the cranial prospective. **I:** Skull X-ray lateral view showing the extent and position of the WRO-barrier. **J:** 3D computed tomography (CT) of the skull base model showing the ideal configuration of the WRO-barrier and its relation with the critical neurovascular structures (internal carotid artery). **K:** Application of the osteoconductive paste via an injector in an S-shaped fashion (inset: endoscopic view of the osteoconductive). **L:** Evaluating the WRO-barrier with CT study. **M:** Endoscopic removal of the WRO-barrier when redo surgery is needed. **N:** Excluded technical errors: risk of mal-configuration (intracranial herniation) or migration via the injured naso-lacrimal duct was documented, treated and excluded from this study.

This experiment included 10 innovative criteria to overcome the daunting challenge of skull base reconstruction in selected patients with large skull base defect when vascularized flaps were not available.

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