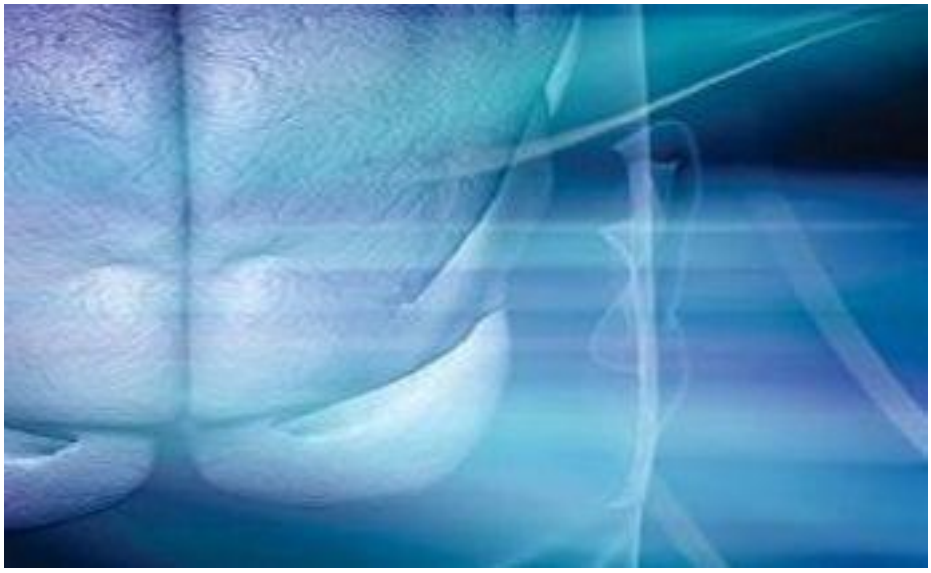

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Papers submitted should be original documentation, including photographs. The papers should be single column, double-spaced. The title should be in title case and bold, followed by Authors, degree, organization and city, state.

The papers should contain an abstract and be separated into sections with bold typing of the section title. The page set-up should be 0-6.5 inches. Paragraphs should be indented 0.5 inches. All tables should be submitted separate from the paper. If possible make the tables up to 3 inches wide so that they could fit into a column. This will allow quicker scanning and preparation.

References should be numbered, tab, name of authors. Title of paper. Journal. Year volume:pages.

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EDITOR'S PAGE

Physicians in training, learn and practice research "To formulate, ingrain, and measure, a method of thought, investigation, and evaluation necessary for physicians to have multi-lateral information exchange and communication with experts in areas of scientific and medical discovery, knowledge, and analysis, in order to continuously and efficiently improve human health and patient care." Understanding and performing quality research provides students and residents the tools to propel quality medical care into the community and into the future.

Welcome to the Journal of the American Organization of Neurological Surgeons and the American College of Osteopathic Surgeons Neurosurgical Section. This volume is composed of the Residents' annual papers that were submitted but not published elsewhere. It is therefore dedicated to the future Neurosurgeons and their education. All papers were reviewed by the peer review committee and selected for awards. The papers submitted are excellent, representing some of our talented colleagues. Issues will be published annually. I hope that this issue will spread the knowledge of our residents and our section. We will continue to solicit annual papers and all papers submitted at the annual meeting. This is your Journal paid for by your annual dues. This issue is available on our website AOANeurosurgery.org. This is your organization; please support it as you can.

Thank you,

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Editor

Annual Resident Achievement Awards 2008

Congratulations to you and your residents on the excellent papers submitted this year.
The winners for the outstanding works are:

1st Place
Jon Taveau, DO
Cerebral Perfusion Pressure Varies in Traumatic Brain Injury and Subarachnoid Hemorrhage Patients
Award: $1500

2nd Place
Omar Qahwash, DO
The Staged, Unassisted Embolization Of Unruptured, Intracranial, Wide-Necked Aneurysms
Award: $1000

3rd Place
Frank Hux, DO
Purely Endoscopic Single Surgeon Access to Cerebellopontine Angle Pathology
Award: $500

Please make sure that the residents present their papers Thursday, September 11, 2008 from 2:30-3:30.

Cerebral Perfusion Pressure Varies in Traumatic Brain Injury and Subarachnoid Hemorrhage Patients

Jon W. Taveau, D.O., Arrowhead Regional Medical Center, Department of Neurological Surgery, Colton, CA 92324

Abstract

Introduction: Treatment of cerebral perfusion pressure (CPP) is critically important in traumatic brain injury (TBI) and subarachnoid hemorrhage (SAH) patients; albeit there are well defined guidelines for management of CPP in TBI patients, this is not the case for SAH patients. This study examined the optimal CPP to maintain brain tissue oxygenation (PbtO2) in TBI and SAH patients, and whether it varies between the two groups. **Methods:** Patients admitted for TBI or spontaneous aneurysmal SAH and whose Glascow Coma Scale (GCS) score was less than or equal to 8 were studied. PbtO2 and intracerebral pressure (ICP) monitors were placed. Patients were treated to maintain a minimum CPP greater than 60 mmHg and ICP less than 25 mmHg. PbtO2 measurements were divided into the following groups according to CPP values: Group 1 (CPP less than 50 mmHg), Group 2 (CPP 51 to 60 mmHg) Group 3 (CPP 61 to 70 mmHg), Group 4 (CPP 71 to 80 mmHg), Group 5 (CPP 81 to 90 mmHg), Group 6 (CPP greater than 90 mmHg). **Results:** There were 23 SAH patients and 34 TBI patients having both ICP and PbtO2 monitors placed. Of the 57 patients, 20 SAH patients and 33 TBI patients met inclusion criteria; 12,720 data points were analyzed. In the SAH and TBI population respectively: Group 1 mean PbtO2 was 8 mmHg and 10 mmHg ($p < 0.05$), Group 2 mean PbtO2 was 13 mmHg and 18 mmHg ($p < 0.025$), Group 3 mean PbtO2 was 29 mmHg and 37 mmHg ($p < 0.02$), Group 4 mean PbtO2 was 32 mmHg and 39 ($p < 0.025$), Group 5 mean PbtO2 was 45 mmHg and 44 mmHg ($p < 0.10$), and Group 6 mean PbtO2 was 42 mmHg and 44 mmHg ($p < 0.10$). There was a trend of decreasing PbtO2 with lower CPP in both SAH and TBI patients. PbtO2 levels were observed to be lower in SAH patients than in TBI patients in Groups 1, 2, 3, and 4 ($p < 0.05$). Patients in Groups 5 and 6 had similar PbtO2 ($p < 0.10$). **Conclusions:** The results of this study suggest that patients with SAH require a higher CPP than TBI patients to maintain cerebral oxygenation. And therefore, this implies that SAH patients require earlier and more aggressive management of parameters affecting PbtO2.

Keywords: subarachnoid hemorrhage, spontaneous subarachnoid hemorrhage, aneurysmal subarachnoid hemorrhage, traumatic brain injury, severe head injury, brain oxygen monitoring, brain tissue oxygenation, intracranial pressure, cerebral perfusion pressure

Introduction

Traumatic brain injury (TBI) is a leading cause of death and disability in trauma patients in the United States. Death or a poor outcome in severe head injury patients results from many

variables; poor management of blood pressure, oxygenation, and/or intracranial pressure (ICP) are the most significant in severe TBI patients.

Management of TBI, according to the *Guidelines for the Management of Severe Traumatic Brain Injury, 3rd Edition*, emphasizes the reduction of elevated ICP, which is observed in more than half of the patients with TBI.[2, 3, 5, 6, 7, 8]

The reason for treating increased ICP in TBI patients is to maintain cerebral perfusion pressure (CPP) and prevent cerebral ischemia and infarction. Several studies demonstrated that infarction occurred despite normal ICP and CPP and that not all episodes of cerebral ischemia were associated with elevated ICP.[11-13] These data corroborated the necessity for monitoring additional variables of brain physiology, for example cerebral oxygenation. Current guidelines recommend monitoring cerebral oxygenation by either measuring jugular venous saturation (SjvO2) or brain tissue oxygenation (PbtO2). Continuous monitoring of cerebral oxygenation, in addition to measuring ICP, is supported by several recent studies. The investigators described the significant relationship between poor patient outcome and the number, duration, and intensity of cerebral hypoxic episodes.[18, 20, 22-25]

Guidelines for the management of CPP in SAH patients are not as well defined as those recommended for the management of CPP in TBI patients. However, PbtO2 monitoring is standard of care for patients suffering from SAH (having poor clinical grade, i.e. Hunt and Hess grade IV or V) because, similar to observations made in TBI patients, there is an association between poor outcome and the number, duration, and intensity of cerebral hypoxic episodes.[1, 4, 9, 10, 14-17, 19, 21, 26]

The objective of this analysis was to examine the optimal CPP to maintain PbtO2 in TBI and SAH patients, and to determine whether it varies between the two groups.

Methods

Patients admitted for TBI or spontaneous aneurysmal SAH to Arrowhead Regional Medical Center (ARMC), a Level II trauma center in Colton, California, between July 2005 and June 2008 were considered for inclusion in the study. Patients were evaluated retrospectively from a database with Institutional Review Board approval. The study period was 5 days starting from the day of admission.

Inclusion criteria for TBI patients consisted of an admission Glascow Coma Scale (GCS) score was less than or equal to 8. Inclusion criteria for SAH patients consisted of: 1) poor clinical grade following an SAH (Hunt and Hess Grade IV or V), 2) administration of nimodipine, 3) hemodynamically stable, and 4) no other active medical comorbidities. Exclusion criteria for TBI patients included: 1) patients suffering from penetrating injuries of the cranium, 2) those patients whose post-resuscitation systolic blood pressure was less than 90 mmHg and their SaO2 was less than 90% or their PaO2 was less than 60 mmHg, 3) those patients who failed to have both ICP and PbtO2 monitors placed at the time of their admission, 4) those patients who had bilateral fixed and dilated pupils and/or met criteria for brain death, or 5) those patients who expired prior to the end of the study period. Exclusion criteria for SAH

patients included: 1) patients whose admission systolic blood pressure was less than 90 mmHg and their SaO2 was less than 90% or their PaO2 was less than 60 mmHg, 2) those patients who failed to have both ICP and PbtO2 monitors placed at the time of their admission, 3) those patients who had bilateral fixed and dilated pupils and/or met criteria for brain death, or 4) those patients who expired prior to the end of the study period.

Patients had both PbtO2 and intracerebral pressure (ICP) monitors placed at the time of their admission. PbtO2 monitors were double-lumen bolt Licox® CMP Brain Tissue Oxygen Monitoring Systems (Integra NeuroSciences; Plainsboro, NJ). ICP monitors were Camino® ICP Monitoring Systems (Integra NeuroSciences; Plainsboro, NJ). PbtO2 monitoring probes were placed into the frontal white matter and ICP monitoring probes were placed, at Kocher's point (right or left side was considered appropriate), intraventricularly. Continuous monitoring proceeded for the entire study period.

Patients were admitted to intensive care unit (ICU), intubated and on mechanical ventilation, and sedated using propofol continuous intravenous infusion. Patients were treated to maintain a systolic blood pressure (SBP) greater than or equal to 90 mmHg, SaO2 greater than or equal to 98%, PaO2 greater than or equal to 115 mmHg, PaCO2 33 to 38 mmHg, ICP less than 25 mmHg, CPP greater than or equal to 60 mmHg, and PbtO2 greater than 28 mmHg. Cerebral perfusion was calculated from the measured parameters, ICP and mean arterial pressure (MAP), using the equation: CPP = MAP – ICP.

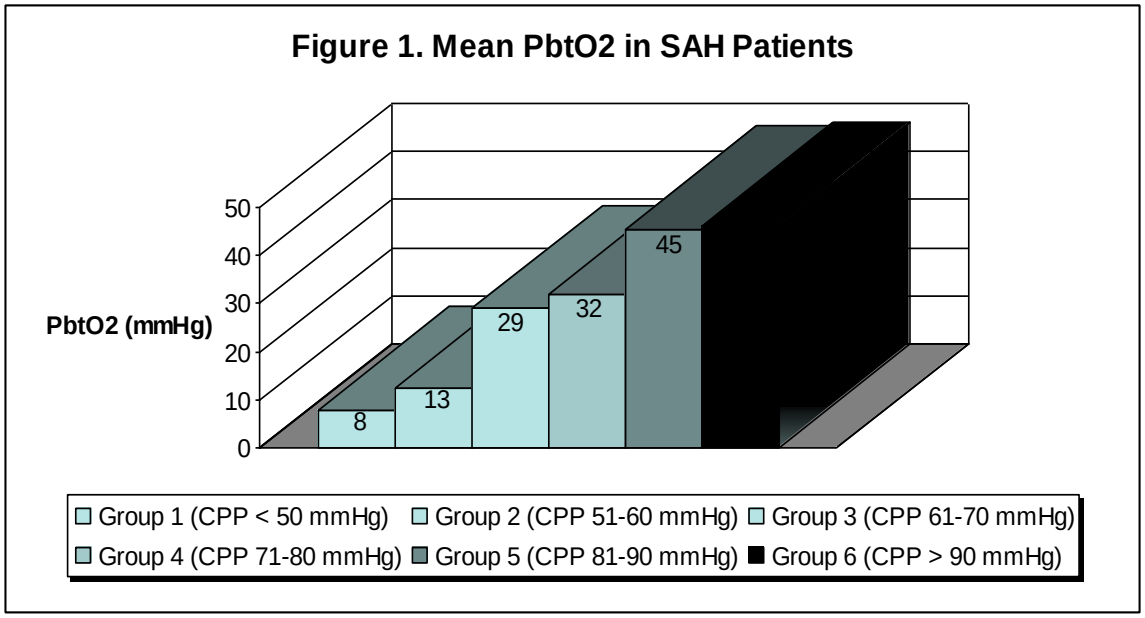
Blood pressure was maintained above 90 mmHg using vasopressors. Ventilator settings were adjusted to maintain parameters for SaO2, PaO2, and PaCO2. Mean arterial pressure (MAP) was increased, using vasopressors, or ICP was decreased, using mannitol or 23.4% hypertonic saline, to maintain CPP greater than 60 mmHg. PbtO2 parameters were maintained by increasing FiO2, MAP, CPP, PaCO2 (decrease ventilator rate), or optimizing hemodynamics (hemoglobin or 10 mg/dL and hematocrit of 30%).

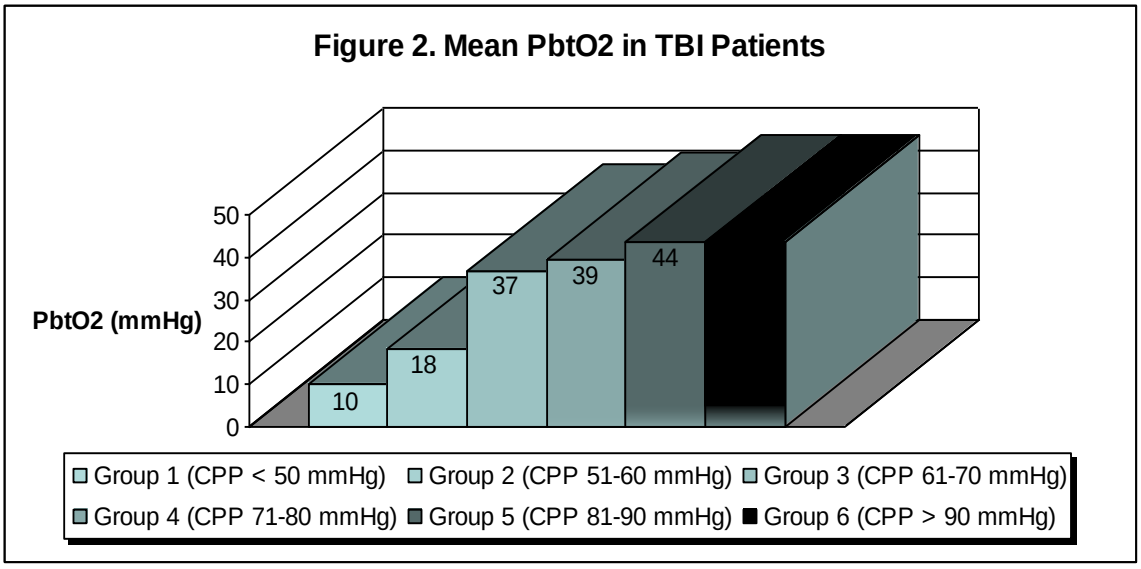
PbtO2 measurements were analyzed between SAH and TBI patients by stratifying PbtO2 according to CPP values: Group 1 (CPP less than 50 mmHg), Group 2 (CPP 51 to 60 mmHg) Group 3 (CPP 61 to 70 mmHg), Group 4 (CPP 71 to 80 mmHg), Group 5 (CPP 81 to 90 mmHg), Group 6 (CPP greater than 90 mmHg). Mean PbtO2 was calculated for each group and then compared between SAH patients and TBI patients. Mean values between SAH group and TBI group were compared using the Student t-test and statistical significance was defined as a probability value less than 0.05.

Results

There were 23 SAH patients and 34 TBI patients having both ICP and PbtO2 monitors placed at ARMC from July of 2005 to June 2008. Of the 57 patients, 20 SAH patients and 33 TBI patients met inclusion criteria; 12,720 data points were analyzed, which represents 5 total days of continuous monitoring.

In the SAH and TBI population respectively: Group 1 mean PbtO2 was 8 mmHg and 10





mmHg ($p < 0.05$), Group 2 mean PbtO2 was 13 mmHg and 18 mmHg ($p < 0.025$), Group 3 mean PbtO2 was 29 mmHg and 37 mmHg ($p < 0.02$), Group 4 mean PbtO2 was 32 mmHg and 39 ($p < 0.025$), Group 5 mean PbtO2 was 45 mmHg and 44 mmHg ($p < 0.10$), and Group 6 mean PbtO2 was 42 mmHg and 44 mmHg ($p < 0.10$).

There was a trend of decreasing PbtO2 with lower CPP in both SAH and TBI patients. PbtO2 levels were lower in SAH patients than in TBI patients when stratified into CPP less than 50 mmHg (Group 1), CPP 50 to 60 mmHg (Group 2), CPP 60 to 70 mmHg (Group 3), and CPP 70 to 80 mmHg (Group 4) ($p < 0.05$) (**Figure 1**). For patients with CPP greater than 80 mmHg (Groups 5 and 6) PbtO2 was similar ($p < 0.10$) (**Figure 2**).

Conclusions

In this retrospective study, the association between CPP and PbtO2 was analyzed in 53 patients with clinically poor-grade SAH or TBI. The goals of the study were to define an optimal CPP to maintain PbtO2 in the most favorable range in SAH and TBI patients, and to compare and contrast the two groups to better understand how PbtO2 is affected by CPP. Given the well documented detrimental effects and poor outcomes data associated with the intensity, duration, and number of episodes of cerebral hypoxic events, these data may provide a rationale that may drive clinical decision-making regarding more aggressive management of SAH and TBI patients.

PbtO2 monitoring in the neurosurgical ICU setting is a common tool which is now regarded as standard of care and is a critical adjunct to ICP monitoring, especially in appropriate SAH and TBI patients.

The results of this study suggest that patients with SAH require a higher CPP than TBI patients to maintain cerebral oxygenation. The optimal CPP appears to be Group 4 (CPP 71-80 mmHg) for SAH patients and Group 3 (CPP 61-70 mmHg) for TBI patients.

These results imply that SAH patients require earlier and more aggressive management of parameters affecting PbtO2.

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THE STAGED, UNASSISTED EMBOLIZATION OF UNRUPTURED, INTRACRANIAL, WIDE-NECKED ANEURYSMS

OMAR QAHWASH, PHILADELPHIA COLLEGE OF OSTEOPATHIC MEDICINE

Key Words: Intracranial aneurysm, endovascular, staged.

Abstract

The past decade has seen a significant paradigm shift in the treatment of intracranial aneurysms due to the development of detachable coils and the subsequent evolution of endovascular techniques. Advances in stent and balloon technology have improved efficacy in treating wide necked aneurysms with an acceptable but significant increase in procedural risk. Thromboembolic complications related to these techniques have been reduced with the use of antiplatelet agents but still remain an issue. This article demonstrates a staged coiling approach in which an initially placed framing coil is allowed to endothelialize before completing the definitive coil obliteration of the aneurysm. This potentially offers an alternate method of treatment for some wide necked lesions, which avoids procedural and long-term risks associated with balloon and stent assisted coiling.

Introduction

The introduction of Guglielmi Detachable Coils into clinical practice in 1991 and later its FDA approval in 1997 revolutionized the treatment of intracranial aneurysms. Initially used for surgically unfavorable lesions and patient condition, decreased procedural morbidity demonstrated by the ISAT in 2002 popularized this approach and demonstrated its utility as a primary therapeutic option for patients with ruptured intracranial aneurysms (14). When compared to open surgery, endovascular intervention demonstrated an absolute reduction in morbidity by 7% at one year. The use of endovascular coiling for the treatment of non-ruptured lesions has increased significantly as well. Data from the Nationwide Inpatient Sample has shown that although the number of surgeries for ruptured and non-ruptured intracranial aneurysms has remained relatively constant, the number of treated, unruptured aneurysms has doubled from 1993 to 2003 (18). Interestingly, there are no randomized trials comparing coil occlusion vs. observation. This would be a major endeavor considering the variability in the natural history of intracranial aneurysms, indications for intervention, and the undetermined long-term durability of endovascular intervention (22,27). Nevertheless, lower morbidity and mortality rates compared to surgical intervention (6,9), and the severe consequences of aneurysmal subarachnoid hemorrhage make a strong and persuasive case for the preventative endovascular intervention of unruptured intracranial aneurysms.

The goal of endovascular coiling is complete obliteration of the aneurysm. This is associated with the lowest incidence of reoccurrence and is achieved in 60-70% of cases (8). Lower rates of complete occlusion have been achieved in lesions with wider necks. This terminology is

typically reserved for lesions with a neck diameter > 4 mm or a dome to neck ratio < 2. In Gonzalez's series only 49% of small aneurysms with a wide neck were completely occluded compared to 75% of smaller neck lesions (6).

Furthermore, published data showing reoccurrence in completely occluded lesions has demonstrated an association with larger neck size or neck to dome ratio (6,11). In a retrospective study of patients treated before 1998, recanalization after endovascular occlusion occurred in 17% of aneurysms < 10 mm with small necks as opposed to 42% of patients with aneurysms <10 mm with a wide neck (7).

The difficulty experienced in effectively treating wide necked aneurysms by endovascular means has required the development of different techniques to aid in complete obliteration. Efforts have been focused on developing devices designed to hold the coils in place within the aneurysmal dome during deployment and thereafter. Balloon remodeling is a technique in which a non-detachable balloon is inflated within the parent vessel after the aneurysm is catheterized. This occludes the aneurysmal inlet and provides a buttress to deflect coils back into the aneurysm during deployment. Initially used for sidewall aneurysms, newer more compliant balloons have allowed for treatment of bifurcation lesions as well (12). Although improved occlusion rates have been documented with balloon remodeling, it is more difficult to objectively demonstrate a reduction in recanalization (17).

The utilization of stents in neuroendovascular intervention was initially limited to extacranial use due to lack of a stent design capable of navigating the tortuosity of the intracranial vascular tree (13).
Over the past decade various types of self-expanding stents have been developed for intracranial use (2). Further revisions have improved maneuverability and facilitated deployment allowing for their usage in various situations. These devices may be used to maintain the coil mass within the aneurysmal sac after balloon assisted packing, or placed across the aneurysmal neck before coil placement eliminating the use of a balloon in amenable lesions.

Although better occlusion rates of wide necked aneurysms are obtained with device assisted coiling techniques, it is associated with a higher rate of thromboembolic events during and immediately after the procedure (12,16,24). This may be related to an increase in procedural time or intraluminal, thrombogenic foreign material, and/or parent vessel intimal disruption related to device manipulation. For this reason, dual anti-platelet agents are recommended at least a week before stent placement and for four to six weeks thereafter. During this period endothelium re-growth occurs over injured intima and covers foreign material placed within the vessel lumen (21). The open cell design of an intracranial stent allows for complete endothelialization, which reduces platelet and fibrinogen adhesion and fixes the stent to the inner wall of the parent vessel. In treating a wide necked aneurysm, the operator may take advantage

of this healing process by initially deploying the stent across the neck of the lesion and then allowing time for endothelialization before actually coiling the lesion. This potentially decreases the likelihood of stent migration and thromboembolic events related to stent associated platelet adhesion.

A staged approach for treatment of wide necked aneurysms is described below in which an initially placed coil is used to frame the aneurysmal sac. This is then allowed to endothelialize before the remainder of coils are placed. Once endothelialized, the framing coil will essentially remodel the aneurysmal neck by partially occluding the inlet and potentially prevent protrusion of subsequently placed coils into the parent vessel during deployment. This technique potentially eliminates the use of coil assist devices thereby decreasing associated procedural complications.

Method

A retrospective review of a prospectively maintained computer database was performed. Two patients were selected to exemplify the staged coiling process. Patients selected for this type of intervention would potentially include symptomatic or incidental, non-ruptured aneurysms with a wide neck conventionally warranting the assistance of a balloon and/or stent for occlusion. Ideally, the diameter of the aneurysmal inlet selected should be equal to or slightly smaller than the diameter of the deployed framing coil.

Patients are placed on aspirin a week before the procedure. After intubation and initiation of general anesthesia, a 6-french access sheath is placed and systemic IV heparinization is utilized to keep the Activated Clotting Time above 250 seconds.

A guide catheter is attached to a continuous, heparinized saline flush with 1 mg of nitroglycerin and placed in the internal carotid artery. Microcatheter and guidewire are utilized to access the aneurysm. The initial coil placed should be large enough to abut the walls of the aneurysm and lie against the inlet but not protrude into the parent vessel. Framing of the dome would be ideal but not necessary in this situation. A three dimensional coil with accelerated thrombogenic potential should be considered for framing. The initial procedure is now terminated and the patient is discharged home on aspirin. Four to six weeks later, the lesion is revisited and the coiling process is completed. By this time the framing coil would have endothelialized and now acts as a retainer for subsequently placed coils preventing herniation into the parent vessel. The goal at this point is complete occlusion of the lesion. Once again the patient is discharged home on aspirin and follow up angiography is scheduled for three months.

Illustrative cases

Case #1

A 57 year old male underwent MR evaluation for head aches and was found to have a saccular aneurysm arising from the anterior communicating artery measuring AP 5.4 mm x CC 5.4 mm x T 4.8 mm.

Invasive cerebral angiography via the right carotid revealed an oblong lesion projecting ventral and anterior, measuring AP 7.5 mm x CC 4 mm. The inlet of the aneurysm measured 4 mm and encompassed the origins of both A2 segments, which filled from this side. The left carotid injection filled only the left A2 without cross filling (figure 1).

The patient underwent the initial framing procedure on 2/21/08 without incident. A 6 mm x 15 cm EV3 axiom 3D coil was placed (figure 2), and dome residual was documented.

He was maintained on aspirin and returned on 4/25/08 for the second stage of treatment. The microcatheter was positioned within the center of the initially placed coil and two more coils were deployed. Initially a 4 mm x 8 cm EV3 axiom helix coil was placed followed by a 2.5 mm x 4 cm ultra soft GDC. Post coiling angiography revealed complete occlusion of the lesion and patency of both A2 segments; the procedure was terminated without incident (figure 3). Later the same day the patient was discharged home without clinical evidence of complication.

The three-month follow-up invasive angiogram revealed complete obliteration of the aneurysm.

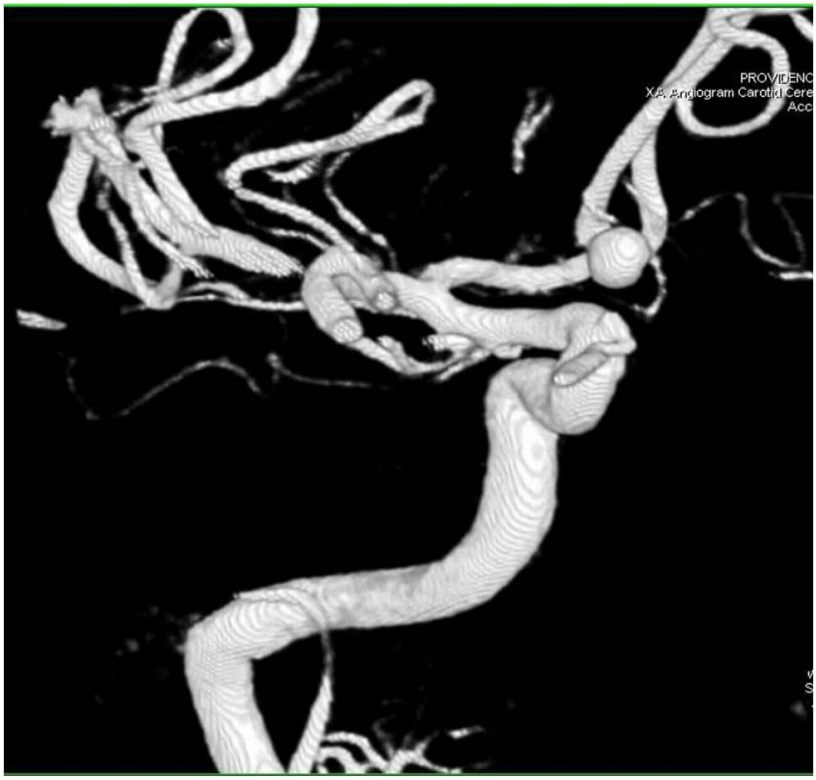

Figure 1. 3D reconstruction of initial diagnostic invasive angiography.

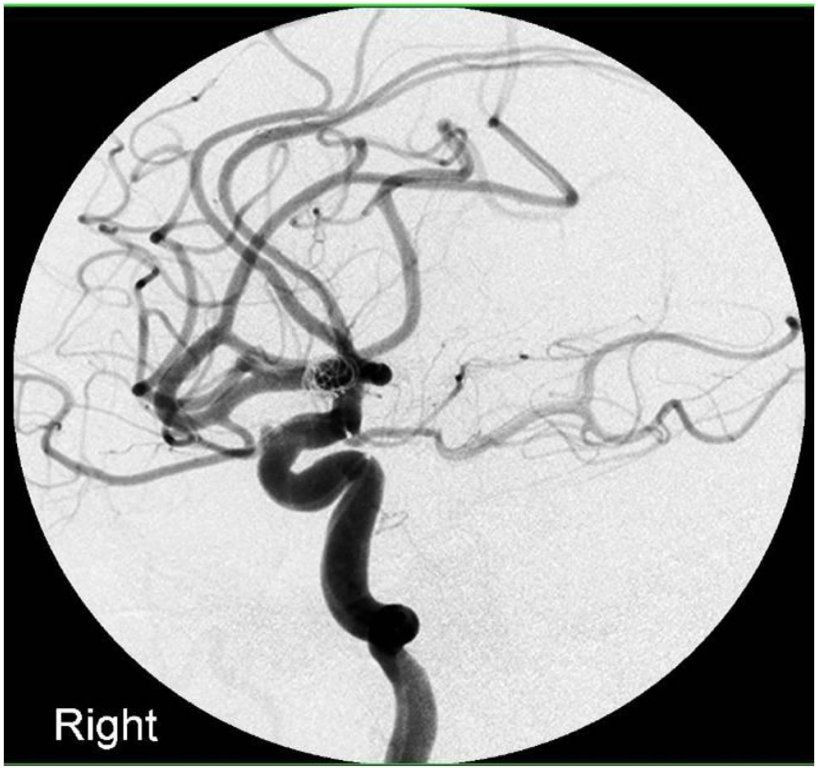

Figure 2. LAO angiography status post placement of initial framing coil.

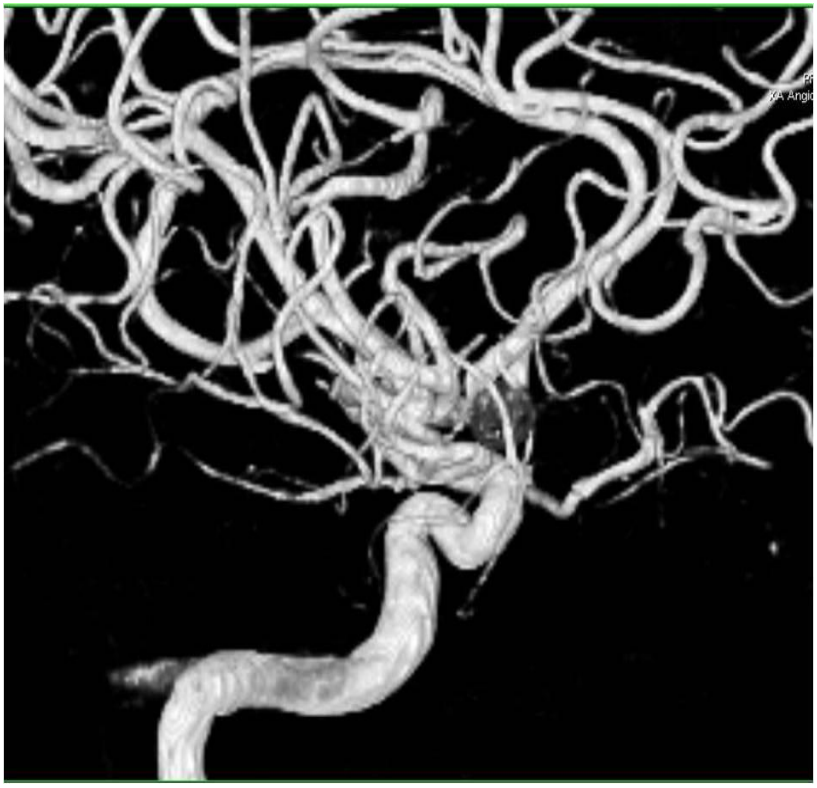

Figure 3. 3D recon s/p second stage of procedure demonstrating exclusion of flow.

Case #2

A 65-year-old male was found to have an incidental AP 3 mm x CC 3.5 mm ACOM aneurysm by non-invasive imaging. Diagnostic angiography revealed an anterior, ventral, and right projecting lesion and verifies the dimension reported above. The neck measures 3.5 mm and fills from a dominant left A1 artery. Both A2 segment filled from this side as well (figure 4).

On 2/28/08 the patient underwent the initial framing stage of the procedure– a 3 mm EV3 axiom 3D coil was placed and the patient was discharged home on aspirin (figure 5).

Six weeks later the patient was returned for the second stage where complete aneurysmal occlusion was achieved with a second 2 mm x 8 cm EV3 Axium helix coil. Post-coil angiography revealed total occlusion of the aneurysm and patency of both A2 branches (figure 6). The patient was once again discharged home on aspirin after no immediate clinical complications were detected. Follow-up angiography was scheduled for three months.

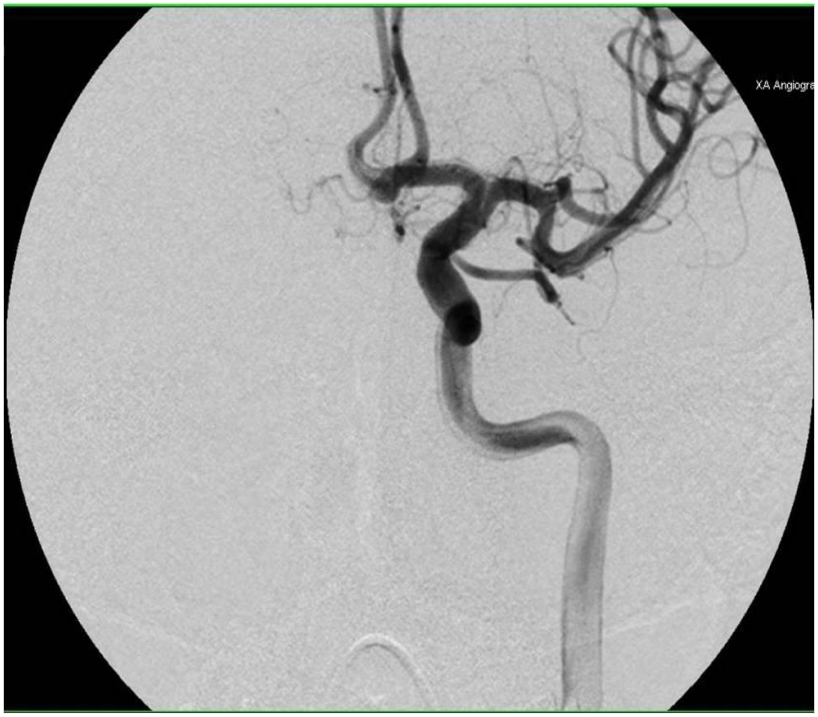

Figure 4. Dominant left A1, ACOM aneurysm and robust filling of both A2 segments.

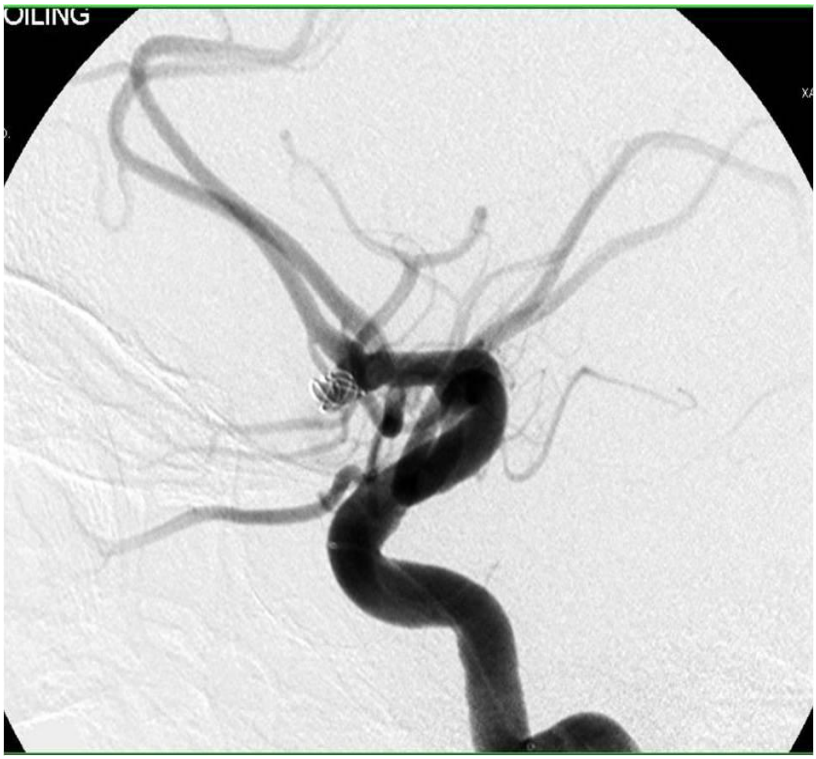

Figure 5. Angiography s/p placement of initial framing coil. Left int carotid

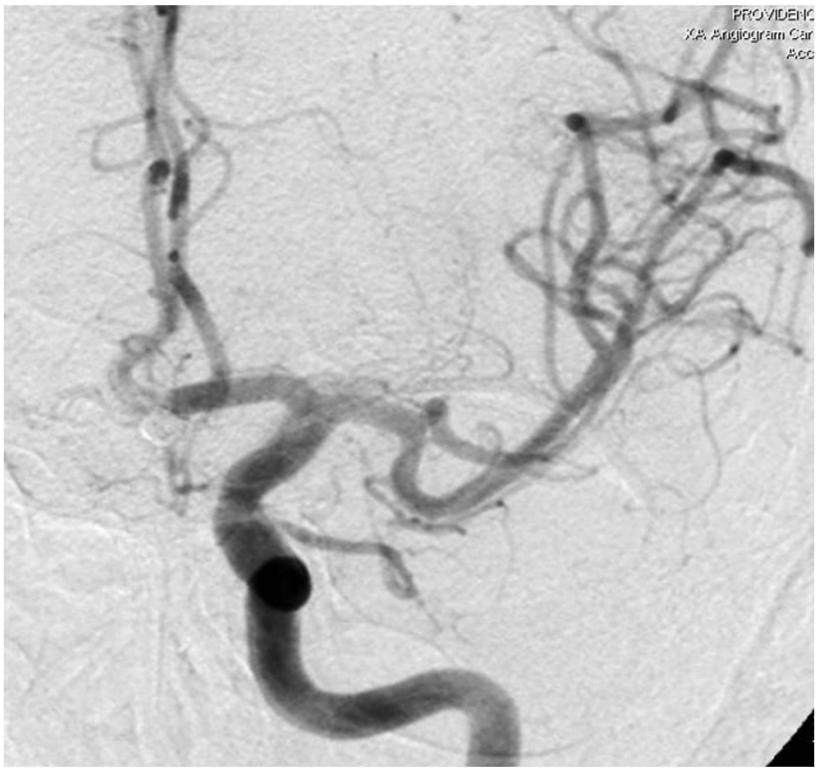
Figure 6. Angiography s/p delayed occlusion of ACOM aneurysm. Complete obliteration achieved.

Discussion

With the increasing availability of non-invasive imaging studies, the reported incidence of asymptomatic and/or unruptured aneurysms is rising. The decision to treat a patient with an unruptured intracranial aneurysm is dependant on its size, location and other clinical factors that have been prospectively associated with an increased risk of rupture (28). The annual risk of rupture is generally reported to be around 0.1-5% but varies significantly making patient specific estimated risk very difficult (22,26,27). Annual hemorrhage rates of both ruptured and unruptured aneurysms treated endovascularly are reportedly 0.15 – 0.3 % (14,21), but these numbers cannot be compared objectively. Ruptured and unruptured aneurysms have different natural histories and should not be considered together. More is known about the efficacy of endovascular intervention to prevent re-hemorrhage of a ruptured aneurysm, but the long term reduction of risk in unruptured lesions is still unknown. It is likely that coiling confers some amount of long-term protection in unruptured lesions. Roy coiled 125 unruptured aneurysms between 1992 and 1999 and no aneurysmal rupture was documented during a mean follow-up of 32 months (23). The amount of protection conferred to a patient by endovascular coiling undoubtedly depends on the efficacy of flow obliteration within the lesion (25). Another retrospective study evaluated outcome in 173 patients with unruptured intracranial aneurysms that had been coiled. Two non-procedural related ruptures occurred both in partially occluded giant aneurysms over a mean follow up period of 3.7 years (25). This study and others evaluating coiled ruptured aneurysms have clearly associated a subsequent risk of subarachnoid hemorrhage with incomplete coiling and aneurysmal recannalization (14,15,23). In the two patients presented above a neck remnant was achieved in one and complete occlusion in the other lesion. Unlike smaller lesions with a narrow neck, recannalization is more likely to occur in wide necked aneurysms with subtotal and even complete occlusion (6,7,8,11,23). Thus, in treating wide necked lesions, it would be reasonable to evaluate all objective means of determining risk of recannalization. The volume of coil packed into the lesion may be used to aid in the determination of adequate coiling. This has been found to be inversely related to recannalization in smaller lesions with ideal dome to neck ratios (10). An aneurysm can accept roughly 30% of its geometrically calculated volume in coil volume (11). This is referred to as the ideal coil packing density. Kai's retrospective analysis of 62 treated lesions revealed major recurrences in all cases where the actual length of coil used was less than 50% of the ideal length required to constitute the predetermined ideal coil packing density (10). This is referred to as the coil-packing ratio. In lesions at higher risk for recanalization, ratios higher than 50% are probably required to avoid reoccurrence. This is conceivably more feasible with balloon assistance and should be measured and evaluated in relation to recanalization rates in future cases performed in a staged, unassisted manner.

Another issue that needs to be considered is the flow altering capability of stents and its relation to aneurysm recanalization. Flow redirection is thought to facilitate endothelialization and vessel

reconstruction. Anecdotal evidence has been presented showing efficacy in treating fusiform lesions, inducing delayed complete occlusion of saccular aneurysmal neck remnants, and decreasing recurrence rates when compared to balloon assistance alone (1,5,6,15). This may be a disadvantage of using only coils to obliterate wide necked lesions making stents a more suitable option for certain cases. Undoubtedly, larger aneurysms or ones with a wider neck require device assistance. Lesions appropriate for unassisted, staged coiling need to be identified objectively. Nevertheless, staged coiling does not exclude the option of later placing a stent if needed.

When treating unruptured intracranial aneurysms, procedural risks should be considered along with the proposed long-term decrease in risk of rupture. Multiple factors contribute to a higher overall rate of immediate and delayed ischemic and hemorrhagic complications when comparing stent and balloon assisted procedures to unassisted coiling of aneurysms (24). This includes the amount of thrombogenic hardware exposed to blood flow, intra-procedural hemostasis, the length of the procedure, amount of contrast utilized, and the peri-procedural prophylactic medical regimen utilized to prevent platelet aggregation and blood clot formation (20). Thromboembolic events constitute a majority of the clinically significant complications that occur during stent assisted coiling and Neuroendovascular procedures in general (4). Although the number of symptomatic cases is within acceptable ranges, anticoagulation and anti-thrombotic measures are fundamental. There is no consensus on the appropriate methods used to decrease thromboembolic occurrences, but the regimen is typically intensified when stenting is utilized. Staged unassisted coiling would potentially decrease the risk of thromboembolic phenomena by limiting foreign thrombogenic material, decreasing procedural time, and the contrast load administered in one sitting. Considering the undefined long-term benefit of coiling unruptured aneurysms, reduced procedural morbidity is paramount.

Conclusion

In summary, the staged unassisted coiling of unruptured wide necked aneurysms may offer a simple and effective alternative to stent and balloon assistance with reduced procedural risk. The long-term stability of lesions treated in this fashion must be compared to the conventional methods of coil assistance to assure comparable and acceptable recurrence rates. Packing ratios and anatomical factors such as neck and aneurysmal size should be studied to identify lesions more suitable for this technique.

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Purely Endoscopic Single Surgeon Access to Cerebellopontine Angle Pathology

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OBJECTIVE: Access to cerebellopontine angle (CPA) pathology has typically been limited to microscope-assisted techniques. More recently, endoscopic-assisted procedures have been described following microscope-assisted approaches. All of these procedures are limited by the visualization of the basal arachnoid cisterns without mobilization and retraction of the cerebellum. The use of a purely endoscopic technique improves the visual field of the entire CPA without cerebellum retraction. The aim of this study is to describe and evaluate our current purely endoscopic technique for access to CPA pathology.

METHODS: A retrospective review of 47 patients over 28 months who underwent purely endoscopic procedures of the CPA. The pathology consisted of 20 CN (cranial nerve) V microvascular decompressions (MVDs), 7 CN VII MVDs, 10 CPA tumor resections, and 10 vestibular neurectomies. After a minimal retrosigmoid craniotomy (<2cm), a purely endoscopic approach was utilized for the entire procedure.

RESULTS: All 47 patients were treated effectively without conversion to microscope. 44/47 (94%) of the patients had complete resolution of symptoms. There was one delayed superficial wound infection 45 days post-op. All patients were discharged without complication with 2.36 days average length of stay except patients with pathology involving the CN VII-VIII complex were discharged at 3.62 days secondary to vertigo. There were no occurrences of post operative edema. Furthermore, there was no incidence of permanent sensorineural hearing loss, facial paralysis, or cerebrospinal fluid (CSF) leaks observed.

CONCLUSION: Endoscopic procedures of the CPA provide increased visualization of the CPA while ensuring surgical success with less postoperative morbidity. Without significant cerebellum retraction, there is a decreased incidence of post operative edema leading to a decreased length of stay. This technique should be considered for accessing all types of CPA pathology.

KEY WORDS: Cerebellopontine Angle, Endoscope, Microvascular Decompression, Vestibular Neurectomy, Acoustic Neuroma, Vestibular Schwannoma, Trigeminal Neuralgia, Meniere's

INTRODUCTION

Access to cerebellopontine angle (CPA) pathology has historically relied on complex skull base approaches. Furthermore, surgeons have debated which techniques provide the best access with the least amount of related risk. With the deleterious effects of excessive cerebellar retraction, other invasive, if not destructive, techniques such as petrous bone resection, division of the sigmoid sinus, sacrifice of hearing, and resection of brain tissue have been used to facilitate exposure of the CPA (1). However, these techniques increase the risk of cerebrospinal fluid (CSF) leaks, infection, brain contusion or infarction, and cranial nerve (CN) dysfunction (2,3). To maximize operative management of CPA lesions, it is important to utilize safe techniques to minimize brain injury that may result from the need for sufficient exposure.

With the introduction of modern endoscopic technology and procedures, the application of the endoscope now includes skull base surgery. However, the utilization of endoscopy of the skull base has been limited to those procedures accessible through the endonasal approach. Access to CPA pathology has typically been limited to microscope-assisted techniques. More recently, endoscopic-assisted procedures have been presented which can be performed following a microscope-assisted approach (4). However, all of these procedures require retraction and/or resection of the cerebellum in order to adequately access and visualize the basal cisterns and brainstem. Additional limitations are attributable directly to the inability of stabilizing the endoscope to allow bimanual surgery, overheating from the light source and lack of instrumentation. We describe our experience utilizing the endoscope as the sole source of visualization. We have overcome many of these obstacles, and introduce our operative set-up and equipment recommendations. We describe our indications and contraindications for the procedure's use. We describe our results in our first 47 patients and describe the nuances of the procedure for a spectrum of CPA pathology including microvascular decompression (MVD), cranial neurectomy, and neoplasm resection.

INDICATIONS

We have utilized CPA endoscopic techniques for MVDs of CN V, VII, and VIII; however, there is no contraindication for its use in MVDs or cranial neurectomies of any cranial nerve in the CPA. The technique has been utilized for the resection of extraaxial lesions of the CPA including petrous meningiomas, epidermoid tumors, and cranial nerve neoplasms. Due to the absence of retraction and the

enhanced image quality and illumination, the rate of cranial neuropathies, especially hearing loss, has been effectively reduced, especially in vestibular neuroma resection.

Despite its inherent advantages we limit the use of CPA endoscopy based on the preoperative radiographic anatomy (Figure 1). Absence of the interpeduncular and/or prepontine cisterns due to mass effect or elevated intracranial pressure is considered a contraindication to endoscopic CPA surgery. In these cases, where accessing the cisterna magna is necessary to create a relaxed environment, it is our recommendation that an open procedure should be considered as cannulating the cisterna magna blindly is unnecessarily risky with the consequences of an unintended neurovascular event being potentially devastating and possibly fatal.

PATIENTS AND METHODS

During a 28 month period, 47 patients underwent purely endoscopic procedures of the CPA. The mean age at surgery was 52.7 years (range, 24-73 yr) with 29 female and 18 male patients. After a minimal retrosigmoid craniotomy (<2cm), a purely endoscopic approach was utilized for the entire procedure. A retrospective review of medical records, preoperative imaging, operative notes, and outcome in these patients was undertaken. The pathology consisted of 20 trigeminal neuralgias, 7 hemifacial spasms, 10 CPA tumors, and 10 Meniere's disease. The post-operative follow-up period ranged from 3-28 months, with a mean time of 12 months.

INSTRUMENTATION

Recent advances in supportive equipment have enhanced the safety and convenience of endoscopic procedures and broadened the indications for their use. For endoscopic approaches to the posterolateral skull base, we recommend using a 0° 4.0mm straight rigid endoscope (Karl Storz, Tuttlingen, Germany) for the majority of the procedure. At the end of the procedure, a 30° 4.0mm straight rigid endoscope (Karl Storz, Tuttlingen, Germany) is utilized to inspect ventral CN root entry zones and the internal auditory canal. This extended viewing angle of the 30° endoscope is used to inspect hidden but important anatomic structures without applying retraction. The endoscope is connected to a video camera

which transmits its image to the video monitor located directly across from the surgeon. A xenon light source provides enhanced illumination of the surgical field.

To perform delicate bimanual procedures in the posterolateral skull base, we utilize a multi-joint, poly-axial, pneumatic holding arm (Mitaka Kohki Co., Tokyo) with an accurate locking and a safe releasing system controlled by a single button that can be controlled by only one hand. Even a tiny movement of the endoscope in the narrow corridor could cause irreversible trauma to the surrounding neurovascular structures. Because of the tight corridors of the posterolateral skull base, specialized rotational pistol grip and straight shaft dissectors are utilized. And finally, because of the inconvenience of removing and cleaning an endoscope during surgery, we utilize a disposable Endoscrub irrigation sheath (Medtronic Xomed) providing effective flushing of surgical debris from the distal viewing end of the endoscope; furthermore, it provides a cooling effect to the xenon light source to protect the neurovascular structures from thermal damage.

OPERATIVE SETUP

After Mayfield pin fixation, the head is turned opposite the side of surgery and elevated to 30° above the horizontal so that gravity aids in the exposure (5). The pneumatic arm is strategically positioned directly opposite the surgeon to provide ease of access from both an inferior and superior trajectory with the monitor in a direct line of sight to the surgeon (Figure 2). We routinely administer 1-2gm/kg of mannitol followed by 20mg of furosemide at the initiation of the anesthetic, unless contraindicated, and reduce the PaCO2 to 28mmHg. Monitoring electrodes are placed depending on the planned neural elements to be monitored. We typically use facial nerve and BAER monitoring, and in some instances, we may also utilize endotracheal tube monitoring electrodes, SSEP, CN XI and XII electrodes as well. Prior to skin incision, the transverse-sigmoid (TS) sinus junction is localized by an intersecting point along the superior nuchal line and the mastoid groove (6).

SURGICAL APPROACH

A 2.5-3.0 cm oblique incision is then made at the locale of the TS junction. After a 14mm craniotomy is performed identifying the edge of the TS junction (Figure 3), a curvilinear dural incision is

made paralleling the TS junction. A 4mm, 0°, rigid endoscope is cannulated along the posterior petrous bone either along the tentorium (if accessing the interpeduncular cistern) or along the ventral aspect of the cerebellum (if accessing the prepontine cistern). The petrosal veins are identified and either mobilized or cauterized and transected to access the CSF cisterns. The CN VII-VIII Complex will be encountered prior to the prepontine cistern arachnoid. Once CSF is released, the cerebellum will adequately relax to allow visualization of the ventro-lateral brainstem and associated CN root entry zones (Figure 4). The 0° endoscope is primarily used during active dissection within the CPA in order to minimize inadvertent injury to neurovascular structures. The 30° endoscope is utilized for ventral inspections of the CN root entry zones, and internal auditory canal (IAC).

Microvascular Decompressions

A thorough 360° inspection of the root entry zone should be performed prior to the formal MVD in order to account for all potential vascular entities. Prior to placement of the pledget, the offending vessels should be dissected from the surrounding arachnoid bands to allow adequate mobility which will minimize any inadvertent vascular injury (Figure 5). Should bleeding be encountered during mobilization of the vessel, it is very important that the endoscope not be withdrawn as this will preclude visualization and make recannulation of the CPA more difficult. Copious irrigation, identification of the source and control with either bipolar cautery or gentle pressure must occur prior to the continuation of the procedure. In the case of CN VII MVD, a pre and post stimulation threshold of CN VII is recommended in order to evaluate the integrity of the nerve prior to closure. An electrical recording of CN VII at a direct stimulation threshold of 0.05 mA is generally consistent with a favorable post operative facial nerve response.

Vestibular Neurectomy

The image quality achieved with the modern endoscopes when partnered with high definition (HD) monitors and HD capable cameras equals the detail visualized by the operating microscope. As such, the delineation of the nerve allows identification of the vestibular and cochlear portions of the CN (Figure 6). The facial and cochlear nerve, nervus intermedius, and the anterior inferior cerebellar artery (AICA) should be identified prior to the neurectomy to avoid injury. During the neurectomy, continuous BAER monitoring is performed to assess the integrity of the cochlear nerve.

Tumor Resection

A 4.0mm endoscope coupled with a polyaxial pneumatic holding arm allows the surgeon accessibility of the entire CPA from the incisura through the foramen magnum. The endoscope allows for enhanced visualization of the neural structures splayed along the tumor capsule. This allows for early identification of the cochlear nerve in hearing preservation cases, and the CN VII which is typically positioned along the ventral aspect of the tumor capsule prior to resection. In microscope procedures, these neurovascular structures are not visualized until late in the dissection. The endoscopic ability to visualize structures ventral to the tumor prior to removal allows identification of CN VII earlier, minimizing risk to the facial nerve. Finally, the use of a 30°endoscope enhances visualization out along the IAC which minimizes the amount bone removal at the porous acousticus as compared to the typical retrosigmoid microsurgical approach (Figure 7). As there is no need for retractors in endoscopic CPA surgery, tension applied to the neural structures, especially the cerebellum is minimized as well.

RESULTS

Microvascular Compression Syndromes

The trigeminal nerve was easily identified after mobilization of the petrosal veins in the trigeminal neuralgia patients. Once the offending vessels were visualized, mobilization and placement of the pledget was achieved with a purely endoscopic technique. 18/20 (90%) trigeminal neuralgia patients obtained complete relief with 2/20 (10%) achieving a good outcome requiring a smaller dose of medication. There were no patients that did not obtain improvement of their preoperative pain scores.

6/7 (86%) hemifacial spasm patients had complete remission with 1 patient having recurrence of facial spasms 9 months after initial success and after undergoing chiropractor treatment of neck pain. Subsequently, this patient underwent re-exploration and a second vascular loop of PICA was found. This patient is now symptom free.

For the MVD patients, operative time (OT) was 70 minutes with a length of stay (LOS) of 1.5 day. There was no incidence of CSF leakage, hearing loss, or facial weakness.

Meniere's Disease

The CN VII-VIII complex was easily visualized allowing identification of the cleavage plane between the cochlear and vestibular nerve. After clear identification of AICA, facial nerve, cochlear nerve, nervus intermedius, and vestibular nerve, a complete neurectomy was achieved in all ten patients with Meniere's disease with a purely endoscopic technique. All (100%) patients had resolution of their preoperative vertigo. OT was 70 minutes with average LOS of 2.5 days. There was no incidence of CSF leakage, hearing loss, or facial weakness.

CPA Tumors

10/10 (100%) tumor resections were successful including 2 meningiomas, 2 epidermoids, 5 acoustic neuromas, and 1 CN V schwannoma with a purely endoscopic technique. OT for cranial nerve neoplasms is typically 90-110 minutes. The LOS was decreased to 2 days for pathology not involving the CN VII-VIII Complex, and 3.5 days for pathology involving the CN VII-VIII Complex. This discrepancy was attributed to the presence or absence of vertigo postoperatively. Complete resection was achieved purely endoscopically. Complications were minimal with one superficial wound infection and one CSF leak, both of which were treated without surgery. There was 1 transient high-frequency sensori-neural hearing loss which improved 6 months postoperatively. There was no incidence of facial weakness.

DISCUSSION

Max Nitze is credited for designing the first surgical endoscope in 1879. His crude invention of multiple lenses illuminated by a light at the tip was sustained by the ongoing passion of improved visualization and magnification in surgery (7). The use of endoscopy in the CPA was first described by Doyen in 1917 for a trigeminal neurectomy (8). However, the technology of the lenses and light source significantly limited the endoscopes utility. With the introduction of the operating microscope in the 1960's, there was little interest in pursuing this crude endoscopic technology as the microscope provided superior lighting and magnification as compared to the endoscopes of the day. The microscope provided superior illumination and magnification especially to the deep, dark recesses of the skull base.

Advances in the field of microsurgical techniques allowed the surgeon to compensate for the shortcomings of the microscope by creating linear corridors of site due to the microscope's inability to see

around corners. These shortcomings were overcome at the expense of retraction. Mobilizing the cerebellum and creating larger cranial openings allowed a corridor for the light source to illuminate the field in a linear fashion from a light source located outside the surgical field to the final target.

Despite the technical advancements of illumination and image resolution, endoscopy was limited to intraventricular and endonasal procedures. It was not until the 1990's that the endoscope was introduced as an adjunct to enhance visualization of the CPA. Since that first report, a limited but growing number of authors have reported their results using the endoscope adjunctively with the microscope for CPA pathology (9-17). The microscope's ability to hold a constant position without the aid of an assistant allowing the surgeon bimanual dexterity has limited the utilization of the endoscope in microsurgery to date. Shahanian, et al were the first to describe a fully endoscopic approach to the CPA for microvascular decompressions (MVD) in trigeminal neuralgia and hemifacial spasm (18,19). Since 2005 we have expanded the utility of the endoscope in the CPA not only for MVDs but for neurectomies, fenestration of cysts and resection of extraaxial neoplasms without the aid of an operating microscope.

Unlike endonasal endoscopy where the surgical field can accommodate two surgeons and four hands working in coordination on either side of the patient's head, the limited space afforded to the lateral suboccipital region precludes this luxury. Additionally, the precision of the CPA necessitates the surgeon to utilize both hands simultaneously which precludes the surgeon from holding the endoscope during the dissection. This last point is one of the major reasons to date that the endoscope has been relegated to visual adjunct during CPA surgery. That being said, the majority of endoscope holders are clumsy, multi-jointed apparatus that are not easily adjusted. These holders are adequate for most of the endonasal and intraventricular approaches as the depth of field is usually stable once the surgical site is reached. This, however, is not the case in CPA surgery where the surgical field and field depth are ever-changing and require the surgeon to constantly change trajectory, especially during tumor resections. We have overcome this hurdle with the use of a multi-jointed pneumatic arm, which like most of the operating microscopes is unlocked and fully mobile throughout all planes of motion and then relocked into a stable configuration with the depression and release of a single button (Figure 8). This allows the surgeon to position and reposition the entire apparatus with one hand.

Overheating is another major concern related to endoscopy. The introduction of a xenon light source has substantially improved illumination, especially in areas like the CPA. Unfortunately, the enhanced illumination is at the expense of the amount of heat generated. This is especially relevant due to the proximity of the endoscope to neural structures of the CPA. This nuance is diminished in microsurgery due to the distance of the microscope form these structures. We have overcome this obstacle by incorporating a thin sleeve over the endoscope which allows for intermittent irrigation of the system, thereby cooling the tip and minimizing heat transfer.

Another dilemma facing endoscopy of the CPA is the loss of depth perception when visualizing the procedure on a 2-D monitor. This factor is especially enhanced in the CPA as compared to other skull base sites as every instrument introduced or removed free-handed can potentially come into contact with a major neurological structure including the cerebellum, brainstem, veins and arteries of the posterior circulation and cranial nerves. Unlike microsurgery where the surgical instruments work in series along the optical trajectory of the microscope lens, the surgeon must now learn to work in parallel to the endoscope. Unfortunately this precludes the use of bayoneted instruments. Additionally, unlike the intraventricular and endonasal endoscopic procedures which allow the surgeon some degree of rotational movement about the point of entry, the point of entry and the trajectory of the instrument is limited in the CPA by the cerebellum, petrous bone and incisura. These limitations necessitated the introduction of an entirely different microsurgical instrument set based on the principle of rotational pistol-grip instruments, as well as straight-shafted dissectors which in some cases incorporate real time neurophysiologic monitoring capabilities (Figure 9).

The benefit of performing CPA surgery completely endoscopically is the decreased tissue manipulation and retraction while enhancing the visualization of the CPA structures. Endoscopic dissection obviates the need for the use of a retractor, thereby limiting the need to sacrifice venous structures which is typically necessary when retracting the cerebellar hemisphere. The wider field of view provided by the endoscope allows essentially unrestrained visualization of the CPA from cranial nerve (CN) IV at the level of the incisura to the superior aspect of the cervical cord using the same 14mm access. With less soft tissue dissection and retraction, this provides the patient with decreased operative time, decreased pain, decreased cerebellar symptoms, decreased cranial neuropathies, and decreased hospital days and recovery time.

While otolaryngology has been at the forefront for the development of endoscopic techniques, neurosurgery has been less than enthusiastic despite the vast range of possible applications in this area. Preserving normal anatomical integrity, while accomplishing other goals of more traditional open approaches in Skull Base Surgery, is revolutionizing the field. The disadvantages of the procedure remain mostly in the limited instrumentation. Tumor removing instruments (i.e. CUSA) are limited due to the presence of the endoscope as they are not intended as parallel instruments. The same difficulty is encountered with many of the drill systems. However, as the field of endoscopy expands, there is little doubt that these challenges will be addressed.

CONCLUSION

The recent advancements made in the field of micro-endoscopy have increased its utility in the realm of skull base surgery. Improved image quality, enhanced illumination and the introduction of new instrumentation has allowed its utility in the realm of CPA surgery. Despite a steep learning curve, our experience suggests endoscopy for CPA surgery provides improved surgical visualization improving neurovascular preservation at the time of surgery. The use of a purely endoscopic technique improves the visual field of the entire CPA from incisura to foramen magnum utilizing a cranial opening of less than 2cm without the use of retractors. Without significant retraction, there is a decreased incidence of bleeding and postoperative edema. The clinical outcomes in our patient population has resulted in decreased postoperative deficits, decreased operative time, and decreased length of stay while maintaining excellent outcomes when compared to traditional microscope procedures. This technique should be considered for all types of CPA pathologies.

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Figure 1: Indications and contraindications for endoscopic CPA surgery.

INDICATIONS	CONTRAINDICATIONS
MVDs of CN V, VII, and VIII	Elevated ICP
Extraaxial Lesions of CPA	Large Solid CPA Mass Obliterating Cisterns
ADVANTAGES	**DISADVANTAGES**
Improved Visualization	Loss of Depth Perception
Less Invasive/Minimal Retraction	Instrumentation
Decreased OR/LOS	Steep Learning Curve

Figure 2: Pneumatic arm holding endoscope with surgeon's view of monitor.

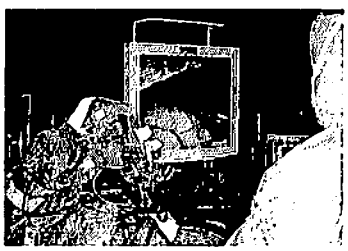

Figure 3: A 14mm craniectomy at the transverse-sigmoid sinus junction.

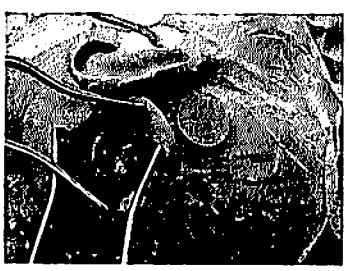

Figure 4: Endoscopic visualization of the CN root entry zones.

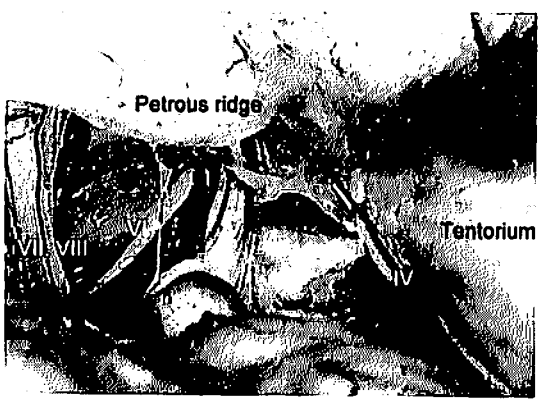

Figure 5: Endoscopic treatment of neurovascular conflict of trigeminal neuralgia.

Figure 6: Vestibular neurectomy with visualization of VII-VIII complex.

Figure 7: A, Acoustic tumor resection with minimal drilling at the porous acousticus. B, Post-op imaging.

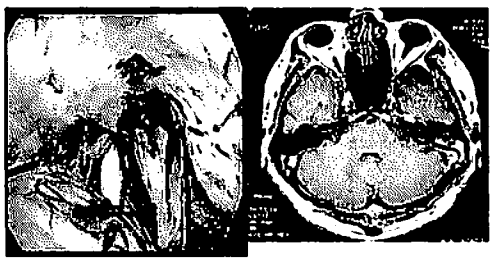

Figure 8: Poly-axial multi-jointed pneumatic endoscope holding arm.

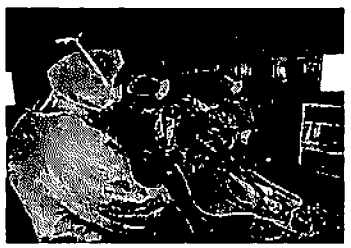

Figure 9: A, Straight shaft dissectors attached to intraoperative monitors. B, Rotational pistol-grip opposable scissors and pituitary pick-ups. C, Rotational pistol-grip opposable bipolar

Malignant Peripheral Nerve Sheath Tumor of the Cerebellopontine Angle
A Case Report and Review of Literature

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ABSTRACT

Objective: Malignant peripheral nerve sheath tumors are rare. The overall incidence range from 2-70% in patients with a history of Neurofibromatosis Type I and .001% in sporadic or de novo cases. They are highly malignant tumors with an overall mortality rate reported from 10 -65 %. Fewer than five cerebellopontine angle or cranial nerves malignant peripheral nerve sheath tumors have been reported in the literature in either spontaneous cases or in patients with neurofibromatosis. We report our results in the treatment of a 23-year–old female with acute onset hearing loss and facial paralysis.
Intervention: Due to the tumor size, location and degree of brainstem invasion this patient was treated with a multi-staged procedure for resection followed by external beam therapy and sterotactic radiosurgery boost for local control of residual tumor.
Conclusion: At one year the patient is alive and neurologically stable at follow up.
Given the current reports for malignant peripheral nerve sheath tumors of the cranial nerves, the survival of this patient at one year considering the rapid onset of symptoms due to brainstem invasion and hydrocephalus is significant.

Key Words: cerebellopontine angle tumor, cranial nerves, malignant peripheral nerve sheath tumor, and malignant schwannoma

Introduction

Malignant peripheral nerve sheath tumors (MPNST) are sarcomas, which arise from peripheral nerves and rarely occur in the cranial nerves. They have pathologic evidence of Schwann cell differentiation and may result from degeneration of neurofibroma or arise in normal peripheral nerves (5). Normal peripheral nerves consist of Schwann cells, perineural cells and mesenchymal cells (i.e. fibroblasts, endothelial cells, pericytes, and epidural lipocytes) (7). These rare tumors are also known as malignant schwannoma or neurofibrosarcoma and are most often associated with Neurofibromatosis type one (NF-1) or von Recklinghausen's disease (2, 4). MPNST are the most common mesenchymal tumors and are responsible for an estimated 5- 10 % of all soft tissue tumors (6). These are highly malignant tumors with an overall mortality rates have been reported from 10 -65 % (2).

Vestibular Schwannoma are the most common tumor of the cerebellopontine angle (CPA). MPNST of the cranial nerves are extremely rare lesions and they typically arise from the fifth, seventh or eight cranial nerves, in order of frequency (3). Cranial nerve MPSNT exhibit more aggressive biology with significant local recurrence and systemic dissemination when compared to its more benign counter part. Even in the face of aggressive chemotherapy and conventional radiotherapy the life expectancy for patients with cranial nerve MPNST is usually a few months. (3).

Case Report

History and Physical Examination. This 23-year old right-handed female who presented to an outside referring otolaryngologist with complaints of a three-month history of progressive ataxia combined with a sudden onset of unilateral hearing loss and hemi-facial paralysis. The patient was then transferred to the primary institution for definitive evaluation and treatment. The patient's medical history was unremarkable. The physical exam was remarkable for left facial nerve paralysis (House-Brackman Grade 6); cerebellar testing revealed dysmetria and dysdiakokinesia of the left upper and lower extremity. The patient also had a wide based ataxic gait. The remaining portion of the patient's exam was unremarkable. The MRI from the outside institution was reviewed and revealed a large heterogeneous enhancing mass in the left cerebellopontine angle which extended to the level of and eroding into the internal auditory canal, producing mass effect of the brain stem, fourth ventricle and cerebral aqueduct. (Figures 1& 2)

Initial Treatment: Due to the size of the lesion, the degree of brainstem displacement and the overall mass effect, a joint effort was utilized between neurosurgery and neurotology to perform a staged procedure aimed initially at debulking the tumor and relieving the brain stem compression. A left transtemporal translabyrinthine approach was performed with a planned subtotal resection. The tumor was noted to be soft and friable. The pathology was consistent with MPSNT. The tumor was removed until the brainstem was identified and decompressed. Cranial nerves V and IV as well as the tentorium were noted to be displaced ventral and superior. Cranial nerves VII and VIII were grossly imbedded in the tumor and were sacrificed with the tumor resection. Cranial nerves IV, V IX-XII were identified along the tumor capsule and were maintained. At the level of the tentorium the tumor was noted to be embedded into the brainstem with violation of the pia-arachnoid membrane. The dissection was continued until the only residual tumor was ventral to the porus acousticus. This was left for the second stage of the resection.

Permanent sections showed a neoplasm with hyper-cellular proliferation of spindle cells, hyperchromasia, nuclear atypia and a high number of mitoses with atypical features. Immunihistochemical staining were positive for S-100, p53, Ki- 67 (50%) all of which combined with the clinical, radiographic and gross pathology are consistent with MPNST (figs 3-5).

The patient at one-month follow up in the office was House Brackman VI on the left and had residual ataxia. The post-operative MRI showed a 1.7 x 2.0 cm residual tumor estimated at 70 % resection.

Second Stage- The patient was to have a planned staged resection but a few weeks prior to this she presented to the office with new neurologic deficits consisting of worsening of ataxia, dysphagia and dysarthria. A repeat MRI revealed increase in residual tumor size resulting in hydrocephalus and brainstem invasion. During this stage a translabyrinthine approach was utilized. The tumor was removed from the lower cranial nerves and the ventral aspect of the brainstem. The resection was limited by the caudal extension of the tumor through the incisura. Grossly the tumor had invaded cranial nerve VI that was sacrificed during resection. A large amount of brainstem edema was noted and a right frontal ventriculostomy was then placed. The wound was closed and after extubation the patient was moving all four extremities and was neurologically stable.

Stage 3- The final stage utilized left petrosal approach. The tentorium was then divided. The residual tumor had encased the cranial nerve IV, invading the tentorium and displacing the midbrain. The tumor was resected its superior extent down to cisterna magna with residual tumor embedded in to the basilar artery.

The patient was scheduled for fractionated external beam radiation but failed to follow up. Approximate two months later the patient began having worsening ataxia, an MRI scan showed 4x4x3.8 cm recurrence. The patient underwent another transpetrosal debulking with subtotal resection. Following surgery the patient underwent external beam radiation and gamma knife radiosurgery

Outcome: At fourteen months one year the patient is alive and living with her family. Her dyspahgia, dysarthria have resolved. She is ambulating independently. She required plastic surgery for a rotation flap for devascularized tissue following radiation therapy and a gold weight for left eye closure.

Discussion

Most CPA tumors are benign. Upwards of 75% of them consist of vestibular schwannomas. (5) MPNST of the vestibular- cochlear complex is extremely rare. They are associated with specific malignant pathologic features: hyperchromasia, mitotic figures and necrosis on permanent section. (3). These tumors are locally aggressive, have a high recurrence rate and have the potential to metastasize (5).

MPNST have an association with NF-1, regardless of the tumor location. The incidence of MPNST in NF-1 patients ranges from 24- 52% while sporadic incidence is .001%. The risk of developing MPNST is over 4000 times greater in NF-1 patients than the general population (4). Patients with NF-1 have a 40 % higher likelihood to have tumors > 10 cm vs. sporadic cases of MPNST. Patients with NF are also more likely to have more histological features of malignancy with a high mitotic rate (>6 mitosis/HPF) (7).

MPNST are highly malignant tumors with mortality rates, ranging from 10 –65 % (2). The overall mean survival rate has been estimated between 2.8- 5.5 years (1, 2). The 5-year survival rate for all MPNST's is 34- 52%. There is no specific survival data for patients with cranial nerve MPNST. Survival for these tumors has been studied extensively and specific factors have been associated with a prolonged survival. Prognostic factors for survival are based on the tumor size, tumor location, history of NF-1, history of radiation exposure, negative surgical margins, histologic grade and histologic subtype (7).

Anatomic location was a specific factor tied to survival. According to Cashen and Wong, trends have shown that patients with peripherally located tumors (i.e. extremities) have a higher survival rate than centrally located tumors (i.e. trunk/abdomen). This may be related to overall tumor size and the possibility for complete surgical resection based on tumor location. Centrally located tumors can become quite large before symptoms prompt patients to see a physician. (1, 2, 7). Patients with tumors less than 5cm have a 5-year survival rate greater than 50 %. . Patient's with larger tumors have a less than 20 % 5 year survival rate). Location is also related to surgical resectability. MPNST located in the extremities are more likely to have disease free surgical margins than abdominal, trunk or head and neck tumors. (1, 7).

Negative surgical margins are one of the most significant prognostic indicators of local control. Complete resection with disease free margins increases local control therefore lowering recurrence rates, which translates into prolonged overall survival (7). Current treatment for MPNST is based on complete surgical excision with disease free margins leading to improved survival (4,5,7).

This is a case presentation of a 23-year-old female with a large CPA tumor, presumptive CN VII/VIII complex MPNST. There have been less than five cases reported in the literature. The patient had a staged procedure followed by aggressive adjunctive radiotherapy. Given this tumor inherently involved the brainstem and vital neurovascular structures complete surgical excision with disease free margins is not possible. The overall treatment strategy however is based on the data from past surgical experience with MPNST of both extremity and truncal forms.

In Gonzalez's s most recently published case report of cranial nerve MPNST the patient lived eight months after presentation. We believe our patient has a longer survival due to several factors. Our patient was 23 years old at the time of presentation; the literature has shown that younger patients have a greater survival and lower mortality (1, 4, 7). This patient also did not have associated NF-1, which is also associated with a better outcome (7). At initial presentation, the patient had a 5.5cm tumor, which is quite large for an intracranial tumor, but is below the median tumor size based on survivability and outcome data (1,4,7). Our patient also had aggressive surgical debulking external beam radiation and gamma knife boost therapy. We feel that this combination would best explain why this patient has survived this lesion one year.

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Appendix

Figure 1 Coronal T1 with gadolinium

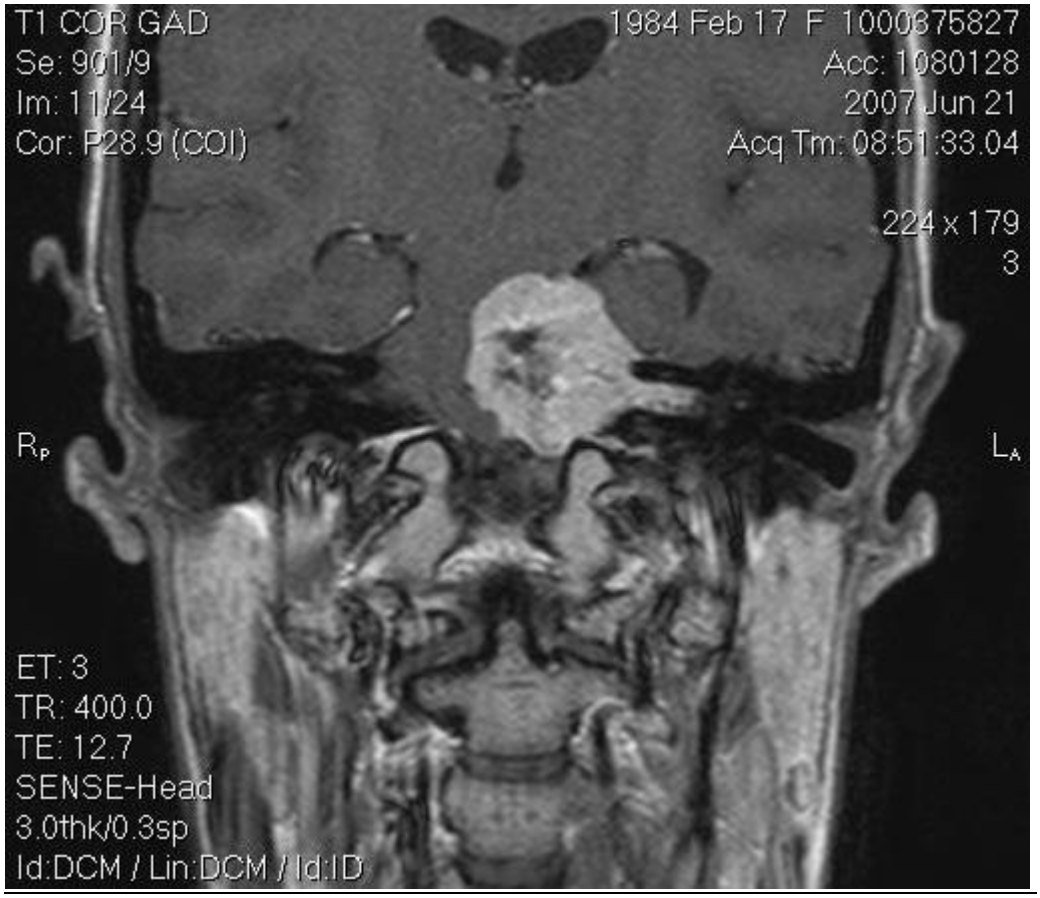


Figure 2
Axial T1 with gadolinium

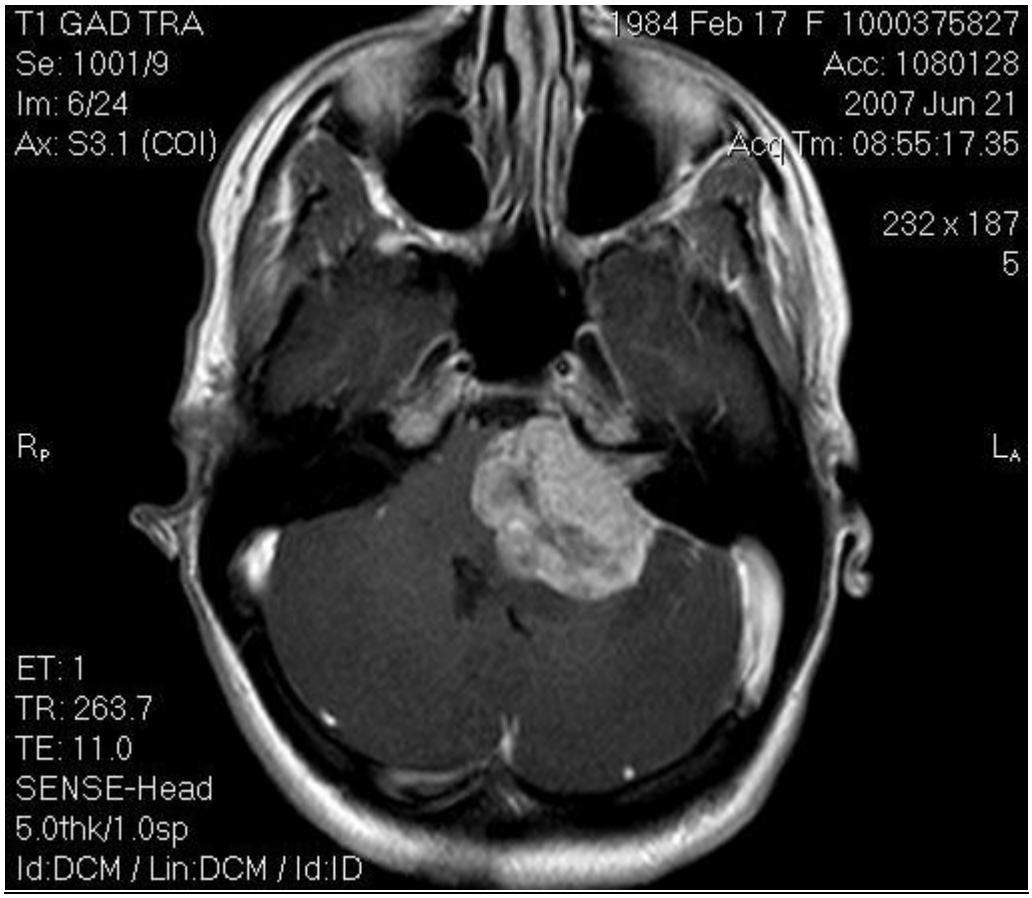
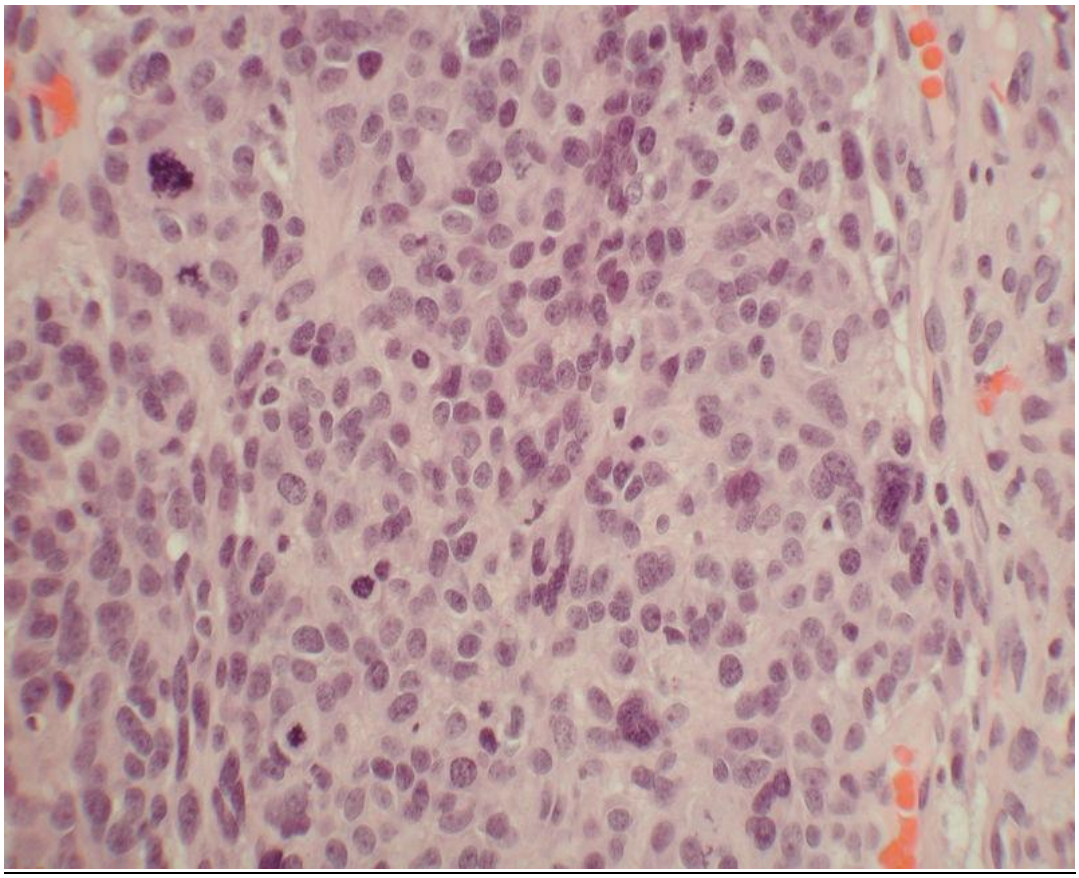
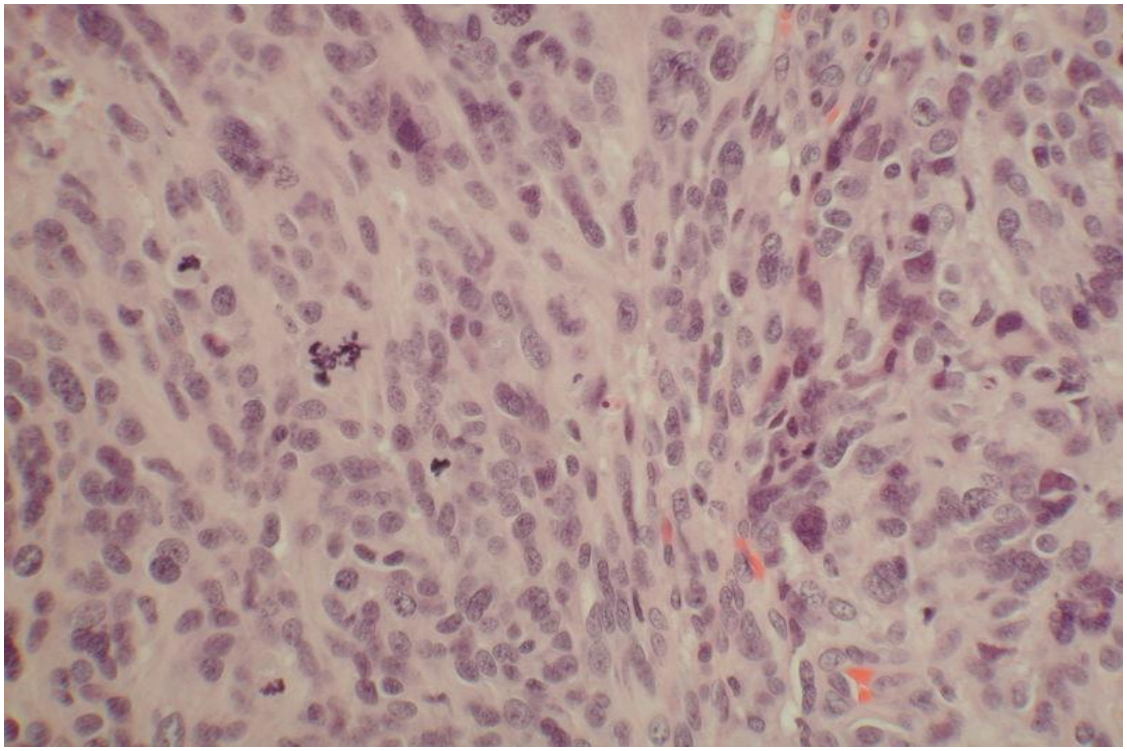


Figure 3



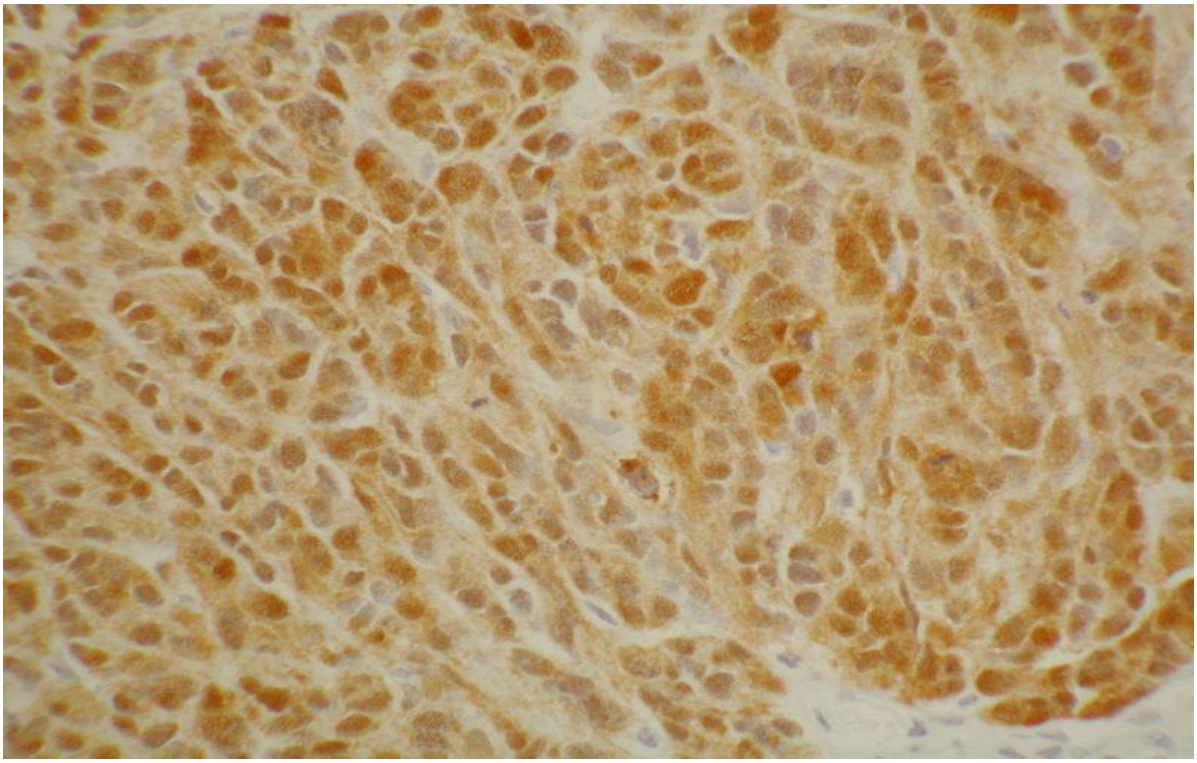
H&E stain- The neoplasm consists of a hypercellular proliferation of spindled, hyperchromatic cells. Some areas of nuclear pallisading are present suggesting nerve sheath derivation.

Figure 4



H&E- with higher magnification. The tumor shows marked nuclear pleomorphism, increased mitoses, including abnormal (tripolar mitoses), and necrosis.

Figure 5



Iimmunohistochemistry- under higher power S-100 stain is strongly positive in tumor cells

A Novel Scoring System for the Assessment and Treatment Timeline of Cerebral Abscesses: C.A.S.S (Cerebral Abscess Severity Score)

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Abstract

Objective: Cerebral abscesses are often difficult to institute a treatment protocol given their rapid nature, unpredictable effect on damaging the brain, and detrimental outcome on the patient. This author has attempted to determine a universal scoring system for the treatment of abscesses based on a wide based literature review of the current treatment modalities, case presentation, and proposed algorithm.

Methods: Internet literature review of cerebral abscesses on the US National Library of Medicine. Key words used included: cerebral abscess, brain abscess, imaging & brain/cerebral abscess, lumbar puncture, cerebral spinal fluid markers (S100B), electroencephalogram & brain/cerebral abscess, steroids & brain/cerebral abscess, stereotactic surgery, craniotomy, bur hole. Various journal articles were process and reviewed for determination of treatment options.

Results: In accordance to the evidence presented within this research article, the mainstay of treatment for cerebral abscess includes surgical intervention and antibiotic regimen. A novel numeric scoring system was formulated and denoted as CASS for Cerebral Abscess Severity Scale. The function of the CASS score is to guide the intervention process as all abscesses should be surgically treated within twenty-four hours.

Conclusions: Despite current advances in imaging modalities, the diagnosis of cerebral abscess remains elusive and difficult to treat. Currently, there is not a universal approach to effectivelymanaging cerebral abscesses. The CASS score is novel scoring system that utilizes constitutional signs and symptoms that are sensitive to CA combining with radiological imaging. Although its effectiveness remains to be tested, The CASS score is based on anecdotal evidence and previous case presentation in the literature, which proves to be proficient. The next rational step is to implement the use of the CASS score within our practice group and determine its utility.

Keywords: Cerebral abscess, brain abscess, imaging (CT/MRI), lumbar puncture, cerebral spinal fluid markers (S100B), electroencephalogram & brain/cerebral abscess, steroids & brain/cerebral abscess, stereotactic surgery, craniotomy, bur hole.

Introduction

Cerebral abscess (CA) is the second most common infection of the central nervous system (CNS) next to bacterial meningitis and it is a common space-occupying infectious lesion of the CNS. The incidence of CA among developing countries is about 8% whereas in developed countries the incidence is far less - about 2%.[i] [ii] [iii] CA among the pediatric population is about 4 cases per million averaging between 4 to 7 years of age.[iv] Systemic sepsis or embolization of infectious material into the CNS gives rise to focal infection of brain parenchyma. The formation of a cerebral abscess results from subsequent tissue destruction and pus formation. They can be found as solitary or multiple lesions and can be considered a form of focal encephalitis.

The availability of magnetic resonance imaging (MRI) and computed tomography (CT) has greatly aided the surgeon in the diagnosis of cerebral abscess.[v] [vi] Although the mortality rate from cerebral abscess has fallen significantly secondary to improved imaging and more effective antibiotics, their mortality rate remains significant. [vii] [viii] Notwithstanding current advances, management of CA remains a formidable challenge and treatment between surgeons is highly variable as it is drawn from individual clinical and surgical experiences. This author will attempt to quantify the current data on the various diagnostic and treatment modalities of CA including lumbar puncture, CSF markers such as S100B, EEG, steroids, antibiotics, imaging, and various surgical interventions to devise a universal scoring system and algorithmic protocol for the modern management of cerebral abscess.

Case Presentation

Patient was a 42 year old right handed Hispanic male that presented to our institution with a one-week history of headaches, difficulty speaking, right-sided weakness and slow thinking according to his spouse. Direct interview with Patient revealed that he had surgery for a "brain tumor" two to three years ago; however, neither Patient nor his wife could recall the diagnosis. Patient also stated that he had received no follow-up from his primary physician or oncologist and only one post-operative follow-up visit with his surgeon. Patient (with the aid of his spouse) denied any additional surgeries and claimed to have diabetes mellitus (DM), but was not currently on medications. According to Patient and his wife, Patient developed a headache about a week prior to our initial evaluation. The headache was described as an intermittent dull ache localized to the left forehead with radiation to the posterior aspect of his neck. It was graded on a severity scale of 6-8 out of 10. The headache was mildly relieved with NSAIDS initially, but became gradually refractory until the day he presented in the emergency department (ED). Over this same time period, Patient developed difficulty "finding his words" and "thinking correctly" (especially while banking and performing arithmetic), according to his wife. Patient denied visual problems, however he described three brief episodes of involuntary right hand shaking the day before visiting the ED. Review of systems revealed that Patient had been otherwise well without any other previously undisclosed medical issues preceding his current visit.

On physical examination, Patient was afebrile and his vital signs were stable within normal limits. General auscultation revealed the lungs to be clear and the heart to be regular in rate and rhythm. The abdomen was non-distended, soft to palpation with no obvious organomegaly or masses. Neurological assessment revealed Patient to be at a Glascow Coma Scale (GCS) of 14 with orientation to name and place (general). Patient could not remember his address without prompting or correctly state the current date. His pupils were asymmetric in size with a right of 4mm and a left of 2-3mm, but both were equally reactive to light. Ophthalmologic examination revealed haziness of the optic cup border on the left retina. Patient's speech was semi-aphasic, but the remainder of his cranial nerve exam was within normal limits. Direct observation of his extremities did not reveal any atrophic changes or involuntary fasciculation; however his right upper extremity graded in strength at 4+/5 and his right lower extremity at 4/5. Patient's deep tendon reflexes were within normal limits without any obvious pathologic changes. Patient sensory examination – pain, temperature and proprioception – was within normal limits. There were no other obvious motor, neurologic or sensory changes noted on examination. Patient's initial blood chemistries were non-diagnostic, but did revealed an elevated BUN at 26, mildly elevated ESR, and INR of 1.3. A CT of the head with and without contrast (Figure 1 and 2) and an MRI of the brain with and without contrast (Figure 3) were ordered.

Patient was admitted to our intensive care unit (ICU) and received hourly neurological examinations, phenytoin (1gram loading dose and 100mg IV every 8 hours) and dexamethasone (10mg loading dose and 6mg IV every 4 hours). Additionally, Patient was started on IV Vancomycin and maintenance normal saline. Given his history of DM, Patient was covered with an insulin sliding scale and blood glucose testing every six hours. Other medications included sucralfate and pepcid (gastrointestinal coverage), bowel medications and pain regimen. At this time, Patient was assessed to be in a guarded condition but deemed stable clinically to be schedule for surgery in a time greater than 24 hours. On the day of surgery, Patient's GCS level was initially 13, but dropped to 5 within a two hour period. Upon this deterioration, Patient was immediately intubated and taken to the OR for an emergent bifrontal craniotomy and resection of the cystic mass in his left frontal lobe. A post-operative CT of the head was obtained (Fig 4).

Intra-operative samples of pus and necrotic bone were sent to microbiology and pathology respectively for analysis. Patient's abscess culture from his left frontal lobe was sterile and there were no concurrent blood culture infections. CSF was also sent for microanalyses, but was clear from infection with the exception of a mildly elevated protein. The pathology of Patient's bone fragment showed osteomyolytic changes with necrosis of bone and dissemination of *Streptococcus Constellus* and *Streptococcus Intermedius*. Post-operatively Patient deteriorated to a GCS level of 3T and a ventriculostomy was placed to measure and manage his intracranial pressure. Subsequent imaging of his brain revealed full tentorial herniation with left hemispheric cerebral stroke (likely from middle cerebral artery vasospasm secondary to vasculitis). Patient was treated aggressively with a broad-spectrum antibiotic course that included Nafcillin, Flagyl and Fortaz. Also, his ICP was aggressively managed with

mannitol, lasix, 23.4% hypertonic saline, pentobarbiturate coma and ventriculostomy with bedside troubleshooting. Despite these aggressive measures, Patient remained at a GCS level 3T and became dependent on blood pressure agents to maintain his cerebral perfusion pressure (CPP). Patient was declared brain dead two days after our emergent craniotomy.

Etiology and Pathophysiology

Cerebral abscesses are caused by one or more pathogens, mainly streptococci and staphylococci and, less commonly, *Pseudomonas, Actinomyces,* and fungi.[ix] Although the source of the infection is frequently apparent, the definitive cause remains unknown (cryptogenic) in 10 to 35 percent of patients.[x] Cerebral abscesses can enter the intracranial compartment by three routes: contiguous, hematogenous and traumatic/iatrogenic.

The most common route is through contiguous suppurative focus, which constitutes about 45-50% of CA cases.[xi] Direct extension may occur through necrotic areas of osteomyelitis in the posterior wall of the frontal sinus, as well as through the sphenoid and ethmoid sinuses.[xii] Abscesses associated with frontal or ethmoidal sinusitis most commonly seed to the frontal lobes. On the other hand, sphenoidal sinusitis commonly seed to frontal and/or temporal lobes, while otogenic can seed to temporal, cerebellum and rarely to brainstem.[xiii] This direct route of intracranial extension is more commonly associated with chronic otitic infection and mastoiditis than with sinusitis (Ref 9). Contiguous spread could extend to various sites in the central nervous system, causing cavernous sinus thrombosis; retrograde meningitis; and epidural, subdural, and brain abscess. Odontogenic infections can spread to the intracranial space via direct extension or a contiguous hematogenous route.[xiv] The valveless venous network that interconnects the intracranial venous system and the vasculature of the sinus mucosa provides an alternative route of intracranial bacterial entry. Thrombophlebitis originating in the mucosal veins progressively and contiguously involves the emissary veins of the skull, the dural venous sinuses, the subdural veins, and, finally, the cerebral veins. By this mode, the subdural space may be selectively infected without contamination of the intermediary structure (e.g bone); a subdural empyema can exist without evidence of extradural infection or osteomyelitis.

The second source of entry for CA is hematogenous origin. They are typically secondary to septic emboli and constitute about 25% of all cases.[xv] Their distribution is most commonly along the middle cerebral artery, followed by the anterior cerebral artery and posterior circulation, consistent with their embolic origin. Hematogenous cerebral abscesses are frequently multiple and multiloculated. These infections are associated with endocarditis, lung infections (eg, abscess, empyema, bronchiectasis), and impaired immune function. Lastly, the third source of entry includes open brain trauma and/or cranial surgery, which combine to be about 10% of all cases of CA (Ref 9). Trauma that causes open skull fracture allows direct seeding of organisms to the brain.

Pathology

Whatever the route of entry, brain abscesses begin as a focal area of microvascular injury, which occurs at the grey-white matter junction where collateral circulation is poorest and the brain, is most readily rendered ischemic. Local infection, as from the middle ear, must always traverse the cortex before it reaches the white matter. Appropriate sections through the meninges and the cortex show their adhesion to dura through which infection must have traveled. A healed or healing track in the grey matter leading to the abscess can also sometimes be found. Five stages in the development of bacterial CA have been observed in humans and correlated in animal model studies. [xvi] [xvii] However, Brittz and Enzmann have correlated the histological findings of a CA to their radiological presentation and four stages of cerebral abscess maturation are currently recognized (Ref 16).

Stage one is an early cerebritis (day 1-3 after inoculation). The initial event on the arrival of bacteria in cortex or white matter is injury to the microvasculature. Spread of organism across the wall of the injured blood vessel and replication of organisms within the devitalized brain result in local inflammation leading to pre-suppurative encephalitis or cerebritis. The lesion is ill defined and is characterized be early necrosis of the cerebral parenchyma with vascular congestion, petechial hemorrhages, microthromboses, perivascular fibrinous exudates and infiltration by polymorphs from local capillaries. The capillary endothelium becomes swollen and leaky, leading to surrounding edema. The mass effect of this abscess edema can spread considerable distances, causing increase in intracranial pressure and possible herniation. Late cerebritis (stage two, day 4-9) is characterized by a necrotic purulent center. The pus is confined by a narrow irregular layer of inflammatory granulation tissue infiltrated by polymorphs, lymphocytes and some macrophages. The perivascular spaces in the vicinity become cuffed with polymorphs and lymphocytes as the cells spread into the surrounding white matter edema.

The third stage, early capsule (day 10-13), is made up of granulation tissue including lymphocytes, plasma cells, monocytes and macrophages, numerous newly formed blood vessels and collagen fibers. The developing capsule is at first poorly defined; it is thickest on its cortical surface and often very thin or even deficient on its ventricular surface. Thus, abscesses tend to expand inwards and rupture into the ventricular system leading to ventriculitis. Stage four, late capsule (day >14), is typically described as a firmer casing that can be stripped easily from the surrounding edema within the white matter. The edema around an abscess is often widespread, giving the white matter a delicate light green tint. Microscopically, more fibroblasts appear. A well encapsulated abscess has six distinct zones: a necrotic center invaded by macrophages, granulation tissue with proliferating fibroblasts and capillaries, long radially orientated blood vessels, a zone of lymphocytes and plasma cells in granulation tissue, and dense fibrous tissue with embedded astrocytes and surrounding edema with gliosis.

Abscesses may vary greatly in size. They are usually oval and in any one plane may appear multiple, but serial cuts will often reveal them to be solitary and multilocular. The white matter around the abscess, at least in the earlier stages, contains fresh foci of suppurative

encephalitis and microabscess; in their further development they may coalesce with the main abscess.

Methods

A search of the English-language literature with relation to different aspects of assessment and treatment of cerebral abscess was conducted. Despite agreement across neurosurgeons regarding the detrimental effects of CA, there continues to be a lack of consensus regarding the proper treatment method and sequence. The purpose of this literature review was to determine the current state of understanding of this complex phenomenon. In addition, this review also examines the role of early intervention for all abscesses and aspires to formulate a novel system that can guide the surgeon in their decisions for management of cerebral abscesses. The US National Health Library as well as the World Wide Web was used to identify key studies on the aspects and trends of CA management and treatment options. The following key words were used: *cerebral abscess, brain abscess, imaging* and *brain/cerebral abscess, lumbar puncture, cerebral spinal fluid markers (S100B), electroencephalogram* and *brain/cerebral abscess, steroids* and *brain/cerebral abscess, stereotactic surgery, craniotomy, bur hole.*

Results

Laboratory Studies

Routine laboratory studies have proven to be of little value in the diagnosis of brain abscess. The peripheral white blood cell count is frequently normal or only mildly elevated in about 65% of patients.[xviii] When present, leukocytosis is more commonly indicative of concomitant meningitis or some other co-existing systemic infection. The erythrocyte sedimentation rate (ESR) is elevated in up to 90% of patients in whom it is measured. Although, an elevated ESR is sensitive to an infectious and/or inflammatory process, it's not specific and provides no help in diagnosing brain abscesses. In some cases, elevated red blood cell count can lower ESR levels in cases of patients with CA and cyanotic heart disease (Ref 18).

Cerebral spinal fluid analysis is also sensitive but not specific for CA. Opening pressures trend to be elevated given the increase in cranial volume from the space occupying mass, which leads to increased production of CSF and rising of ICP (Ref 18). Typical CSF results may show a mild pleocytosis (commonly <100), but are more commonly normal. Pleocytosis greater than 100 characteristically have coexisting meningitis. The protein level also generally is found to be slightly elevated. The glucose content in the presence of CA is typically normal except in the face of frank meningitis, where they are typically low or hypoglycorrachia. Unden et al, has shown that a dimeric calcium binding protein known as S100B is known to be elevated in infectious diseases such as is bacterial meningitis, viral encephalitis and cerebral abscesses.[xix] S100B has been shown to increase in CSF and serum after various neurological diseases including head injury, subarachnoid hemorrhage and cerebral infarction. The limitation for the testing of S100B is having the ability to properly assay for the protein since it is not universally

available for immediate testing. In all, the results from CSF are non-specific at best and there are potential dangers to performing a lumbar puncture in the presence of an intracranial mass.

Neuroimaging of Cerebral Abscesses

The development and widespread use of CT scanning has made other tests, such as angiography, ventriculography, pneumoencephalography, and radionuclide brain scanning, almost obsolete. As such, it probably represents the single most important change in the diagnosis and management of CA. CT scanning allows early diagnosis, accurate localization, and even staging of the abscess according to criteria developed by Britt and Enzmann (Ref 16). CT scanning, preferably with contrast administration, provides a rapid means of detecting the size, the number, and the location of abscesses. It is the mainstay of diagnosis and the preferred method to monitor treatment progression and follow-up care.

However, CT scan results can lag behind clinical findings, giving an inaccurate picture of abscess stage. After the injection of a contrast material, CT scans characteristically show the brain abscess as a hypodense center with a peripheral uniform enhancement ring. Rarely, a well-organized abscess wall fails to generate such ring enhancement.[xx] In the earlier cerebritis stages, CT scans show nodular enhancement with areas of low attenuation without enhancement. As the abscess forms, contrast enhancement is observed. After encapsulation, the contrast material cannot help differentiate the clear center and the CT scan is similar in appearance to those obtained during the early cerebritis stage.

Many authorities consider MRI to be the diagnostic method of choice for the diagnosis of brain abscess. It can permit accurate diagnosis and excellent follow-up of the lesions because of its superior sensitivity and specificity. Compared with CT scanning, it offers better ability to detect cerebritis, greater contrast between cerebral edema and the brain, and early detection of satellite lesions and the spread of inflammation into the ventricles and subarachnoid space.[xxi] Contrast enhancement with gadolinium diethylenetriaminepentaacetic acid (a paramagnetic agent) helps differentiate the abscess, the enhancement ring, and the cerebral edema around the abscess. T1-weighted images enhance the abscess capsule, and T2-weighted images can demonstrate the edema zone around the abscess. Interestingly, the hypointense rim does not correspond exactly to the ring of enhancement seen after contrast administration and is not thinned medially like the collagenous capsule.[xxii] A direct comparison between the stage of the abscess, pathology and neuroimaging is described in table 1 for correlation.[xxiii]

Electroencephalogram

EEG occasionally reveals a focus of high voltage with slow activity. It is completely non-specific and rarely of value in confirming the diagnosis. Kepa and Oczko-Grzesik have studied the value of EEG in patients with purulent, bacterial meningoencephalitis and have determined that (in the acute phase) EEG may be helpful in the estimation of severity of the patient's clinical state.[xxiv] In all, the role of EEG in the acute setting of cerebral abscess have not yet been determined to be management altering in the treatment of cerebral abscess

Corticosteroids

Corticosteroids continue to be utilized as an adjunct in the management of CA, although their use remains controversial. Steroids have clearly been shown to reduce mass effect from cerebral edema, which typically accompanies an abscess. However, their potential positive benefit maybe be undermine by their detrimental side effects. The positive benefit from steroid administration includes the decrease of both the rate and degree of capsule formation. On the other hand, this effect can lead to increased adjacent tissue destruction and a negative impact on outcome. Steroids have also been shown to reduce the degree of contrast enhancement on CT scans, particularly in the cerebritis stages. The effect of steroids to CT imaging is misleading because it appears that the abscess is resolving when, in fact, it is not being visualized well. In such cases, reduction in the diameter ring should be the criteria used to determine abscess regression. Overall, steroids should be limited to patients with significant cerebral edema and mass effect and their benefit must outweigh their risks (Ref 18).

Antibiotics

Initial empiric antimicrobial therapy should be based on the expected etiologic agents according to the likely predisposing conditions, the primary infection source, and the presumed pathogenesis of abscess formation. When abscess specimens are available, staining of the material can help guide selection of therapy. Whenever proper cultures are taken and organisms are isolated, the initial empiric therapy can be adjusted to specifically target the isolated bacteria. Mampalam and Rosenblum reported an eightfold greater number of sterile cultures in patients receiving preoperative antibiotics.[xxv] Xiao et al reported that cultures of intracerebral material remained sterile for 39 (34%) of their 115 surgical patients. Of the 76 patients whose cultures were positive, in 68 (89%) a single pathogen was identified and in 8 (11%) 2 pathogens were found.[xxvi] Tseng and Tseng performed blood cultures in 49 of 122 patients who had a clinical presentation of systemic infection (fever and leukocytosis). Only 13 of those patients had blood cultures that grew bacteria (positive rate 26.5%); 7 of them had the same pathogen in both blood and brain abscess cultures.[xxvii]

Coverage for streptococci can be attained by a high dose of penicillin G or a third-generation cephalosporin (eg, cefotaxime, ceftriaxone). Metronidazole is included to cover penicillin-resistant anaerobes (ie, gram-negative bacilli). When *S aureus* is suspected (following neurosurgery or trauma), nafcillin or vancomycin (when methicillin resistance or penicillin allergy are present) is administered. Cefepime or ceftazidime are administered to treat *Pseudomonas aeruginosa* infection. Patients with HIV infection may require therapy for toxoplasmosis. Penicillin penetrates well into the abscess cavity and is active against non–beta–lactamase-producing anaerobes and aerobic organisms. Chloramphenicol penetrates well into the intracranial space and is also active against *Haemophilus* species, *S pneumoniae,* and most obligate anaerobes. Its use has been curtailed dramatically in most US centers because of the availability of other equally efficacious and less toxic antimicrobial combinations (ie, cefotaxime

plus metronidazole). Metronidazole penetrates well into the CNS and is not affected by concomitant corticosteroid therapy. However, it is only active against strict anaerobic bacteria, and its activity against anaerobic gram-positive cocci may be suboptimal. Third-generation cephalosporins (eg, cefotaxime, ceftriaxone) generally provide adequate therapy for aerobic gram-negative organisms. If pseudomonas are isolated or anticipated, the parenteral cephalosporin of choice is either ceftazidime or cefepime. Aminoglycosides do not penetrate well into the CNS and are relatively less active because of the anaerobic conditions and the acidic contents of the abscess. Beta-lactamase–resistant penicillins (eg, oxacillin, methicillin, nafcillin) provide good coverage against methicillin-sensitive *S aureus*. However, their penetration into the CNS is less than penicillin, and the addition of rifampin has been shown to be of benefit in staphylococcal meningitis. Vancomycin is most effective against methicillin-resistant *S aureus* and *Staphylococcus epidermidis* as well as aerobic and anaerobic streptococci and *Clostridium* species. Generally, most of the anaerobic pathogens isolated are sensitive to penicillin. Although fluoroquinolones have good penetration into the CNS, data are limited regarding their use in treating brain abscesses. Therapy with penicillin should be added to metronidazole to cover aerobic and microaerophilic streptococci. The administration of beta-lactamase–resistant penicillin or vancomycin (if methicillin-resistant staphylococci are isolated) for the treatment of *S aureus* is generally recommended.

Neurosurgical Intervention

Common knowledge among surgeons regarding abscesses indicates that surgical drainage provides the most optimal therapy. The procedures commonly used by neurosurgeons are aspiration through a bur hole, stereotactic biopsy, and complete excision after craniotomy. There continues to be some debate regarding which procedure represents optimal management. Aspiration is the most common procedure and is often performed using a stealth protocol or stereotactic procedure with the guidance of CT scanning or MRI. Excellent outcomes have been reported in patients managed by aspiration alone.[xxviii] Craniotomy is generally performed in patients with multiloculated abscesses and for those whose conditions failed to resolve after less invasive procedures. The advantages of craniotomy over bur hole have been well document in previous literature as the most definite form of treatment.[xxix xxx] Ventricular drainage combined with administration of intravenous or intrathecal antimicrobials or both are used to treat brain abscesses that rupture into the ventricles. If not recognized early, both subdural empyema and brain abscess can be fatal (Ref 28). Management of subdural empyema requires prompt surgical evacuation of the infected site and antimicrobial therapy. Failure to perform surgical drainage can lead to a higher mortality rate (Ref 28, 29, 30).

Even though proper selection of antimicrobial therapy is important in the management of intracranial infections, surgical drainage may be required. Optimal therapy of fungal brain abscess generally requires both medical and surgical approach (Ref 29). A delay in surgical drainage and decompression can be associated with high morbidity and mortality[xxxi]. Recent studies illustrate that brain abscess in the early phase of cerebritis may respond to antimicrobial

therapy without surgical drainage (Ref 27). However, surgical drainage may be necessary in many patients to ensure adequate therapy and complete resolution of infection. Stereotactic aspiration has a number of advantages. It can be accomplished rapidly and safely through a single bur hole under local anesthesia, making it particularly attractive in patients who are seriously ill. It allows precise localization and decompression of the abscess cavity using a minimally invasive technique. Stephanov et al, recommends that a stereotactic approach is particularly valuable in treating deep-seated lesions, lesions in eloquent areas, and multiple abscesses.[xxxii] Indeed, with stereotactic systems (framed or frameless systems) currently available, multiple lesions can frequently be aspirated through a single bur hole (Ref 32). During the earlier stages of cerebritis in which antibiotics alone may be curative, open procedures are more likely to cause significant neurological deficit whereas stereotactic biopsy can safely retrieve tissue for culture (Ref 32). Additionally, removal of the purulent material creates a more favorable local environment in which antibiotics function effectively.

Discussion

Based on this author's assessment from the literature review, the mainstay of treatment for brain abscess involves a combination of antibiotics and surgical intervention. This is in accordance with the overall consensus (among surgeons) that brain abscess is a surgically treated disease and antibiotics are considered adjuncts to treatment (Ref 29 and 30). The overall goal of surgery is to not only obtain samples for accurate bacteriological diagnosis but also to decrease the number of pathogens and amount of necrotic tissue present and, most importantly, reduce mass effect and intracranial pressure.[xxxiii] According to Taken, there is a general consensus that surgical treatment is indicated for abscesses larger than 2.5cm located in noneloquent areas and causing significant mass effect. Free hand aspiration, stereotactic aspiration, endoscopic aspiration, and craniotomy with excision are the surgical modalities used to treat brain abscesses (Ref 33). However, given our current knowledge of CA, there is not a current rational and/or universal approach to abscesses.

In lieu of the data listed in the previous sections, the most important resource to guide the surgeon in the right direction is to establish a timeline of the symptoms that may relate to an infectious etiology. Cerebral abscesses can have an indolent or fulminant process. However, in about two thirds of patients, onset of symptoms commonly average two weeks or less (Ref 6). Most symptoms are a result of the size and location of the space-occupying lesion or lesions. The tetrad of lethargy, headache, seizure, and focal neurologic deficit are sensitive to cerebral abscesses. The frequency of common symptoms and signs in CA are as follows: headache - 70%, mental status changes (may indicate cerebral edema) - 65%, focal neurologic deficits - 65%, fever - 50%, seizures - 25-35%, nausea and vomiting - 40%, nuchal rigidity - 25%, and papilledema- 25%.[xxxiv] A suddenly worsening headache, followed by emerging signs of meningismus, is often associated with rupture of the abscess. The second tool that can aid in the diagnosis of a suspected CA is imaging, specifically CT or MRI. Although many authors state the use of MRI with contrast as the gold standard of cerebral abscesses; CT with contrast is

inexpensive, quick and readily available in any tertiary hospital setting. There are numerous amount of literature stating the importance of imaging beginning with the initial work by Britt and Enzmann in the early 1980's about CT imaging.

Based on the extensive literature review within this article, it was apparent that to properly guide surgeons in their treatment of cerebral abscesses, a numeric scoring system based on current data should be formulated. The novel system in question is illustrated in table two and it is aptly named: Cerebral Abscess Severity Scale or C.A.S.S. (CASS). The total possible CASS score is ten, which indicates that the patient needs immediate surgical intervention, while a minimal score of zero can warrant further investigation modalities. A CASS score range of 0-4 indicates that the patient's clinical status is guarded but stable and more tests are needed to fully assess the lesion and to tentatively plan for an intervention within twenty-four hours (depending on the outcome of the studies). A CASS score range of 5-7 represents that the patient's overall condition is guarded and definite treatment should be instituted within less than 12 hours. Any further studies, such as an MRI of the brain with contrast should be ordered urgently and should be done at the time of admission. Finally, a CASS score equal to or greater than 8 warrants immediate intervention and treatment. An MRI of the brain with contrast would be desirable, but it would be dependant on the patient's clinical status. The patient's clinical status should be considered critical and the surgeon should have a definite mode of treatment formulated for immediate intervention or (at the very least) within 6 hours. The function of this system is to guide the intervention process as all abscesses should be surgically treated within 24 hours. Currently, there is no literature that can support the absolute treatment of an abscess within the time frame listed previously. However, it is this author evaluation of the literature (mainly from anecdotal evidence and case presentations) offered within this article to support the recommendation of treating abscesses early.

The CASS assessment scale is formulated irrespective of the patient's age, gender, or nationality, as they have no premise in the decision for surgical intervention. Additionally, constitutional symptoms like nausea and/or vomiting and fevers were specifically excluded from the table because of their subjectivity to interpretation among practitioners. The CASS score is not specific for cerebral abscesses, but it should be used along with the presentation of the patient as well as image representations. Eloquent areas of the brain are basal ganglia, thalamus/hypothalamus, motor strip, and brain stem and are considered sensitive for aggressive intervention. Lastly, the signs and symptoms listed in table two can be subject to scrutiny due to their subjectivity and their lack of specificity to cerebral abscesses. However, their sensitivity level maintains a broad differential diagnosis. Quantifying the data with the patient's history of illness and presentation can help to narrow down the diagnosis to a small differential, which can include cerebral abscesses. A sample scheme is represented in figure 5 exemplifying the utility of the CASS score.

The mode of surgical intervention can be formulated based on size of the abscess, multiplicity of the abscess, and location of the abscess (i.e. eloquent versus non-eloquent). The proposed operative treatment options (described in table 3) include: stereotactic aspiration, bur

hole aspiration, and craniotomy. Regardless of the framing system available for stereotactic aspiration, any CA found within an eloquent area of the brain (regardless of size or multiplicity) should only be aspirated. A bur hole aspiration should be limited to unifocal CA of less than 2.5 cm and within non-eloquent areas of the brain. Also, bur hole aspiration (depending on location) can optionally be guided with a stealth or brain lab protocol for better trajectory. Cerebral abscesses of greater than 2.5 cm in diameter and/or multiple foci found in non-eloquent areas should be treated with craniotomy. Bur hole or stereotactic aspiration of complex CA would not be an adequate form of treatment due to the increased risk of rupture, especially into the ventricles. A craniotomy allows for a definite treatment of an abscess by obtaining adequate sample for analysis, as well as decompressing the lesion to reduce the mass effect and vasogenic edema (as in the case of Patient after the craniotomy was performed). The main purpose for surgical intervention is to obtain an adequate sample volume and specimen for laboratory and microanalysis in order to identify the organism(s) and employ an antibiotic regimen tailored specifically for the patient.

Based on the assessment of the patient, general common measures should be used during hospitalization. Admission to a neurological intensive care unit with recurrent assessment of the patient's GCS level is absolutely necessary. Other common orders needed are to keep the patient as none per oral, but hydrated with isotonic saline; seizure coverage with phenytoin; and gastrointestinal coverage with pepcid and/or a Histamine blocker or proton pump inhibitor of choice. In light of the current literature, the pre-operative use of antibiotics and/or steroids is not recommended because of the risk of producing sterile cultures or reducing the ability to visualize the abscess with contrast, respectively. Steroid regimen should only be used if there is severe mass effect and vasogenic edema present; other options include mannitol, lasix, and hypertonic saline. Antibiotics and steroid regimens should be reserved post-operatively in order to enhance the success of treatment. Post-operatively, the antibiotic regimen should broad base and should include coverage of aerobes, anaerobes, gram positive and negatives organisms, and atypicals. A broad antibiotic regimen commonly used includes Vancomicyn, Nafcillin or Rocephin, and Flagyl. If fungal etiology is suspected, than coverage can be extended to azole agents such as fluconazole. Once preliminary data is obtained, the surgeon can tailor the antibiotic regimen based on culture results. Sequential cultures should be obtained to monitor the treatment; however, once the antibiotic regimen is narrowed specifically for the patient, it should be continued for a total of 6 weeks to ensure proper eradication of the organism. Consultation to an infectious disease specialist would be advantageous, given the appropriate setting and availability. In addition to following the patient's clinical status, daily sequential CT imaging of (at the very least) three to five days should be ordered to identify any abscess recurrence.

Conclusion

Despite advances in diagnosis and treatment of cerebral abscesses, they remain a life-threatening and important disease. Although the advent of modern imaging has allowed surgeons to diagnose CA earlier, their management remains convincingly challengeable. The

current literature of cerebral abscesses lacks a universal approach to a rational assessment and treatment option(s) to date. This article presents a novel scoring system that utilizes constitutional signs and symptoms that are sensitive to CA combining with radiological imaging. Anecdotal evidence and specific case presentations in the literature suggest that an early surgical intervention and antibiotic regimen improves the morbidity and mortality of patients afflicted with cerebral abscesses. The next rational step would be to implement the validity of the CASS score in patients with lesions or masses consistent with a cerebral abscess. Indeed, all cerebral abscesses should be treated with surgical (aspiration) and medical (antibiotic) management.

Surgeons should have a high index of suspicion for cerebral abscesses because early diagnosis may reduce morbidity and mortality. Infections, regardless of their etiology, that have seeded to the brain should be treated promptly and adequately with close follow-up of the patient. In all, prevention of complications from cerebral abscesses could potentially decrease the cost to the health care community as well as positively affect the overall outcome of the patient.

Abcess Stage	***Time Course (days)***	***Histopathology***	***CT imaging***	***MRI imaging***
Early Cerebritis	0-3 days	* Central zone of necrosis * Local inflammatory response * Marked peri-lesional edema * Poor demarcation from near brain * Enlargement of necrosis * Formation of pus	* Poorly marginated area of hypodensity * Minimal contrast enhancement	* Presence of edema
Late Cerebritis	4-9 days		* Hypodense area with poor margination * Patchy enhancement * Ring-enhancement in late phase	* Early patterns of ring enhancement noticable * Surrounding edema hypointense * Rim of lesion hyperintense to white matter in T1W
Early Capsule	10-14 days	* Continued pus formation * Development of collagen capsule * Edema surrounding capsule	* NC-faint ring enhancement * Early phase may enhance with contrast * Capsule usually thin, relatively, uniform and smooth	
Late Capsule	>14 days	Five distinct histological zones 1. Necrotic center with pus 2. Peripheral zones of	* Thick rim enhancement * Satellite abscess formation that can form	Components of T2W

	inflammatory cells and fibroblasts 3. Dense collagen capsule 4. Peripheral neovascular formation 5. Peri-lesional edema and gliosis	from: 1. Deep core margin 2. Hypointense capsule 3. Vasogenic edema and gliosis

Table 1: The imaging characteristics of brain abscess using CT are time dependent and roughly correlate with the histopathological stages described by Britt and Enzmann (Ref 16, 23).

Cerebral Abscess Severity Scale		
Size	<2.5cm	1
	>2.5cm	2
Location	Eloquent	1
	Noneloquent	0
Number	Unifocal	1
	Multifocal	2
GCS	15	0
	14	1
	<14	2
Headaches	Yes	1
	No	0
Seizures	Yes	1
	No	0
Focal Weakness	Yes	1
	No	0
	Total Score	**0-10**

Table 2: Cerebral Abscess Severity Score or CASS. The scoring system can be used to guide the neurosurgeon the type of intervention process to use as well as the timing to drain the abscess and start on an antibiotic regiment. Eloquent areas of the brain are basal ganglia, thalamus/hypothalamus, and brain stem.

Proposed Operative Treatment		
Stereotactic Aspiration	**Bur Hole**	**Craniotomy**
Cerebral abscess in eloquent area(s) regardless of size or multiplicity	Cerebral abscess of < 2.5 cm and in non-eloquent area(s); stealth or brain lab protocol as an option	Cerebral abscess of >2.5 cm or multiple and in non-eloquent area(s)

Table 3: Operative treatment options for cerebral abscesses based on their CT or MRI presentation.

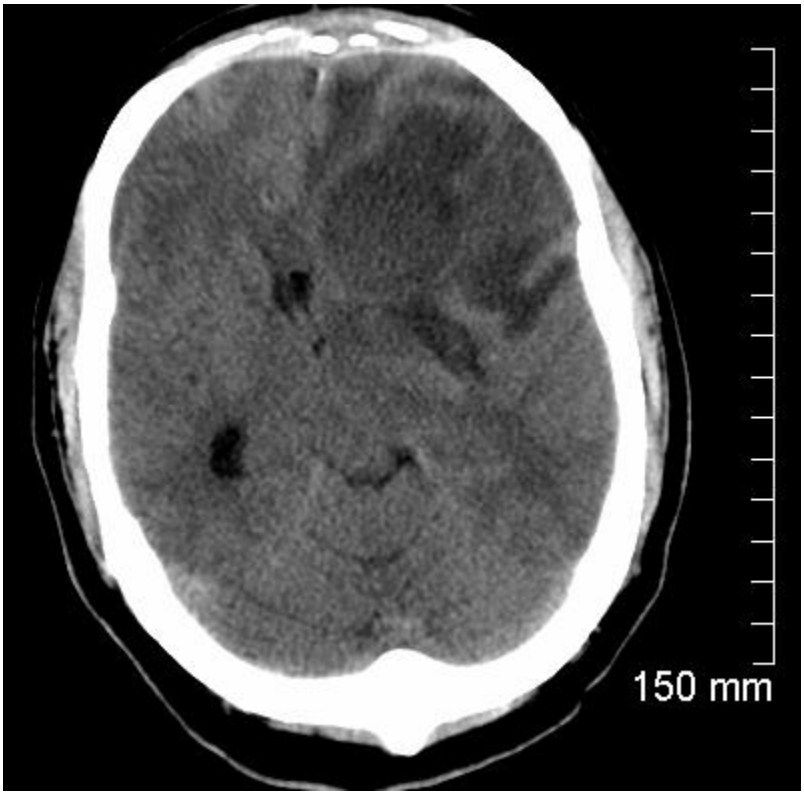

Figure 1: CT image with no contrast shows significant vasogenic edema involving the left frontal lobe suggesting either an underlying mass or abscess. There is significant mass effect with left-to-right midline shift measuring 1.6 cm in length. There is subfalcine herniation and partial obliteration of the suprasellar cistern. Dilatation of the right lateral ventricle suggests obstruction at the level of the foramen of Monro.

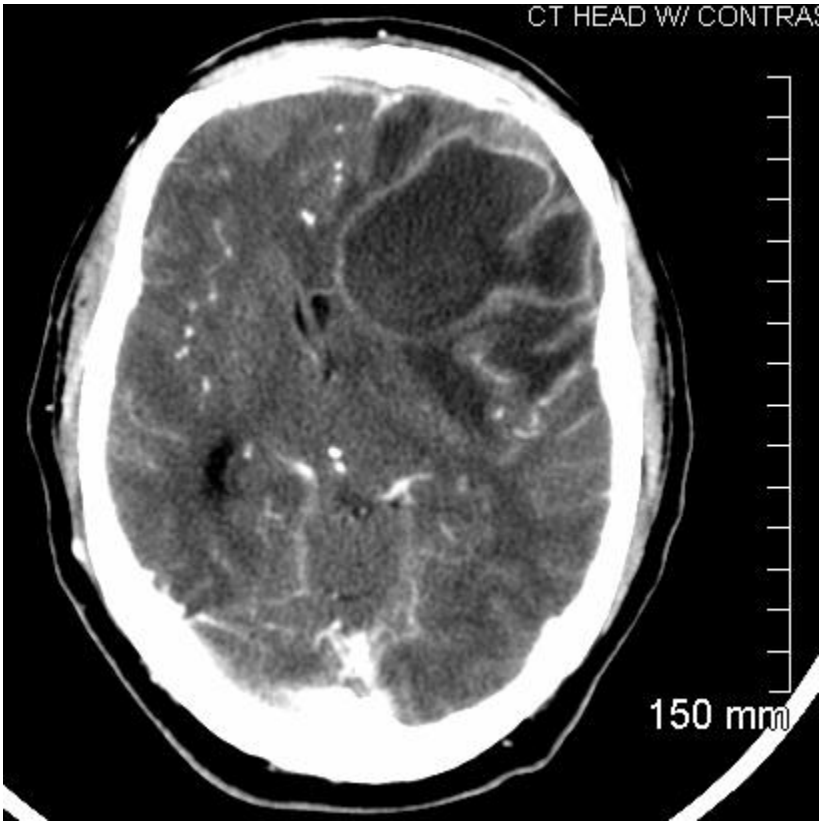

Figure 2: CT image shows a contrast study demonstrating a 4.4 x 6.3 cm ring-enhancing lesion in the left frontal lobe with hypodense center suggesting either a necrotic mass or a brain abscess.

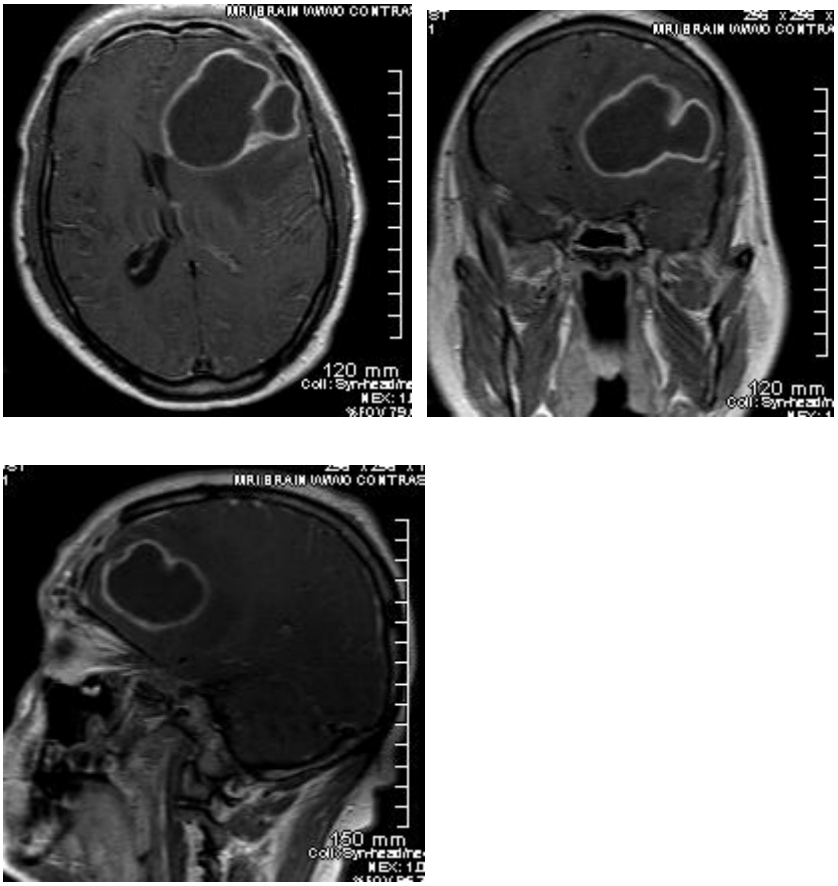

Figure 3: Within the left frontal lobe there is a 5.2 x 6.2 x 4.5 cm lesion with rim enhancement and central fluid like area. This lesion is surrounded by extensive vasogenic edema causing significant mass effect. There is up to 1.8 cm left-to-right midline shift. Subfalcine herniation is demonstrated anteriorly. There is partial obliteration of the mesocephalic cistern with only transtentorial herniation of the medial left temporal lobe. Slight dilatation of the right temporal horn suggests obstruction at the level of foramen of Monro. Edema or encephalomalacia is also noted involving the right frontal lobe. There is mucosal thickening and enhancement in the ethmoid sinus and also bilateral frontal sinuses. The mucosal abnormality in the frontal sinuses is of unclear significance given findings of prior frontal craniotomy. However, if there is clinical evidence of sinus disease, there is higher likelihood of the left frontal lesion being an abscess.

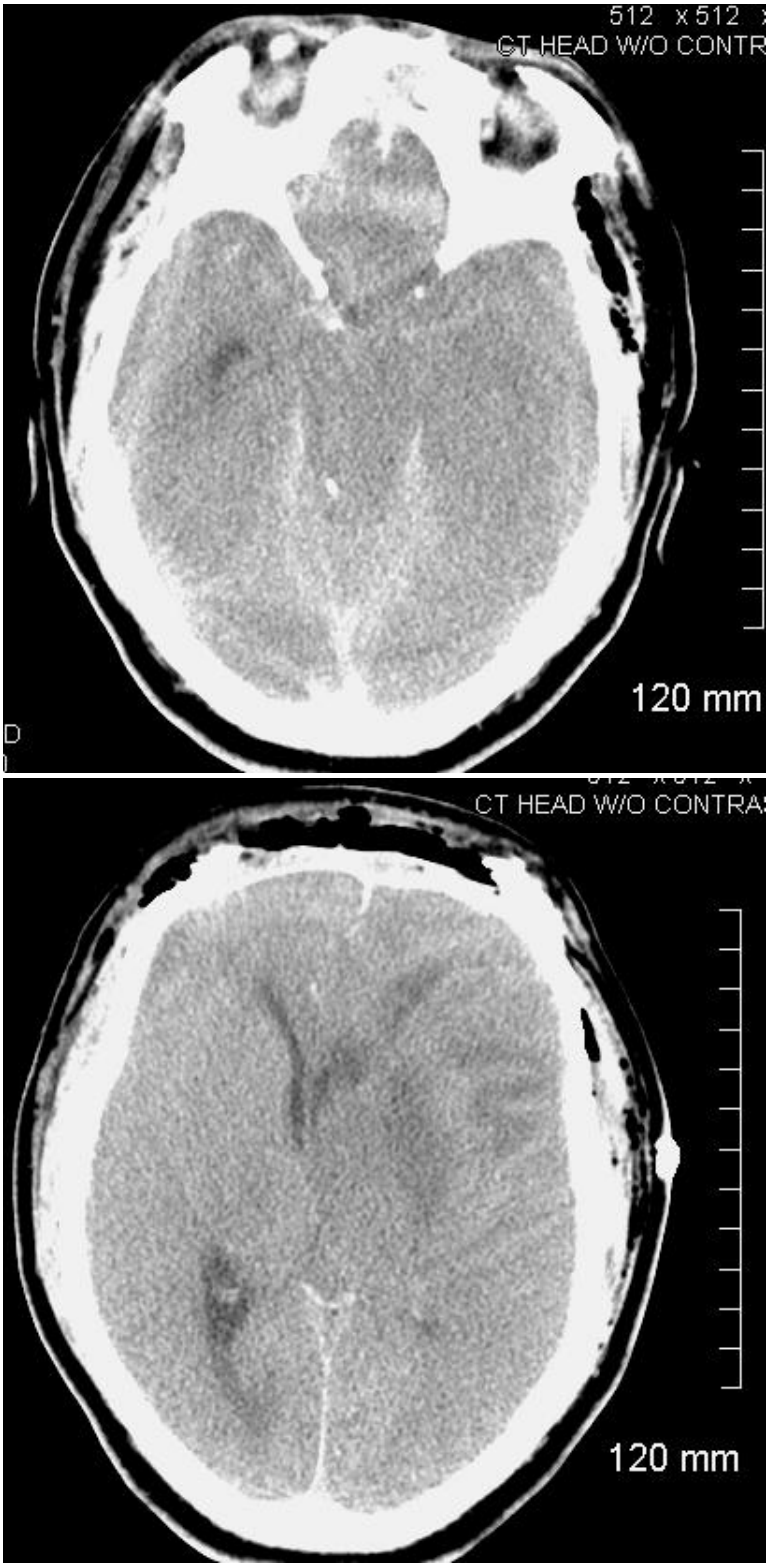

Figure 4: There is obvious resection of the left frontal parietal temporal mass. Subcutaneous air on the left is seen. Some residual edema changes on the left persist. A midline shift from left to right measuring 6.5 mm still remained. Diffuse cerebral edema changes persist with

loss of the sulci. Images through the sinuses show opacification of the ethmoid, maxillary, and sphenoid sinus.

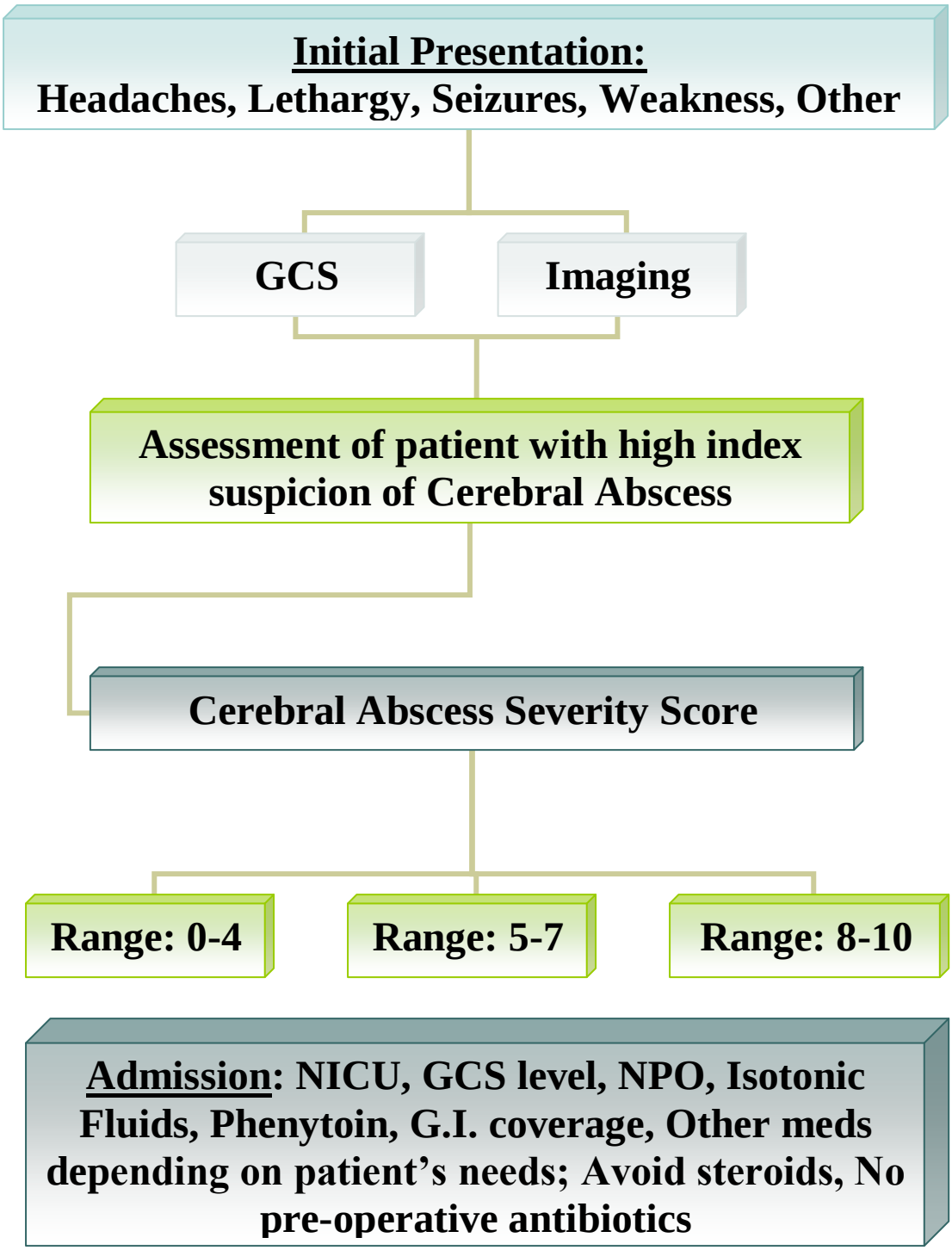

Figure 5: Sample Schematic representation of a patient with a suspected cerebral abscess with suggested initial admission instructions. The CASS assessment represents that time interval for surgical intervention. A CASS score range between 0-4 should be surgically intervening within 24 hours; a range of 5-7 should be surgically intervening within less

than 12 hours; a CASS score greater than 8 should warrant immediate intervention or within less than 6 hours.

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Treatment of thoracolumbar burst fractures by balloon vertebroplasty with calcium phosphate cement in combination with short-segment pedicle screw instrumentation and fusion

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Abstract

Study Design. Prospective consecutive series.

Objective. To evaluate the outcomes of the treatment of thoracolumbar burst fractures by balloon vertebroplasty with calcium phosphate cement and short-segment pedicle screw instrumentation and fusion.

Background Data. Hardware failure and loss of reduction after posterior short-segment instrumentation are complications caused by insufficiency of anterior column support. This is due to migration of disc tissue through the endplate into the fractured vertebral body that cannot be restored with posterior instrumentation.

Methods. Eighteen consecutive patients who sustained thoracolumbar A3-type burst fractures without neurologic deficits were included in this prospective study. After posterior reduction and fixation, bilateral transpedicular balloon reduction of the endplate was performed, and calcium phosphate cement was injected. Preoperative and postoperative Cobb angle and central and anterior height were assessed with radiographs and computed tomography.

Results. Eighteen patients underwent surgery without technical difficulties, and a substantial reduction of segmental kyphosis and restoration of vertebral body height could be achieved with the technique. All patients recovered uneventfully, and the neurologic examination revealed no deficits. The postoperative radiographs and CT images demonstrated a good fracture reduction and filling of the bone defect without unwarranted bone displacement. Overall sagittal aligment was improved from an average preoperative 11.5° to -1.4° kyphosis at final follow-up observation. The central and anterior height of the vertebral body could be restored to 82.7 and 91.1% of the estimated intact height, respectively. Cement leakage was observed in 3 cases without clinical implications. Posterolateral radiological fusion was achieved within 3 to 6 months after operation. There was no instrumentation failure or measurable loss of sagittal curve and vertebral height correction in any patient.

Conclusions. Balloon vertebroplasty with calcium phosphate cement secured with short-segment pedicle screw fixation and fusion provided excellent reduction of segmental kyphosis and restoration of vertebral body height in thoracolumbar burst fractures.

Key Words: spine, burst fracture, vertebroplasty, balloon, calcium phosphate cement, pedicle screw instrumentation

Introduction

A traumatic fracture of the spine is a serious medical condition that can have a major impact on the quality of life of the patient (1,2). Although no consensus has been reached by treating physicians, surgical fixation of a traumatic fracture of the thoracic or lumbar spine is considered necessary if axial and rotational stability is severely impaired or if a neurologic deficit is present or imminent. Short-segment pedicle screw instrumentation is a well described technique to reduce and stabilize thoracic and lumbar spine fractures (3,4). It is a relatively easy procedure but can only indirectly reduce a fractured vertebral body, and the means of augmenting the anterior column are limited. Hardware failure and a loss of reduction are recognized complications caused by insufficient anterior column support (5). Anterior procedures using iliac grafts or cages have been proposed to address the problem of this anterior column insufficiency, sometimes also in combination with posterior instrumentation. The anterior approach offers good visualization of the fracture and allows a direct restoration of the defect. Disadvantages compared with pedicle screw instrumentation are a longer duration of the procedure, higher blood loss, and an increase in postoperative morbidity (6,7,8). Combined anterior/posterior approaches are major surgical undertakings for the patient and do not seem to provide any real advantages over the anterior procedure alone (10,11,12). Transpedicular spongiosaplasty, in which autologous bone grafts are impacted in the vertebral body through the pedicles after reduction to increase the stiffness of the anterior column, was developed and promoted by Daniaux in 1986 as an interesting addition to posterior surgery (13). Recent studies have shown that this technique does not prevent the recurrence of kyphosis reliably and reproducibly (5,14). It has been noted by several authors that the loss of reduction after treatment of a fracture takes place mainly in the disc space. Previous studies suggest that intrusion of the disc through the fractured endplate into the weakened vertebral body, instead of degenerative disc changes, is the likely cause of this collapse (5,15). Preventing the disc intrusion by restoring the endplate anatomy after fracture reduction/fixation and filling of the resulting bone defect was the subject of a recent cadaveric study. It was concluded that anterior column augmentation by transpedicular balloon vertebroplasty with calcium phosphate cement (CPC) injection was safe and feasible. In a recent animal study, CPC and polymethyl methacrylate cement were injected in artificially created defects in the vertebral body of goats and studied histologically. Although both cements were suggested to be suitable vertebral bone void fillers, CPC showed superior biocompatibility, since the polymethyl methacrylate cement sometimes provoked a mild inflammatory reaction in the surrounding tissue (16).

The hypothesis of this prospective clinical investigation in patients with thoracolumbar burst fractures was that balloon vertebroplasty with calcium phosphate cement, supplemented with short-segment pedicle-screw instrumentation and fusion, could sufficiently restore fractured vertebral body and reduce segmental kyphosis.

Materials and Methods

Eighteen consecutive patients with an average age of 38 years (from Desert Regional Medical Center and Riverside County Regional Medical Center, California), who sustained

thoracolumbar burst fractures (AO classification A-3) without neurologic deficits were included in this prospective study (Table 1). Exclusion criteria were a complete rupture of the posterior longitudinal ligament on MRI, and preexistent pathology that could compromise the surgical procedure. Preoperative anteroposterior and lateral radiographs, CT scans of the fractured spine were obtained as well as MRI scans (sagittal and transverse; T1 and T2 weighted) for assessment of damage to the endplate, vertebral body, and discoligamentous structures. All patients signed an informed consent agreement after being informed about the procedure. The patients were operated on a priority rather than an emergency basis within a week after trauma. Short-segment pedicle screw-and-rod reduction and fixation under general anesthesia was performed in all cases. The goal of the posterior instrumentation was to realign the adjacent vertebral bodies anatomically. The pedicles of the fractured vertebral body were subsequently identified and probed. Two cannulas were inserted into each pedicle under fluoroscopic guidance and placed with the tips just ventral to the posterior wall in the vertebral body to prevent the balloons from accidentally being inflated inside the pedicles and from expanding in a posterior direction. A hand drill was introduced in the vertebral body to create space under the impressed endplate for the inflatable bone tamps (KyphX Introducer toolkit, Kyphon Inc.). Subsequently, both KyphX inflatable bone tamps were introduced through the cannulas into the fractured vertebral body. After positioning the balloons with fluoroscopic guidance under the most impressed part of the endplate, the bone tamps were inflated simultaneously with 1-mL increments of contrast fluid, while the pressure on the digital pressure readout on the KyphX inflation syringe was observed and recorded. After each increment, a fluoroscopic image was obtained to assess the amount of reduction achieved and to monitor unwarranted posterior displacement of bone fragments. Subsequent individual inflation of the bone tamps allowed some fine tuning of the endplate reduction and correction of asymmetrical scoliotic deformities. The amount of calcium phosphate cement needed to fill the resulting defect in the vertebral body was estimated from the total balloon volume and prepared. For each gram of CPC powder, 0.34 mL of physiologic saline was used to produce an injectable paste. The time for CPC to set is approximately 20 minutes at room temperature, giving ample time for injection. When sodium phosphate is used as a solvent, the setting time decreases to 5 to 10 minutes, according to the manufacturer. The reaction between the dicalcium and tetracalcium phosphate powder is completed after approximately 24 hours when using saline as solution, although a considerable compressive strength is already achieved within 4 hours. The 10 mL syringe and needle that were used to inject the cement were flushed first with physiologic saline to reduce friction and allow for a controlled injection. The balloons were actively deflated and removed, and the reduced state of the endplates was monitored carefully. The cement was slowly injected under fluoroscopy to monitor the distribution. Injection continued until the defect was filled completely fluoroscopically, without any attempt to pressurize the cement. See Figure 1, A-C for graphic details of the experimental procedure. Following posterolateral autografting with iliac crest cancellous bone, the cannulas were removed, and the wound was closed. Immediately after waking up, a neurologic examination was performed. The first 24 hours after surgery, the patients were confined to bed in

a supine position. The upright anteroposterior and lateral radiographs were obtained to evaluate the reduction of the fracture, the distribution of the cement, and/or any possible complications. The patients were then allowed to ambulate wearing removable TLSO brace. At discharge, patients were encouraged to resume their daily routine but advised to wear the TLSO brace for 8 weeks. One month after surgery, patients were seen at the outpatient clinic, screened for neurologic complications, and again underwent for upright anteroposterior and lateral radiographs and CT scans. Pre- and postoperative Cobb angles were measured on the lateral radiographs. The central and anterior vertebral body height was measured from the midsagittal CT scan images. The fractured and restored heights were calculated as a percentage of the estimated, intact vertebral body height by averaging the respective central and anterior heights from the adjacent levels. The CT images were also used to evaluate a possible bone displacement towards the spinal canal. Differences between the preoperative and postoperative Cobb angles and vertebral body heights were analyzed with a single-sided paired *t* test.

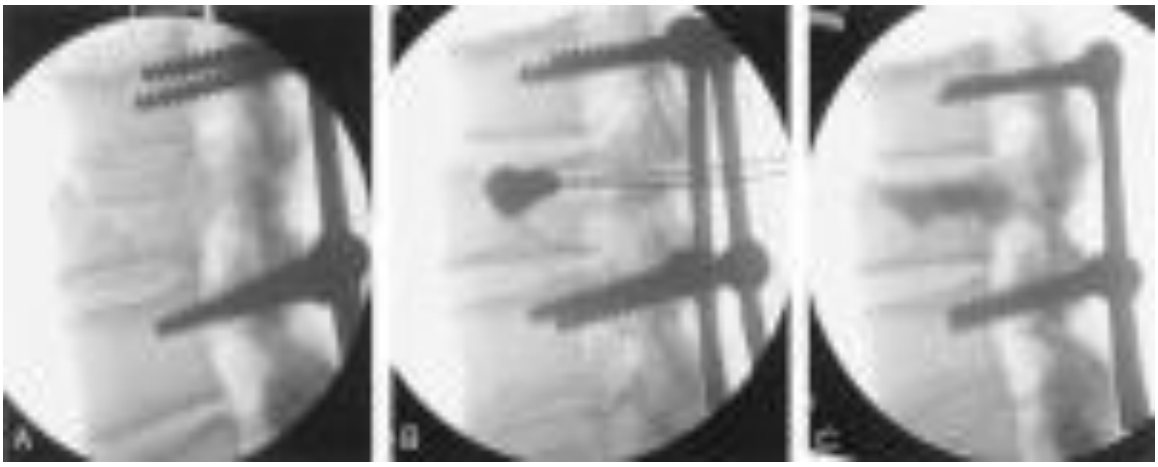


Figure 1. Sequence of fluoroscopic images demonstrating the balloon vertebroplasty procedure. **A,** Lateral fluoroscopy image of an instrumented vertebral fracture showing a central depression of the cranial endplate. **B,** Image of the same fracture with inflated balloons after optimal reduction of the cranial endplate. **C,** Complete filling of the defect without evidence of extracorporal leakage after bilateral injection of CPC in the void

Results

Eleven male and 7 female patients (age, 19–65 years) with burst fractures (AO classification A-3) that resulted from a motor vehicle accident or a fall from height were included in the study. The affected levels were T12 (n = 4), L1 (n = 8), L2 (n = 2), L3 (n = 3), and L4 (n = 1). No complications of instrumentation were seen, and following reduction, substantial incomplete canal clearance was observed in every patient. The peak pressure in the balloons varied from 60 to 150 psi with a mean maximum pressure of 107.5 psi after "setting," in which phase the balloon actually expanded and reduced the endplate. In all cases, substantial reduction of the fractured endplates was achieved with the bone tamps. The total amount of injected CPC varied from 15 to 25 g (Table 2). The median duration of the total procedure was 142 minutes (range, 120–180 minutes), and the median blood loss was 316.7 mL (range, 200-500 mL). In all patients,

the postoperative radiographs and CT images demonstrated a good position of the pedicle screw construct and the CPC in the fractured vertebral body (Figure 2, A and B). Cement leakage, defined as any cement out of the confines of the vertebral body, was observed on the postoperative radiographs and CT images in three patients; one in the cranial disc space, one in the caudal disc space and once anterior of the fractured vertebral body. All patients recovered uneventfully, and the neurologic examination revealed no deficits. The average Cobb angle before surgery was 11.5° (range, -10.5–16.0; standard deviation, 9.0) and -1.4° after surgery (range, -20.6–12.5; standard deviation, 9.3). The average central vertebral body height increased from 65.4% before surgery (range, 44–92%; standard deviation, 10.6) to 82.7% of the estimated intact central height after surgery (range, 72–100%; standard deviation, 6.31). The average anterior vertebral body height increased from 69.2% before surgery (range, 48–88%; standard deviation, 11.98) to 91.1% of the estimated intact anterior height after surgery (range, 80–100%; standard deviation, 7.25) (Table 3). Both the Cobb angle correction and the central and anterior vertebral body height gains were highly significant ($P < 0.0001$) (Figure 3 & 4). No posterior bone displacement was seen in any patient following the instrumentation and balloon vertebroplasty. Posterolateral radiological fusion was achieved within 3 to 6 months after operation. There was no instrumentation failure or measurable loss of sagittal curve and vertebral height correction in any patient. The patients were followed for an average of 9 months (range, 3–15 months).

Table 1. Patient Characteristics

Case	Age	Gender	Level	Classification	Cause
1	20	Male	T12	A3.1	Motorcycle Accident
2	28	Male	L1	A3.2	Fall from height
3	51	Male	L1	A3.1	Motor Vehicle Accident
4	25	Female	L2	A3.2	Motor Vehicle Accident
5	42	Male	L3	A3.1	Fall from height
6	29	Male	L1	A3.3	Motor Vehicle Accident
7	32	Female	L1	A3.1	Fall from height
8	37	Female	L2	A3.1	Motor Vehicle Accident
9	45	Male	T12	A3.2	Fall from height
10	50	Male	L4	A3.3	Fall from height
11	27	Male	L1	A3.3	Motorcycle Accident
12	19	Female	T12	A3.1	Motor Vehicle Accident
13	65	Male	L3	A3.1	Fall from height
14	62	Female	L3	A3.2	Fall from height
15	21	Male	L1	A3.1	Motorcycle Accident
16	30	Female	L1	A3.1	Motor Vehicle Accident
17	40	Male	T12	A3.1	Fall from height

18	57	Female	L1	A3.1	Fall from height

Table 2. Surgical Details

Case	Duration (min)	Bloodloss (ml)	Mean Pressure (psi)	Total Balloon Volume (ml)	Injected CPC (gr)
1	180	500	120	6	16
2	150	450	90	12	22
3	130	250	100	10	25
4	140	200	90	7	24
5	120	250	110	6	20
6	150	350	100	8	24
7	120	300	130	7	16
8	180	500	150	10	15
9	150	400	100	12	20
10	120	300	130	7	16
11	130	200	60	7	15
12	180	450	100	8	16
13	120	250	75	10	18
14	130	300	60	8	20
15	140	250	140	8	20
16	150	200	140	7	15
17	150	300	120	8	15
18	120	250	120	8	16

Figure 2. A, lateral radiograph demonstrating a L1 burst fracture. B, radiograph of the same fracture 1 day after pedicle screw fixation and balloon vertebroplasty with CPC.

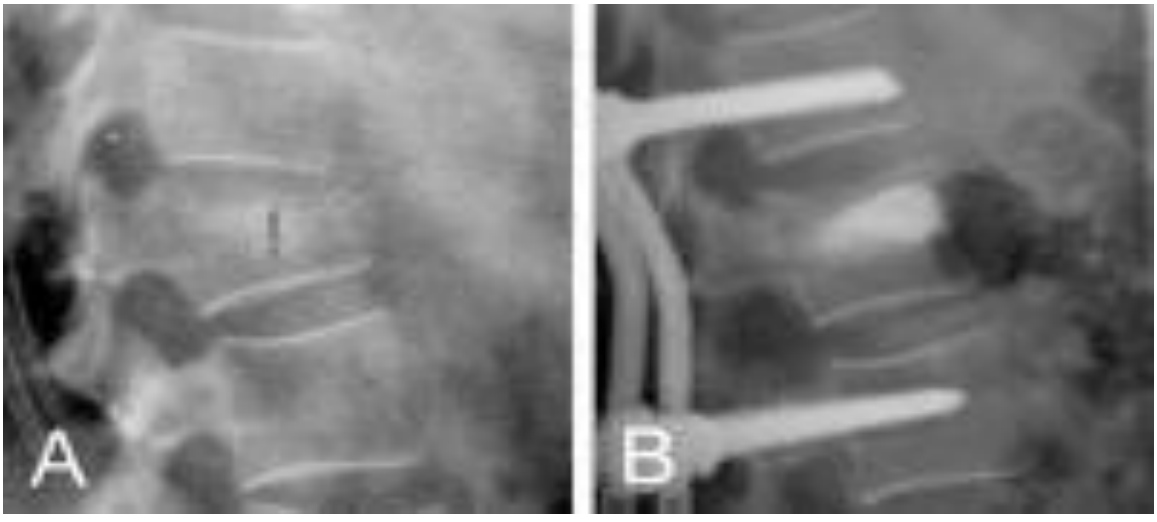


Table 3. Percentage of Central and Anterior Height

Case	% Central Height Preoperative	% Central Height Postoperative	% Anterior Height Preoperative	% Anterior Height Postoperative
1	65	84	70	97
2	62	80	63	96
3	59	79	86	98
4	69	88	64	88
5	62	79	84	94
6	44	76	49	80
7	60	77	66	82
8	72	82	70	80
9	73	90	65	100
10	58	78	71	89
11	66	85	64	86
12	59	72	57	85
13	64	86	88	100
14	76	80	85	96
15	51	84	48	85
16	72	81	71	86
17	92	100	82	100
18	74	87	63	98

Figure 3. Comparison of Preop vs. Postop Central Vertebral Body Height

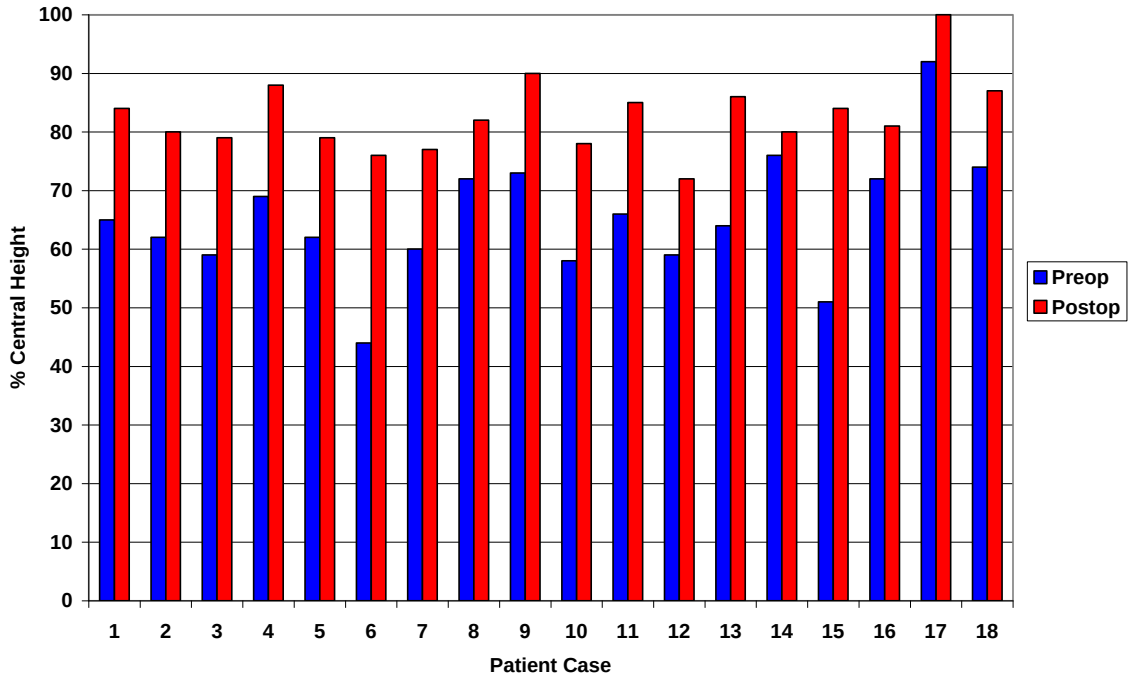
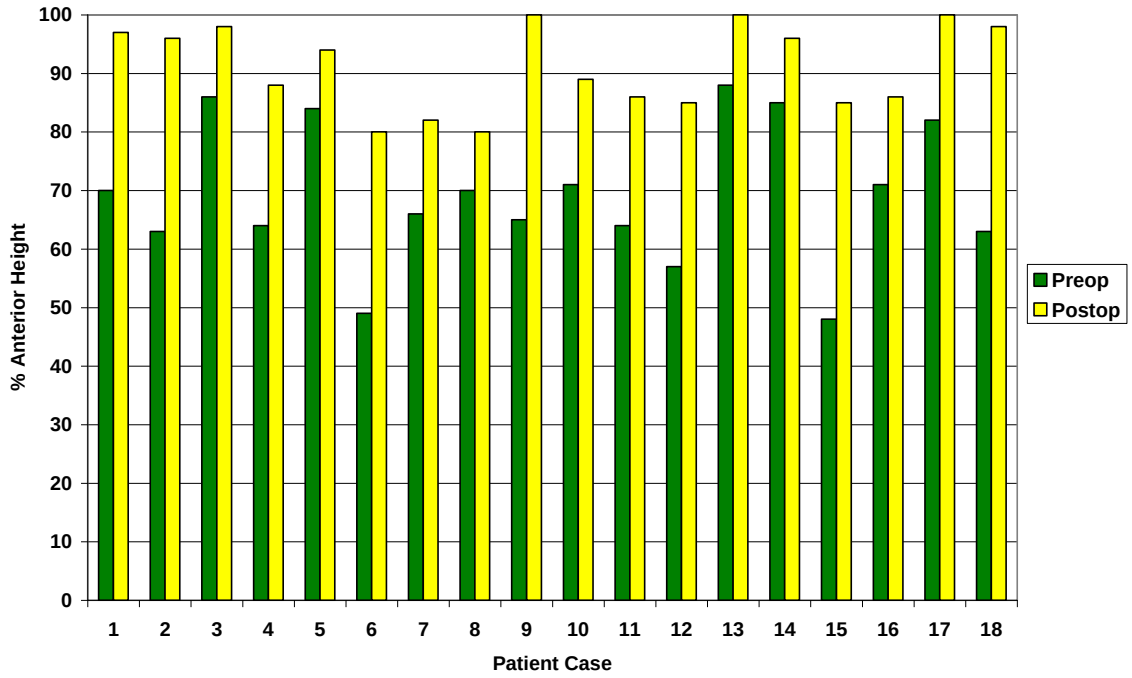


Figure 4. Comparison of Preop vs. Postop Anterior Vertebral Body Height



Discussion

In the present study, the author demonstrated the feasibility and relative safety of balloon vertebroplasty to directly reduce the fractured vertebral body and reinforce the anterior column after posterior indirect reduction and stabilization. Several studies have been conducted to assess the strength and stiffness of vertebral compression fractures after vertebroplasty with polymethyl methacrylate cement and CPC (16,17). It was found that both types of cement were able to restore the strength and stiffness to intact values, even increase them, in osteoporotic specimens. In the cadaveric biomechanical study by Mermelstein *et al*, it was found that the injection of CPC in a burst fracture reduced the load on the pedicle screw construct that was inserted for fracture stabilization (18). They concluded from their *in vitro* work that vertebroplasty with CPC after posterior instrumentation might reduce hardware failure and anterior column collapse and decrease the need for a secondary anterior approach.

It has been proposed by some authors that the fractured and impressed endplate increases the chance of intrusion of the intervertebral disc in the corpus and may cause subsequent spinal deformity (15). However, the possibilities of vertebroplasty to reduce the endplate impression are limited and can only be achieved by building pressure on the cement, which is strongly associated with an increase in cement leakage that can result in spinal cord compression and pulmonary embolism (19,20,21). The use of inflatable bone tamps in the treatment of osteoporotic compression fractures has received a lot of attention the last few years (22,23). Although invented primarily to correct the deformity by lifting the compressed part of the vertebra to a more physiologic position before polymethyl methacrylate cement injection, a

positive side effect was noticed resulting from the use of the balloons. During inflation, the balloons push aside intravertebral cancellous bone, effectively autografting it around them. This results in a layer of higher-density bone, lining the cavity in which the cement is to be injected. In addition to decreasing the chance of cement leakage due to the presence of a cavity that allows for a lower injection pressure, this bone lining might act as a shield. Whatever factor predominates, in practice, the number of cases with cement leakage is considerably lower for balloon vertebroplasty than for conventional vertebroplasty (24). Reducing a traumatic fracture by ligamentotaxis before performing balloon vertebroplasty might also decrease the risk of cement leakage due to the resulting alignment of cortical bone fragments. In the present study, the inflatable bone tamps were used for yet another purpose besides creating a lined cavity. Since the study by Oner *et al* demonstrated the recurrent kyphosis to be the result of a change in the disc space morphology, the author aimed to reduce the endplate fracture directly with the balloons, thereby restoring the morphology of the disc space (15).

The choice for calcium phosphate cement instead of polymethyl methacrylate cement stems from long-term biocompatibility concerns with the latter. Various studies have demonstrated the superior biocompatibility of CPCs over polymethyl methacrylate cement in terms of biocompatibility and osteoconductivity, although most of these studies were of the appendicular skeleton of animals (25). Since the mean age of the human population with traumatic spine fractures is considerably lower (37.8 years in the present study) compared with the population where vertebroplasty with polymethyl methacrylate cement is usually performed, the author preferred to use a cement that performs favorably in these long-term areas of biocompatibility.

Patients were followed long enough to detect any immediate complication from the surgical procedure. Potential hazards included retropulsion of bone fragments following balloon expansion, extracorporal cement leakage resulting in pulmonary embolism, or spinal cord compression and infection. None of these serious complications were observed; however, the finding that three of 18 patients displayed cement leakage emphasizes the delicacy of the procedure.

Conclusions

Balloon vertebroplasty with calcium phosphate cement combined with short-segment pedicle screw instrumentation and fusion provided excellent immediate reduction of post-traumatic segmental kyphosis and restoration of vertebral body height in thoracolumbar burst fractures. Cement leakage occurred but had no clinical consequences. The next logical step is to start a full-scale study with adequate controls (randomized controlled trial). Furthermore, prolonged and stringent follow-up examinations will demonstrate whether this technique is sufficient to prevent the recurrence of kyphosis and limit the number of secondary anterior procedures or whether it carries the potential for unforeseen long-term complications.

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Novel Technique to enhance the use of PMMA for cranial reconstruction

Technical note

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Abstract:

With a combined effort between the Sections of Neurosurgery and Craniofacial Plastic Surgery we have adapted one particular technique to help us better facilitate the use of cranioplasty and limit the morbidity that may occur following this procedure. The use of PMMA for cranioplasty by plastic surgeons and neurosurgeons is a widely accepted technique that has shown merit in many different situations. Although this technique has been used for many years there are still associated problems that may cause significant morbidity for the patients undergoing these procedures. Because of this awareness at our institution we have implemented a new technique that incorporates the use of mini-screws within the inner table combined with the use of antibiotic impregnated PMMA that increases the strength of the construct, limits extraneous motion that may lead to pain, and decreases the risk of infection both for patients undergoing the initial procedure or those that may require multiple operations. Through a simple technique we have had excellent results while adding little extra operating time or cost to the procedure.

Keywords:

polymethylmethacrylate, PMMA, screw fixation, cranial reconstruction, cranioplasty

Introduction:

Repair of surgical defects can be dated back to the times of the Ottoman Era[1]. However, despite the advances in technology since that time there is still no consensus on

which surgical technique or material is superior for use in cranioplasty [2-21]. At our institution cranioplasty is a commonly performed procedure with a large caseload showing the superiority of PMMA as the primary substance for use in cranioplasty [22]. In addition to our works there are many other published articles on the excellent outcomes achieved with the use of PMMA [2,4-8,15,16,22]. Despite the documented superiority of the material, as with all procedures there are still instances in which the final result is less than acceptable from a clinical standpoint. Because of this we have developed a new technique to help combat the associated morbidity with the use of PMMA for cranioplasty. Several theories have been proposed for the associated morbidity surrounding the procedure. These are: poor adherence of PMMA to bone, pain associated with micro-motion and failure of adequate bony ingrowth into the construct, settling of the cranioplasty construct with pain and poor cosmetic results, poor cosmesis associated with the use of a mini-plate system on areas where the skin is thin or not covered by the hairline, and infection at the operative site[22].

The procedure that we will describe in this paper alleviates all of the above concerns and has decreased the post-operative morbidity of our patient's. Because of the clinical success of this procedure over the last several years we now implement these techniques on all of our patients undergoing cranial reconstruction with the use of PMMA for cranioplasty.

Materials and Methods:

Over the last 8 years at our institution the Section of Neurosurgery has implemented this technique on 73 patients, 28 males and 45 females for various reasons shown in Tables 1-1 and 1-2. We altered our initial technique secondary to previously documented morbidity associated with cranioplasty both at our institution and throughout

the literature [2,6,7,9,12,13,16,22].

Table 1-1 Patients undergoing cranioplasty

Surgical Procedure	# of Patients
Tumor Resection (i.e. Meningioma, skull base lesion, skull lesion, etc.)	50
Trauma	12
Vascular lesions (i.e. Aneurysm clipping, avm resection)	8
Infection	3

Table 1-2 Indications for use of PMMA in cranial reconstruction

I. When there is significant bony removal following excision of a tumor or removal of lesion with bony involvement (i.e meningioma, osseus lesion, etc.)

II. Repair of post-traumatic craniectomy defect (frontal, parietal, occipital)

III. Patient's with osteomyelitis of the skull

IV. Skull base procedures where the defect is amenable to cranioplasty

V. With bony removal following clipping of aneurysm or avm resection

Surgical Technique:

The cranioplasty procedure is carried out under the same guidelines as a standard procedure. The area of interest is prepped and draped in sterile fashion and the appropriate incision is made. If this is a previously operated on site, after the exposure of the cranial defect the soft tissues that have become adherent to the skull edges and dura are separated using a mixture of sharp and electrocautery devices, taking care to limit any damage to the underlying dura or intracranial contents. Following this any bony or soft tissue elements that would limit adequate alignment of the cranioplasty implant are then addressed at this time.

The next step is to use a high speed drill with the appropriate attachment that would be used to pre-drill holes in the skull, most commonly a Midas Rex drill with C1 attachment (Figure 1). After selecting the appropriate attachment make several holes in

the inner table surrounding the entire defect, at approximately 0.5 to 1.0 inches apart. It is important during this stage of the procedure to maintain perpendicular alignment of the drill so that the screws will be inserted at a right angle to the inner table (Figure 2). At this time it is appropriate to begin mixing the antibiotic impregnated PMMA. The use of antibiotic is surgeon dependant and has consisted most commonly of gentamycin or vancomycin.

Next insert 3-4mm miniscrews into the pre-drilled holes so that there is complete coverage of the entire diameter of the defect (Figures 3 and 4).

Following insertion of the mini-screws the PMMA can be placed in an onlay fashion and contouring may take place at this time until the appropriate cosmetic result is achieved (Figure 5). Upon hardening of the construct the final cosmetic result should now be achieved (Figure 6). The defect and associated covering are closed using standard technique, dependent upon surgeon preference.

Discussion:

The use of PMMA for cranial reconstruction is well documented. Over the years this method of cranioplasty has found favor secondary to being cost-effective, a relative low morbidity, and ease of use [22]. Despite this there is still a subset of patients that experience morbidity associated with its use for various reasons [22,26,27,30,32]. Because of this a technique has been developed to enhance the use of PMMA and decreases some of the possible morbidity associated with these procedures. The mini-screw system helps stabilize the construct and prevents pain associated with micro-motion, this is accomplished by acting as a scaffold to allow increased strength on the peripheral as well as centrally located construct thereby limiting any motion that may be felt by the patient and perceived as uncomfortable. Another advantage of the mini-screw system is that

there has been decreased settling of the construct at the bone-PMMA interface where little if any bony ingrowth has been found to occur. The inherent poor adherence of PMMA to the bony interface has been documented in the past and substantiated by recent evidence at our institution [33]. By placing the mini-screws within the inner table the construct is allowed extra support at the bone-PMMA interface limiting the settling that would naturally occur. Throughout our experience this issue has been resolved and excellent outcomes have been achieved. To complement the above indications there is also no need to use external fixation (i.e. burr hole covers, etc.) which can be perceived as an unfavorable cosmetic appearance by the patient when used on areas where the skin is thin or not covered by the hairline. We have also found that in patients who are older, undergoing radiation therapy, or have had multiple surgeries that there is a risk of skin breakdown and erosion from the surface attachments, this risk can be eliminated with the use of our technique. Finally, by adding antibiotics directly into the PMMA we have had excellent results in limiting postoperative infection that can occur when adding an alloplastic material within the cranial vault. This has been especially valuable in patients with post-tumor reconstruction who will need radiation treatment and those patients undergoing multiple procedures; both of which groups are at the highest risk for infection post-operatively documented in a previous study at our institution [22]. From the onset of the use of PMMA impregnated with antibiotics the incidence of post-operative infections has been dramatically reduced.

Conclusions:

The use of PMMA for cranioplasty has many advantages over other alloplastic materials [30,32]. Despite its widespread use there are still associated problems that may cause significant morbidity to this patient population. At our institution we have seen all of

the complications listed and sought to find a better approach to limit the associated morbidity. Through the technique described in this paper we have shown excellent outcomes and decreased the morbidity associated with the use of PMMA in cranial reconstruction. While accomplishing our goal of improved results the described technique is also easily implemented, taking little extra operative time, and cost effective considering the decreased postoperative morbidity that can be achieved and ability to apply the mini-screw system solely with no need for extra fixation devices.

Figure 1

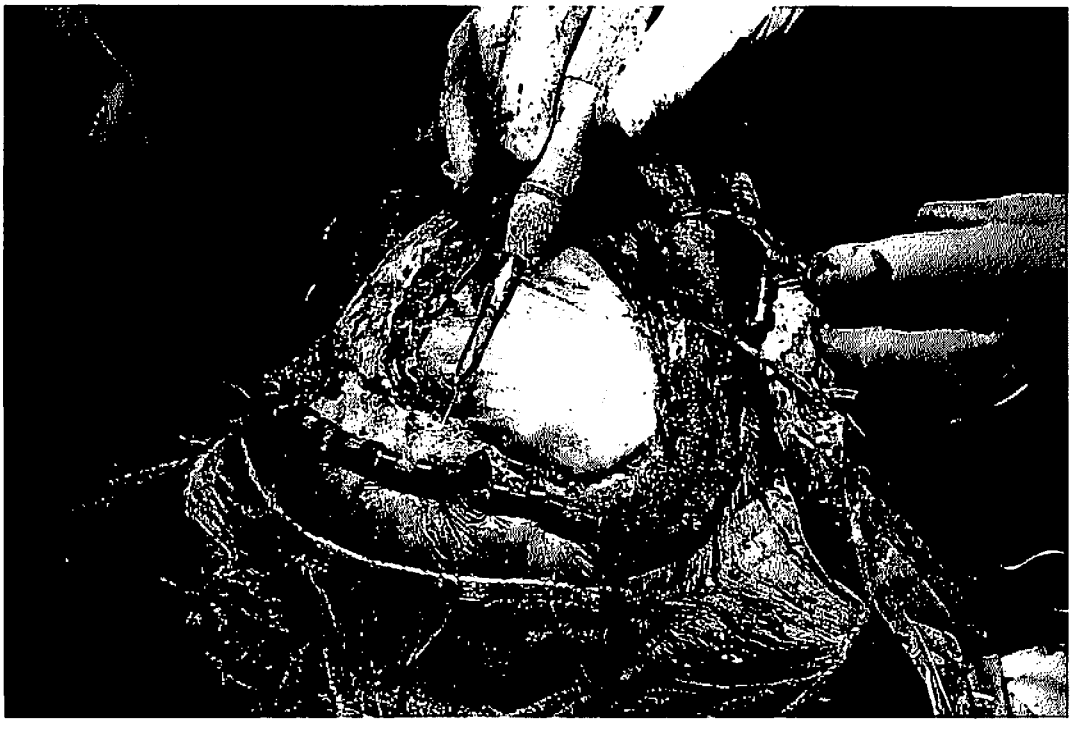


Figure 2

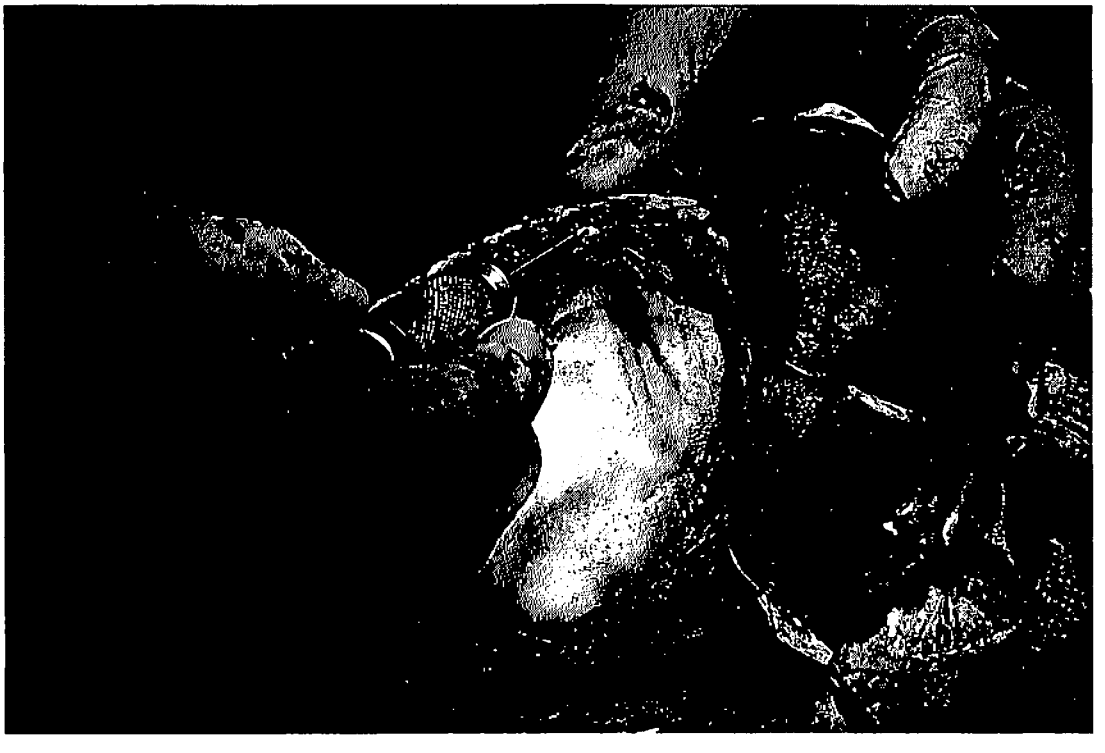


Figure 3

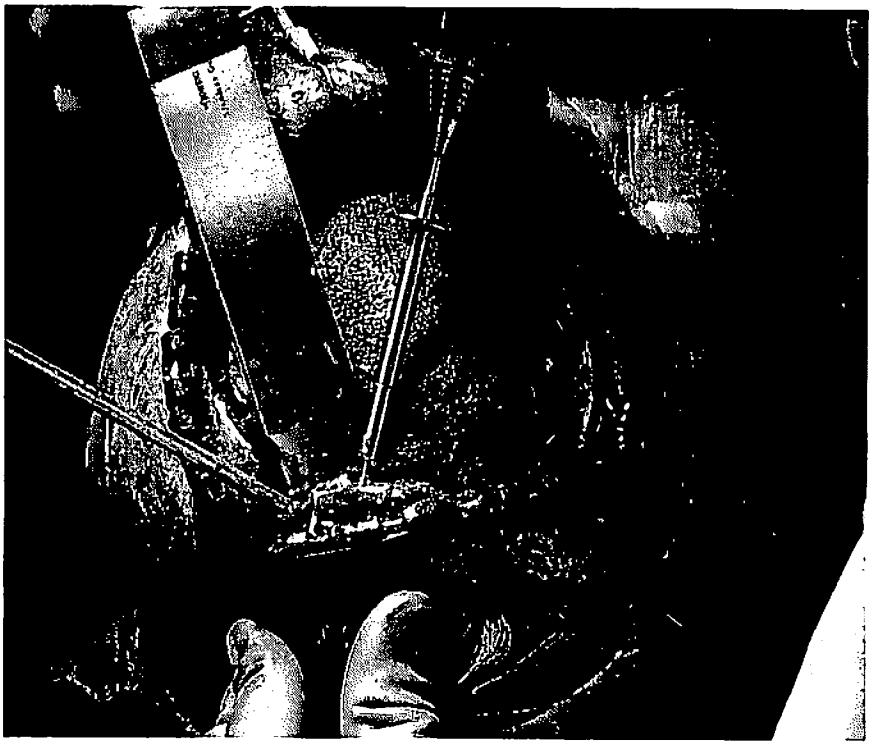


Figure 4

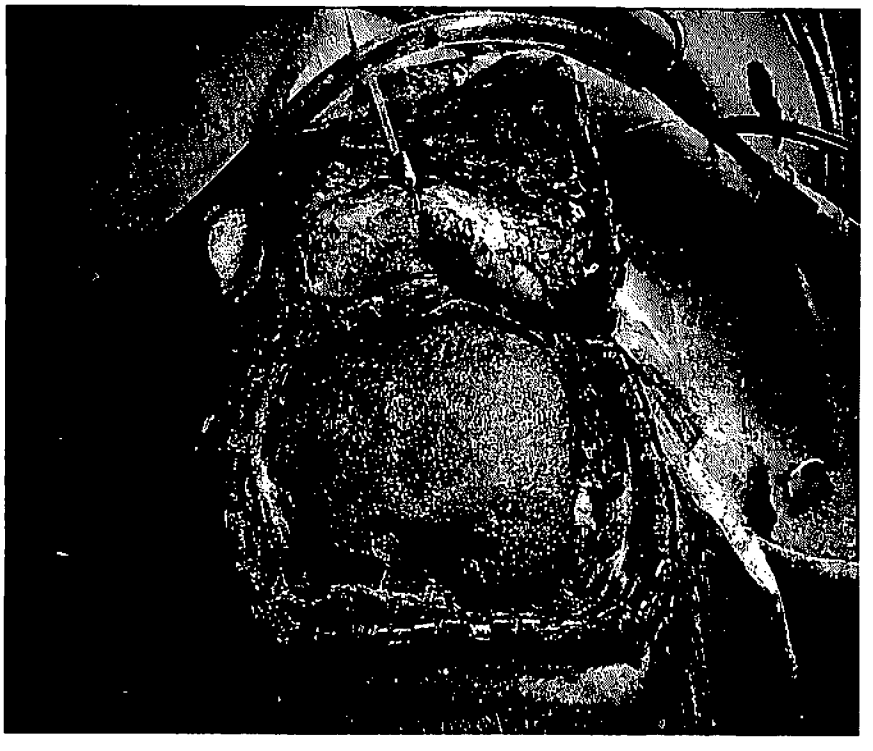


Figure 5

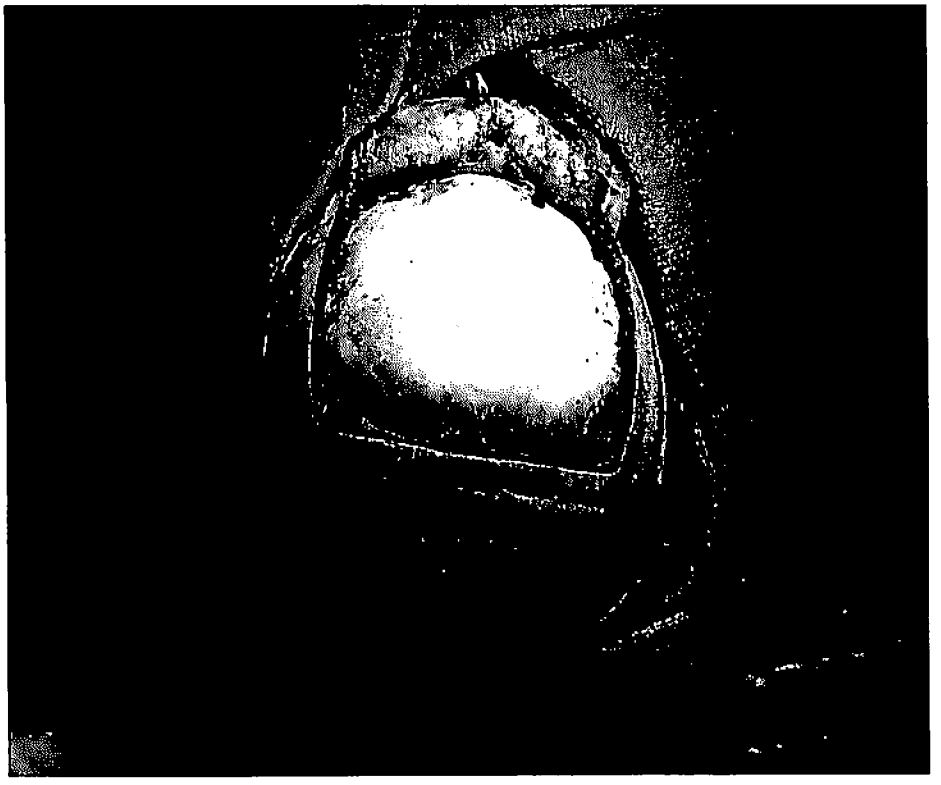
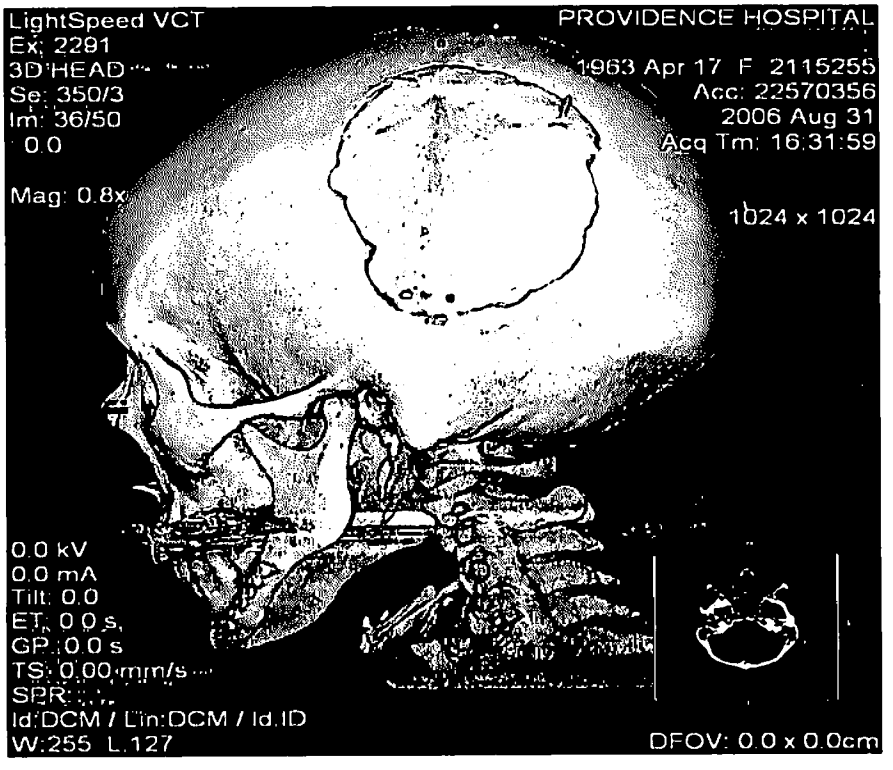


Figure 6



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PSEUDO-SUBARACHNOID HEMORRHAGE:
Case report and literature review

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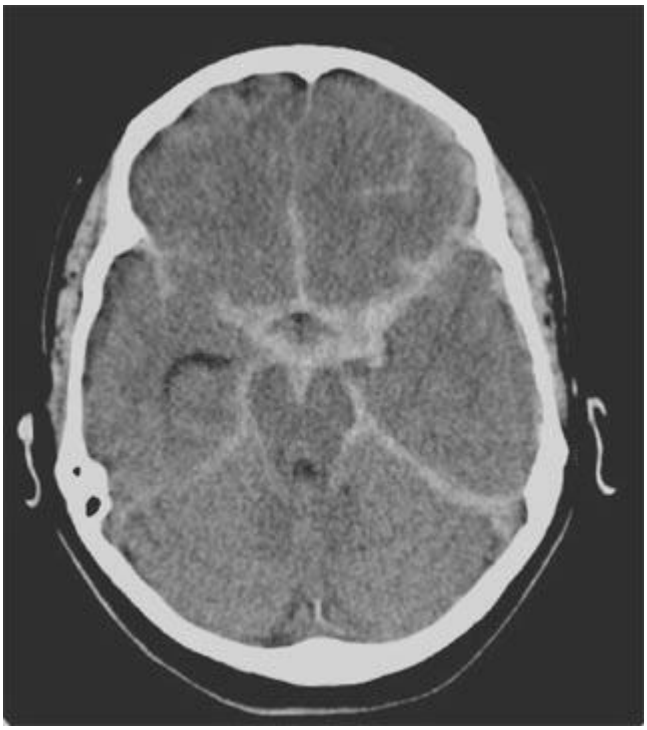
The work-up of subarachnoid hemorrhage entails finding, or ruling out, an aneurysm. Rarely the subarachnoid hemorrhage seen on imaging, usually computed tomography, does not exist at all but is an imaging artifact created by a myriad of other phenomenon. This must be kept in mind by the astute neurosurgeon during the diagnostic stages of a subarachnoid hemorrhage work-up. The case below is illustrative of this point.

CASE REPORT

A 36 year old right handed Hispanic man, employed as a mechanic, presented to the Emergency Department one morning after awakening from sleep with the worst headache of his life. He experienced nausea and vomiting immediately upon waking. He noticed that his neck pain, which began the previous night, was now much worse.

This gentleman did not have any significant past medical history nor family history. He was born in Mexico and moved to the United States at age 5. He occasionally drinks but does not smoke nor use drugs. On examination this gentleman was oriented, although lethargic, and had nuchal rigidity along with photophobia . He was not found to have any focal neurological deficits on examination. A non-contrast head CT showed what was presumed to be a diffuse subarachnoid hemorrhage.



The patient was referred to neurosurgery for admission and work-up for his CT findings. A CT-Angiogram was performed on day one of his admission which did not show any signs of aneurysm. The patient was placed on SAH precautions and a 4-vessel cerebral angiogram was performed at the end of one week which was also negative. The patient was discharged home with a residual headache after follow up head CT's showed diminishing subarachnoid hemorrhage.

One month later the patient returned to the emergency department with increased headache and neck pain. Again a head CT showed subarachnoid hemorrhage and a cerebral angiogram was performed which was negative for signs of aneurysm. The patient was observed in the ICU for one week and discharged with minimal improvement in his symptoms. He was scheduled for a repeat angiogram in six months.

Three weeks after his last admission he returned to the hospital after having a seizure and also had fever, headache, photophobia and nausea. A head CT was obtained which showed increased subarachnoid hemorrhage and cerebral edema. The patient had a CT-Angiogram which was again negative for any aneurysm. A ventriculostomy was inserted for signs of hydrocephalus and increasing lethargy in the patient. The fluid was noted to be clear, non-bloody and without xanthochromia grossly The cerebral spinal fluid was sent for the standard studies along with India ink stains, Cystercercosis antigen, Cryptococcal antigens, Coccidioidomycosis antigens, HSV, Mycobacterium cultures and bacterial antigen panel. The CSF profile showed a mildly decreased glucose with increased protein and a normal white count. A centrifuge spin also did not show any xanthochromia. An infectious disease consult was obtained after the *Coccidioidomycosis immitis* Ag returned positive.

The patient ultimately received a PICC line and was treated with six weeks of intravenous antibiotics and a very short course of intrathecal antibiotics. He was discharged home after two weeks of hospitalization and follow-up visit in clinic showed no return of symptoms after completion of his antibiotic treatment.

This patient's initial presentation was quite typical for an aneurysmal subarachnoid hemorrhage. However, the differential for enhancement of the subarachnoid spaces must also be considered in patients without signs of a causative aneurysm. Earlier recognition of the significance of the imaging findings may have prevented multiple procedures and their associated risks and helped establish a diagnosis much earlier in his disease course.

LITERATURE REVIEW

Subarachnoid hemorrhages are found to be cryptogenic in 15% of cases. Accordingly diagnostic strategies must be considered which do not neglect to consider less obvious conditions. In a study by Andaluz and Zacarello (2008) 12% of 719 patients admitted for subarachnoid hemorrhages had negative angiograms. 16% of these negative

angiogram patients had other non-aneurysm related sources for their presumed hemorrhage.

The literature is sparsely populated with studies on etiology and prevalence of pseudo-subarachnoid hemorrhages. This is a radiographical phenomenon that is encountered mostly by neurosurgeons and neurologists, and their neuroradiology colleagues. Increased attenuation of the basal cisterns is the characteristic finding of a subarachnoid hemorrhage. The differential for this radiographic finding include pyogenic basal meningitis, intravenous contrast material leaked into the subarachnoid space, and malignant cerebral edema. As subarachnoid enhancing patterns are overwhelmingly aneurysmal in nature, the yield of research into this phenomenon must be retrospective by necessity. Largely these are case reports of single patients or limited small series. Avrahami et al. reported in a small case series that several non-traumatic comatose patients showed the CT findings of subarachnoid hemorrhage without evidence of aneurysm. Basal meningitis has also been found to produce attenuation of the basal cisterns (Prockop et al.). This is felt to be due to the breakdown of the blood brain barrier and subsequent leakage of protinaceous material into the adjacent subarachnoid space. In severe cases of meningitis the CSF protein concentrations are high enough to produce basal cistern enhancement. This is an ominous sign in a patient with suspected meningitis as in most case reports the patient with this finding dies from the disease process (Al-Yamany et al.). Meningitis this severe is normally associated with diffuse cerebral edema as well. Erly et al. reported two cases of Coccidomycosis meningitis with a complicating vasculitis and pseudo-subarachnoid hemorrhage, one of which became an actual subarachnoid hemorrhage. These patients presented with headache, nausea, vomiting, lethargy and after lumber puncture were identified as having cerebral coccidiomycosis. Both of these patients had attenuation of their basal cisterns. One of them developed a sudden worsening in his symptoms and repeat imaging found a basilar aneurysm where one had previously been excluded. The aneurysm had ruptured and the patient soon died. Both patients had angiograms performed previously which showed evidence of cerebral vasculitis. Vascular complications of *Coccidioides immitis* are reported to occur even as the CSF profile continues to improve.

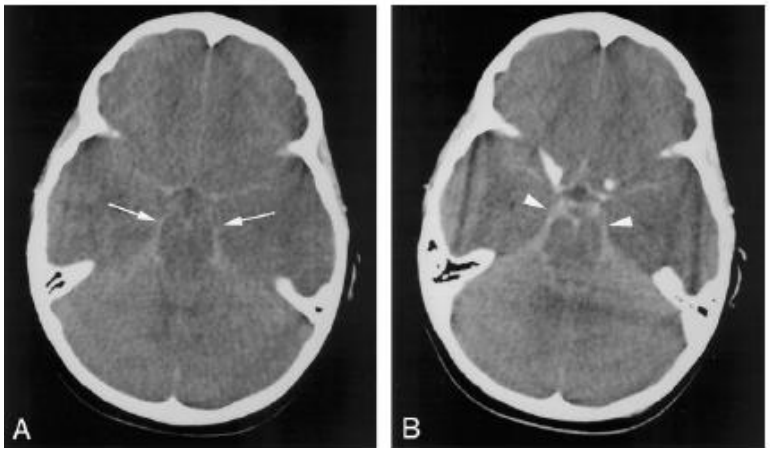
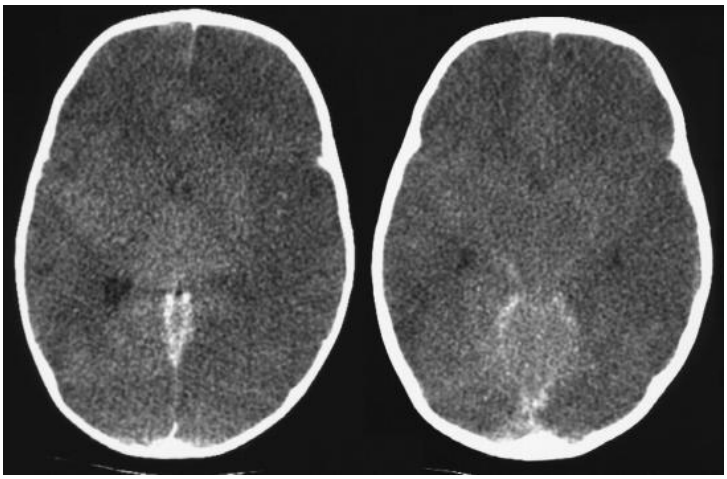


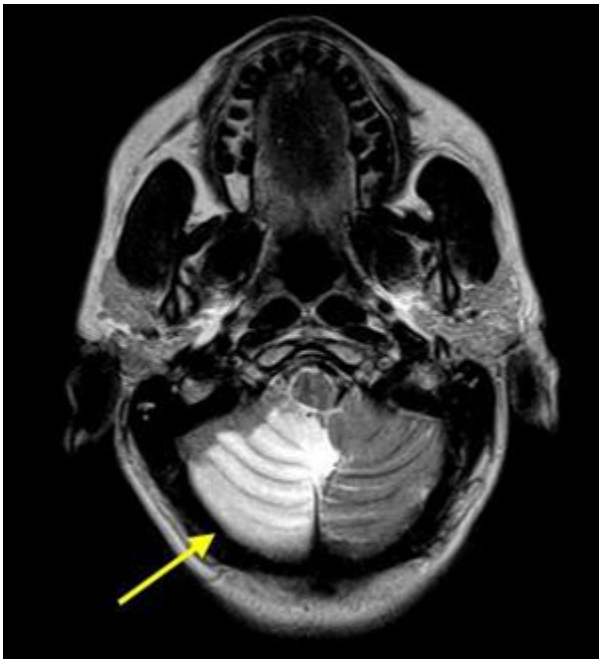
FIG 1. Case 1. Axial nonenhanced CT images through the basal cisterns.
A, Image obtained before contrast enhancement reveals abnormally increased attenuation within the basal cisterns (*arrows*).
B, The basal cisterns (*arrowheads*) are enhancing after the intravenous administration of contrast material.

The most common cause of basal meningitis is tuberculous meningitis and it is not surprising that case reports of pseudo-subarachnoid hemorrhage exist with this disease. Lan et al. looked at 70 patients with tubercular meningitis over a five year period. Twenty-eight patients had infarcts related to their meningitis, the majority having multiple infarcts. Of these patients five had a suspicion of subarachnoid hemorrhage based on CT attenuation of basal cisterns. None proved to have an aneurysm.

Trauma patients have also been found to have this radiographic finding (Barton et al.) During the acute phases of cerebral injury vasogenic edema predominates and this is normally cleared by CSF reabsorption. The narrowing of the subarachnoid spaces displace CSF and the cisterns are replaced with engorged pial structures, meninges and blood vessels. This creates a hyperdense collection of structures in the basal cisterns as hypodense CSF is displaced. The basal cisterns then attenuate abnormally.



Infarctions can also produce acute focal cerebral edema which can mimic a subarachnoid hemorrhage. The pathophysiology is the same as for diffuse cerebral edema and produces an asymmetrical distribution of the basal cistern attenuation, more similar to an aneursymal rupture. Lee et al. reported a case of a PICA infarct in a patient who presented with severe headache. Initial CT showed hydrocephalus and what appeared to be a subarachnoid hemorrhage. A ventriculostomy was performed which did not drain any bloody CSF. Subsequent MRI showed an acute PICA infarction.



Intracranial hypotension should also be included in the differential diagnosis of pseudo-subarachnoid hemorrhage. Increased attenuation in both the basal cisterns , along the falx, and along the sylvian fissure are the key imaging findings in this condition. Schievink found that 4 out of 40 patients who had a spinal CSF leak showed pseudo-subarachnoid hemorrhage on CT. These patients all underwent CSF removal via a lumbar drain or lumbar puncture and experienced severe positional headaches afterwards. One correlation seen on CT with these particular cases were small subdural fluid collections related to the sudden drop of intracranial pressure and the downward displacement of the brain. MRI proved to be useful in demonstrating the deformity of the optic chiasm and cerebellar tonsillar ectopia consistent with acute intracranial hypotension.

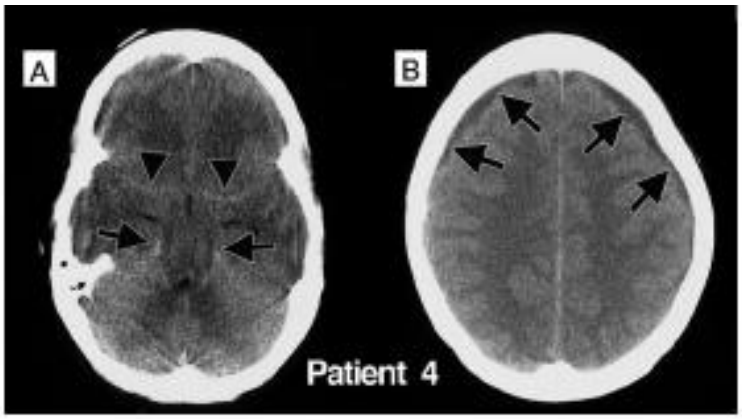


Figure 1. Nonenhanced CT of the brain shows increased attenuation along the tentorium cerebelli (A, arrows) and in the basilar cisterns/sylvian fissures (A, arrowheads), in addition to subdural fluid collections (B, arrows).

Another causative agent is post-myelogram pseudo-subarachnoid hemorrhages (Given et al.). These appear occasionally and usually after patients complain on severe headache post-procedure a CT is preformed which may show this imaging pattern. The contrast material has pooled in the basal vessels and may even show a lateralization that corresponds to the position the patient was in during the procedure.

Only recently have studies shown neuropathological correlation with the imaging findings. Opeskin and Silberstein in 1998 showed that in five patients (the largest imaging to pathology comparison to date) with pseudo-subarachnoid hemorrhage, all five cases demonstrated increased attenuation in the basal cisterns and autopsy findings which showed histologic evidence of congested and dilated subarachnoid and pial vessels. These patients also all showed signs of cerebral edema. This is consistent with the above listed differential diagnoses that produce not extravascular hemorrhage but intravascular congestion causing this phenomenon.

Identification of a pseudo-subarachnoid hemorrhage should be contemplated from the early stages in a patient that does not have signs of an aneursymal rupture. One tool to use is the Housfield units (HU) of the CT scan. Normal subarachnoid hemorrhage clot ranges from 60-70 HU's while case reports of pseudo subarachnoid hemorrhage range from 29-50 (Fujita et al.). Further, it has been suggested to follow up non-contrast studies with a contrasted study to differentiate between engorged vessels in the subarachnoid space and a blood clot occupying the same area (Opeskin et al). Once an aneurysm has been ruled out as a cause of a possible subarachnoid hemorrhage the differential must be expanded to exclude potentially serious causes of pseudo-subarachnoid hemorrhages.

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Primary Intraosseous Meningioma

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Introduction

Primary extradural meningiomas are rare lesions, accounting for less than 2% of all meningiomas (11). They may arise in locations such as the skin, nasopharynx, or neck. "Primary intraosseous meningioma" is a term used to describe a subset of extradural meningiomas that arise in bone (19). This type of meningioma represents approximately two thirds of all extradural meningiomas (11). The vast majority of intraosseous meningiomas arise in cranial bones, although a few cases in which the tumor originated in the mandible have been reported (12). The clinical, radiological and pathological findings are discussed, and the relevant literature is reviewed.

Case Report

A 17-year-old female was referred for neurosurgical consultation due to a mass in the high midline vertex area. She has noticed the area of concern for the last couple of months. The mass has not increased or decreased in size. The patient had no prior medical problems or surgical history, and no history of head trauma. She showed no neurological deficits on examination. The mass was not tender or mobile and measured approximately 6-7 cm in diameter. No pathological changes in the overlying skin were detected.

Initial workup consisted of a skull radiograph revealing hyperostosis involving the posterior parietal region (Fig. 1). A computed tomography (CT) scan without contrast revealed a mixed lytic and blastic expansile cortical lesion involving the high right and left parietal bones crossing the sagittal suture (Fig. 2). Magnetic resonance (MR) imaging with and without gadolinium enhancement showed calvarial expansion over the posterior vertex involving the right parietal greater than the left parietal skull. Signal intensity within the bony components showed low T1 and subtly bright T2. The apparent extradural lesion measuring at least 6 cm in craniocaudal dimension appears to be centered within the marrow cavity and demonstrates both extracranial and intracranial, extradural enhancing soft-tissue mass. The underlying brain parenchyma is entirely normal (Fig. 3). CT computer reconstruction shows the calvarial mass measuring approximately 7 cm in diameter (Fig. 4). Radiographic differential diagnosis included aggressive primary sarcoma of bone, either fibrous, osteogenic or Ewing's.

The patient underwent elective craniectomy with excision of mass via a bicoronal occipital incision and exposure. After scalp reflection, a nondescript expansion of calvarium measuring approximately 7 cm was noted. The skull was cut 2 cm away from the tumor border providing a 10 x 12 cm pathologic specimen. No part of the lesion was

soft and was not adherent to the dura. A large titanium mesh was cut to size for calvarial reconstruction.

Gross examination by the pathologist revealed a 10 x 12 cm piece of hard skull. The concave surface had a centrally located area that was roughened and variegated. The overall dimension was 7 x 5.2 cm with a central 4.2 x 4.3 cm area of dark tan discoloration with a few fibrous threads radiating through approximately fifty percent of the area. This darker area was surrounded by a rim of grey-white discoloration. The permanent sections of the specimen after decalcification showed combined meningothelial and fibroblastic patterns (Fig. 5). Immunohistochemistry revealed patchy membranous and cytoplasmic staining for epithelial membrane antigen (EMA). MIB-1 immunohistochemical stain shows scattered positive nuclei comprising less than 5% of lesional cells. Final histopathological diagnosis was primary intraosseous meningioma.

The patient experienced no difficulties in the postoperative period. A noncontrasted head CT with reconstructions obtained three weeks after surgery showed post resection calvarial defect with mesh in place. Surgical margins did not show evidence of permeative disease (Fig. 6). Three months later, patient underwent cranioplasty with a Stryker© custom implant. Follow up imaging in one year will consist of MR imaging of the brain with and without gadolinium contrast.

Nomenclature and Classification

Extradural meningiomas that arise in the skull have been referred to as calvarial, intradiploic, and intraosseous (4). The term "primary extradural meningioma" differentiates tumors that arise separately from the dura from those that originate in the dura but have an extracranial extension. This name also differentiates these tumors from extracranial meningiomas that represent distant metastases from primary intradural meningiomas (8).

The following summarizes the classification scheme for primary extradural meningiomas developed by Lang and colleagues (11): Tumors that are purely extracalvarial are Type I, purely calvarial tumors are Type II, and calvarial tumors with extracalvarial extension are Type III. Each category is further divided into convexity (C) or skull base (B) subtypes based on their anatomic location. Thus, intraosseous meningiomas could be considered Type II or III primary extradural meningiomas based on whether extracalvarial extension is observed.

Clinical Presentation

Extradural meningiomas, including intraosseous meningiomas, are reported to occur with the same frequency in each sex or with a slight female predominance, unlike intradural meningiomas, which occur twice as frequently in women as men (20). Like intradural meningiomas, extradural meningiomas predominantly occur later in life, with a median patient age at diagnosis in the fifth decade. These tumors have a bimodal

incidence peak in patients, with one peak in the second decade, and a second peak during the fifth through seventh decades of life (11).

The convexity and the skull base are the two primary locations for intraosseous meningiomas. Like many intracranial lesions, the clinical presentation and resulting differential diagnosis depend largely on the size and location of the lesion (8).

Radiographic Appearance

The tumors are typically either the osteoblastic or osteolytic subtype, although mixed versions have been reported. Like intradural meningiomas, osteoblastic intraosseous meningiomas may induce hyperostosis (5, 7). In fact, the majority of intraosseous meningiomas are of this osteoblastic subtype (1, 2). Skull radiographs can detect abnormalities in 30 to 60% of cases of intraosseous meningioma, including hyperostosis, irregular foci of calcification, and atypical vascular markings (20). Computed tomography with bone windows shows a focally thickened, hyperdense lesion expanding the calvaria. The tumor is usually hyperdense on a nonenhanced CT scan, ranging from 65 to 85 Houndsfield units, and enhances densely after contrast administration, similarly to intradural meningiomas (3). The differential diagnosis for an osteoblastic or sclerotic lesion includes osteoma, intracranial meningioma with an overlying hyperostosis (with or without true bone involvement), metastatic cancer, as well as, endocrine and metabolic derangements such as hyperparathyroidism, hypervitaminosis A, and hypervitaminosis D (5)

More rarely, primary intraosseous meningioma may present as an osteolytic lesion (1, 20). The lesion may appear hypodense on plain radiographs, similar to other primary lytic calvarial lesions. Rather than the more common CT findings of thickened sclerotic bone, osteolytic lesions typically cause thinning, expansion, and interruption of the inner and outer cortical layers of the skull (1). The lesions are similarly hyperdense compared with brain on a nonenhanced CT scan and enhance homogenously after contrast administration (3, 12). The differential diagnosis for an osteolytic lesion includes chondroma, chondrosarcoma, giant-cell tumor, hemangioma, epidermoid cyst, osteogenic sarcoma, myeloma, eosinophilic granuloma, metastatic cancer, or fibrous dysplasia (5).

Magnetic resonance imaging findings for both osteoblastic and osteolytic subtypes of intraosseous meningiomas are similar to those for intradural lesions and allow better delineation of tumors that have extracalvarial soft-tissue extension. The tumors are typically hypointense on T1-weighted images and hyperintense on T2-weighted images. Prominent homogenous enhancement after gadolinium (Gd) administration is typical. These tumors do not usually exhibit the “dural tail” often found with intradural meningiomas, but Gd enhancement of the underlying dura may be noted. This dural enhancement could be secondary to dural irritation or tumor invasion (2)

Histopathology

Intraoperative pathological examination of an intraosseous meningioma may be limited, especially in cases where hyperostosis may be present, due to presence of bone throughout the specimen (8). In these cases, decalcification of the specimen is required prior to histopathological assessment. Microscopic pathology often reveals findings pathognomonic for intradural meningiomas, including psammoma bodies and eosinophilic tumor cells with indistinct borders grouped in clusters and whorls (4, 6). The nuclei are typically oval and regular, and nuclear pseudoinclusions may be observed. The bone may appear normal, with replacement of the marrow by fat, fibrosis, and tumor cells. Although the reported histopathology commonly reveals a meningotheliomatous meningioma, other histological types including microcystic, psammomatous, transitional, choroid, atypical, malignant, and fibroblastic intraosseous meningiomas have been reported (8).

Although intraosseous meningiomas are largely described as slow-growing, histologically benign lesions, atypical and malignant histological subtypes have been frequently reported (11). Recent studies indicate that intraosseous meningiomas have a higher incidence of malignant features than intradural meningiomas (9, 17). These malignant features may be indicated by microscopic tumor invasion of underlying dura or overlying soft tissue structures (9). Osteolytic lesions, although a more rare form of intraosseous meningioma, have a higher likelihood of atypical or malignant features compared with osteoblastic tumors.

Conclusion

Intraosseous meningiomas are rare lesions that originate in the skull and represent the most common type of extradural meningioma. The lesions are often asymptomatic, but can cause proptosis and neurological symptoms depending on their size and location. Radiographic and clinical presentations generate diagnostic suspicion that may assist with preoperative planning. The majority of these tumors cause hyperostosis that may mimic fibrous dysplasia. Although most are benign, intraosseous meningiomas are more likely to be malignant than their intradural counterparts. The osteolytic subtype of intraosseous meningiomas are more likely to be malignant than the osteoblastic subtype. Intraosseous meningiomas should be considered in the differential diagnosis for patients presenting with osteoblastic or osteolytic skull lesions.

The treatment of choice is resection, which is potentially curative. Using three-dimensional neuronavigation and operative planning, tumor resection and cranioplasty can be performed simultaneously. Tumors that cannot be completely resected may require adjuvant therapy, which may include radiation therapy, chemotherapy, or bisphosphonate therapy. However, further work is required to elucidate any optimal adjuvant therapy regimens.

Appendix

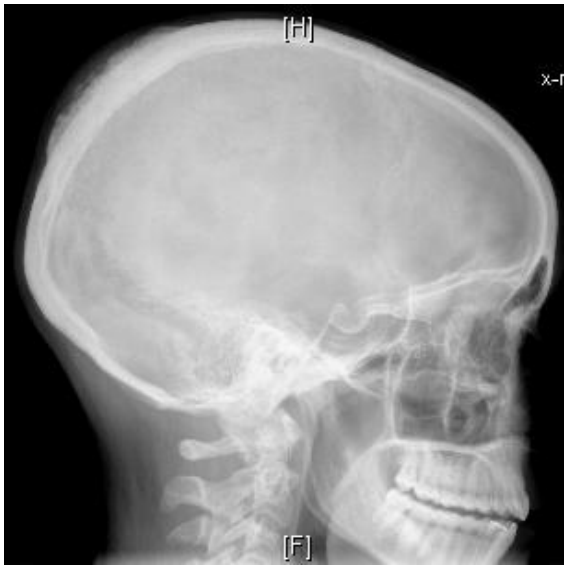

Figure 1

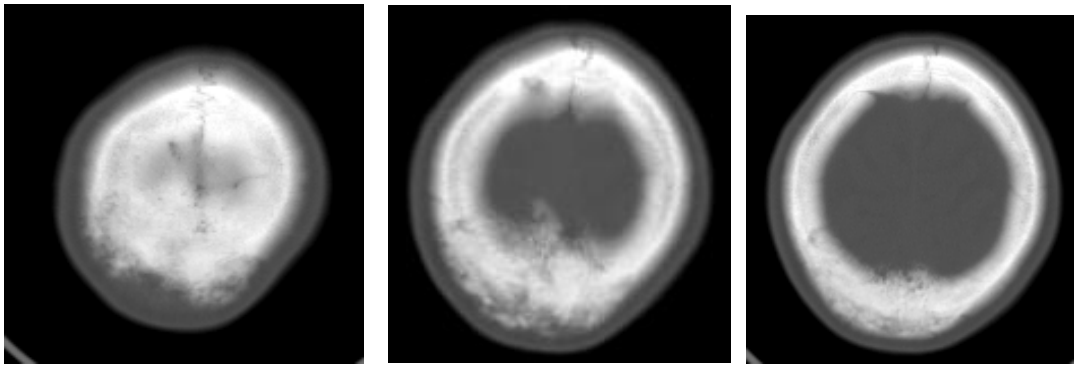

Figure 2

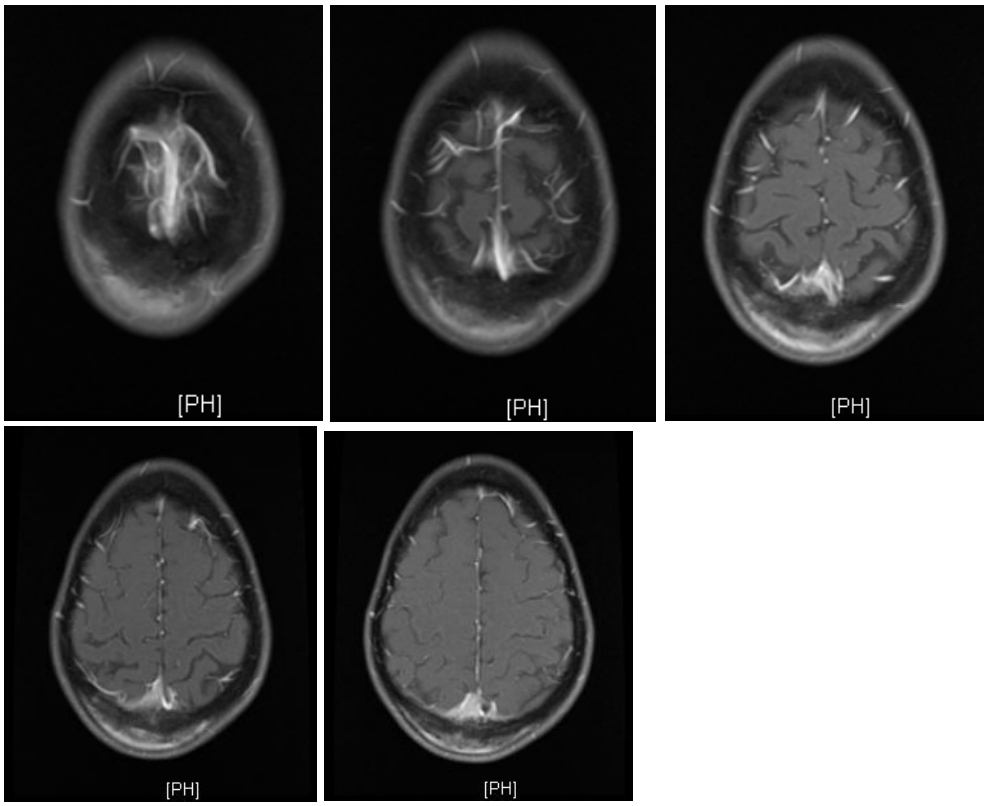

Figure 3

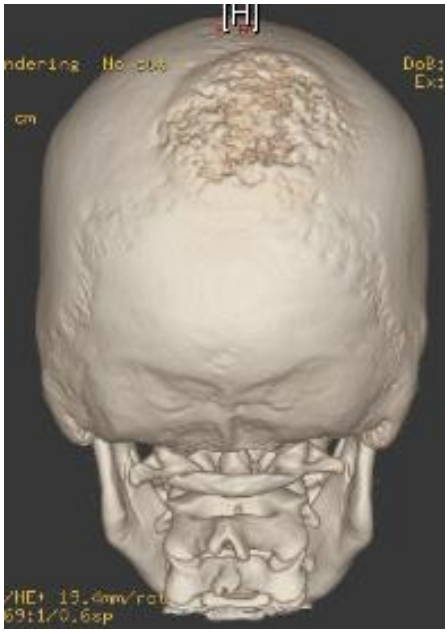

Figure 4

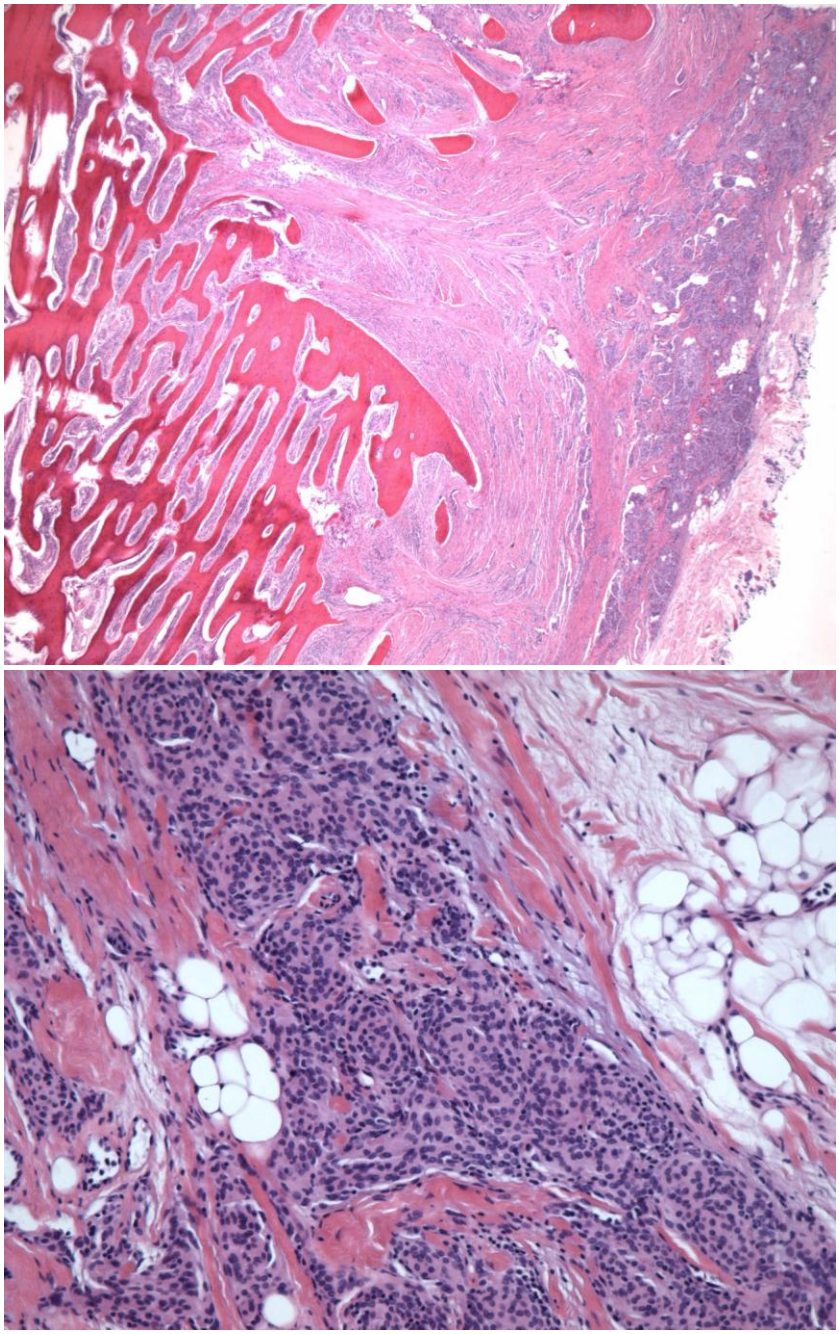

Figure 5

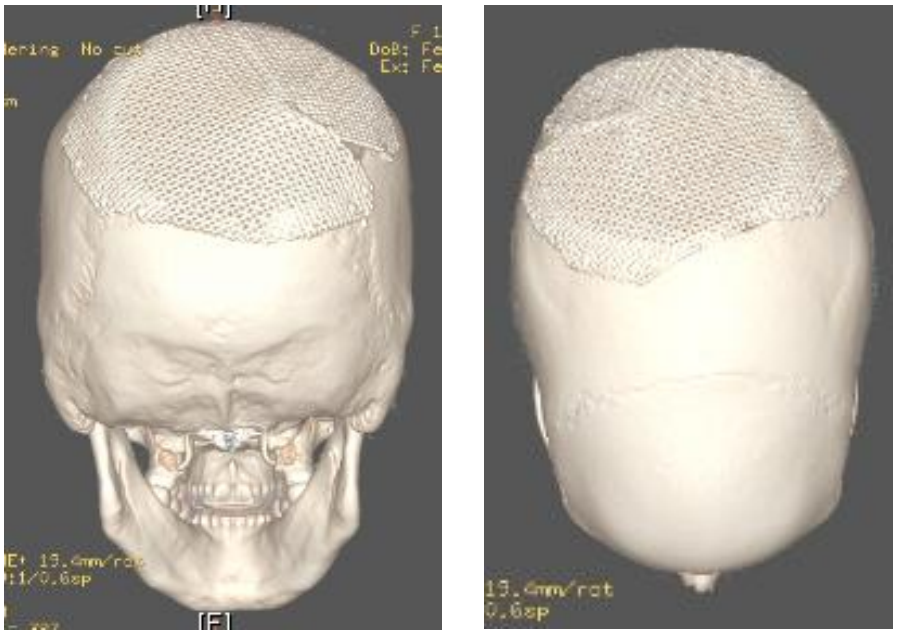

Figure 6

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Interbody Fusion With Antibiotic-Impregnated Polymethylmethacrylate for the Treatment of Discitis and Vertebral Osteomyelitis

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Key Words: Interbody Fusion, Polymethylmethacrylate, Discitis, Osteomyelitis

Abstract

Object: The treatment of discitis and vertebral osteomyelitis (DVO) can at times prove to be challenging clinical scenario. Therapuetic options range from conservative management including bracing and antibiotics to aggressive debridement and primary reconstruction. The use of antibiotic-impregnated polymethymethacrylate (AI-PMMA) has long been used in the orthopedic community for the treatment of osteomyelitis seen outside of the spine. The idea of a biomechanical device that offers immediate stability and the local delivery of antibiotics represents an appealing option in the setting of DVO. We aim to evaluate the safety and feasibility of this novel surgical approach for treatment of discitis and vertebral osteomyelitis. *Methods:* The authors retrospectively reviewed 23 consecutive patients requiring surgical debridement and spinal reconstruction for DVO. Analysis included preoperative risk factors, clinical presentation, surgical procedure, clinical and radiographic outcomes. *Results:* Twenty-three patients (mean age 59±13 yrs) were reviewed at a minimum of 53 days (mean 319 days) postoperatively. Reasons for surgery included one or more of the following: neurologic deficit, mechanical instability, failure of medical management, failure to make a diagnosis, and intractable pain. All patients underwent aggressive tissue debridement at the affected level, followed by a one or two level transforaminal lumbar interbody fusion (TLIF) with AI-PMMA and pedicle screw fixation. The AI-PMMA was prepared with 1 gram of vancomycin and 1.2 grams of tobramycin. At follow-up, all patients were alive and subjectively reported improvement compared to preoperative symptoms. Twenty-two patients (96%) clinically showed no evidence of infection and radiographically showed stable constructs. One patient (4%) was non-compliant with treatment and follow-up recommendations and remains positive for spinal and knee osteomyelitis as well as radiographic evidence of pseudoarthrosis. *Conclusions:* The surgical management of discitis and vertebral osteomyelitis remains

controversial. However, primary reconstruction with structural allograft and instrumentation is gaining wider acceptance. Several studies refute concerns that foreign material may lead to persistent infection and construct failure. Additionally, significant experience exists in orthopedics with AI-PMMA for the treatment of osteomyelitis. Our findings represent a natural extension and novel application of this knowledge. The use of AI-PMMA offers the advantage of immediate stability along with local delivery of antibiotics that has been applied successfully in other settings of osteomyelitis.

Introduction

Spinal infections in adults may affect the vertebral bodies, the intervertebral disks, the spinal canal, and the paravertebral tissues and structures. They remain a rare disease entity with an estimated incidence of 5-5.3 patients per million patients per year. [12]

However the number of pyogenic spinal infections has been increasing the past 15 years.[3] This increase could be a result of the improved diagnostic studies. [2,3] However, it may also be attributed to other factors such as advances in the surgical management of spinal conditions, longer survival of high-risk patients with comorbidities, and increasing use of immunomodulatory medications such as corticosteroids and biologic treatments. [1,2,3] Therefore it is imperative that physicians providing care for these patients attempt to improve the method in which spinal infections are treated.

The current primary treatment regimen involves 6-8 weeks of intravenous antibiotics for bacterial infections and up to 12 months for tuberculous infections. [4] However, in some patients antibiotic treatment is not successful and surgical intervention becomes necessary. The indications for surgical treatment of pyogenic infection of the spine include failure of antibiotic treatment, spinal instability, neurologic deficit, unknown organism or continued back pain. The percentage of patients that eventually require surgery ranges from 10-58%. [3, 5]

Surgical treatment of pyogenic spinal infections has evolved from simple debridement and decompression to the current trend of decompression and spinal fusion. The two primary surgical goals in the treatment of osteomyelitis are radical debridement of the infected area, decompression of the spinal cord and/or nerve roots, and restoration of stability. Spinal instrumentation has been

shown to be safe in the setting of pyogenic spinal infection.[6, 7] Increased resolution of the spinal infection has also been achieved by limiting motion at the disc space joint, which can be provided by a spinal fusion.

The orthopedic surgery literature reports the use of AI-PMMA in the treatment of osteomyelitis of long bones. The results show increased resolution of the osteomyelitis. [8,9,10,11] In vitro studies have also shown the presence of antibiotics in the surrounding tissues for up to six months.[12,13] This method has been used to treat patients with open fractures, chronic osteomyelitis, total joint arthroplasty, and soft-tissue infections of abdomen, rectum, and neck. [14,15]

The use of polymethylmethacrylate has also been mentioned in the spinal surgery literature. The use of PMMA in an interbody fusion as a valid option has been proven in the literature.[16,17] We propose a technique which is extrapolated from all of these ideas. It promotes resolution of the infection as well providing immediate stability of the spine.

Methods

Patient Population

After obtaining approval from our institutional review board, we performed a search of the hospital database and clinic records. Results revealed that between July 2003 and December 2005, 23 patients underwent interbody fusion with AI-PMMA for the treatment of discitis and vertenral osteomyelitis. In the present study we retrospectively review the surgical, clinical and radiographic outcomes of these 23 patients with discitis and vertebral osteomyelitis refractory to conservative treatment.

Pre-Operative Work-Up

All patients enrolled in this study had surgical treatment of pyogenic spinal infections. Indications for surgical intervention included failure of medical management, evidence of spinal instability, neurologic deficit, intractable back pain, and for culture/diagnosis. There were a total of 23 patients enrolled in the study. Patients were taken to the operating room for spinal decompression, evacuation of abscess/infection and spinal stabilization. The procedure is described below.

Surgical Procedure and Outcome

Each patient was taken to the operating room and after successful induction of general anesthesia, the patient was placed in the prone position on the Jackson table. Routine exposure of the spine from the posterior approach was achieved. Pedicle screws were inserted in the normal fashion followed by decompression of the spinal cord/thecal sac depending on the spinal level. Each screw was soaked in bacitracin prior to insertion. (FIGURE 1)

Subsequently, a transforaminal approach to the disc space was employed in the lumbar spine and an extracavitary transthoracic approach was utilized in the thoracic spine. Complete radical discectomy was subsequently performed. All grossly infected bone was also removed.

To reconstruct the disc height, antibiotic impregnated polymethylmethacrylate was utilized as a structural support in the removed disc space. The polymethylethacrylate was prepared in the normal fashion but to the powder (prior to mixing) 1 gram of Vancomycin and 1.2 grams of Tobramycin were added to the mixture. (FIGURE 2) The polymethylmethacrylate subsequently thickened. When appropriately thickened, the cement was formed into small spheres approximately 0.5 cm in diameter. (FIGURE 3) These are subsequently placed in the disc space.

As the cement continues to harden, care is taken to assure that there is no contact with the dura or surrounding nerve roots.

Subsequently, posterior lateral as well as facet fusion was performed in each case. This was followed by completion of the pedicle screw and rod construct. The surgical wound was subsequently closed in the normal sterile fashion.

All patients were subsequently treated with 6-12 weeks of intravenous antibiotics for the bacterial infections and 12 months for the tuberculous infections per the recommendation of infection disease physicians.

Operative data including operative time, blood loss, and complications were analyzed. Clinical complications were also analyzed. Outcomes were assessed by review follow-up medical records.

RESULTS

This study included 23 patients total; 15 male and 8 female. Patient ages ranged from 38 to 73 years (mean, 59 years). All patients had clinical and radiographic evidence of diskitis and osteomyelitis. Fourteen patients (61%) and evidence of epidural abscess.

Six (26%) patients had undergone previous spine surgery at the level of their current infection. Seven (30%) patients had diabetes mellitus, 6 (26%) patients were intravenous drug abusers, 8 (35%) patients had end-stage renal disease, 5 patients (22%) had previously been treated for other malignancies with chemotherapy, and one patient was on chronic steroids for lupus.

A preoperative clinical evaluation was performed by the attending surgeon prior to surgery. All patients had significant back pain, 7 patients had symptoms of radiculopathy, 6 patients had

clinical evidence of myelopathy. Ten patients had leg weakness prior to surgery and one patient was paralyzed prior to surgery. Three patients had bladder dysfunction and four patients had sensory deficits prior to surgery.

Leukocyte counts were determined in all patients, whereas erythrocyte sedimentation rate (ESR) was determined in 16 patients (69%). Only 7 patients (31%) of the patients had elevated leukocyte counts and the mean was 9.6. The mean ESR was found to be significantly elevated at 70.5. Twelve patients (52%) had CRP levels determined with a mean of 8.3. Only 5 patients (22%) had elevated temperature prior to surgery and the mean was 98.9 degrees Fahrenheit.

Cultures were taken during each operation. Seventeen of 23 patients (74%) had positive cultures. Eleven of the 17 patients with positive cultures were found to have *staph aureus* of which 8 were sensitive to methicillin. Two patients had *pseudomonas aeruginosa* and one patient had *mycobacterium tuberculosis*, *candida albicans, strep pyogenese,* and *E. Coli* each. Six patients (26%) were found to have negative cultures. All postoperative antibiotic choices were made by the infectious disease physician, with patients receiving a total of 6-12 weeks of postoperative antibiotics. The patient with TB was treated for 12 months postoperatively.

All surgeries were performed by two surgeons: a neurosurgeon and an orthopedic spine surgeon. Mean EBL was 915 cc; mean OR time was 210 minutes. Postoperative hospitalization ranged from 4-23 days, with a mean postoperative stay of 9.5 days.

Follow-up data was obtained from office charts and hospital records from subsequent admissions. Follow-up up data ranged from 1 to 24 months. Mean follow up time was 319.3 days. Twenty-two patients (96%) showed no signs of residual infection at their last follow up. One patient (4%) has residual infection in her left knee at 12 months follow-up. All patients have had postoperative x-rays and bony fusion is evident in every case. Three patients (13%) returned

to the operating room within one month following the initial surgery for wound washout. None were taken back to the operating room to revise the interbody cement or the instrumentation. Pre and post-operative X-rays and MRIs of a sample patent are presented in figure 3.

Five patients (22%) remain on narcotic drugs for back pain control. One patient has residual radiculopathy, and 7 of the 10 patients with initial leg weakness had improvement of their motor function. Two of the 3 patients that had bladder dysfunction preoperatively regained normal bladder control.

DISCUSSION

Osteomyelitis of the spine continues to be a challenge to successfully treat. Despite advanced diagnostic techniques and antibiotic treatment, diagnosis and optimum treatment is often delayed.[1819] The diagnosis of pyogenic vertebral osteomyelitis should be considered in patients who present with acute onset severe back pain associated with fever and other systemic symptoms. Suspicion should also be increased in patients of advanced age, with diabetes mellitus, who are immunocompromised, who are intravenous drug abusers, or who have undergone prior surgery or have an established focus of infection. As in previous studies, the diagnosis in our patients was often delayed at an average of 12 days. [20]

Most patients with pyogenic vertebral osteomyelitis can be treated conservatively with parenteral antibiotics, pain control and immobilization. [21, 22] However, surgery becomes necessary in a small subset of patients. Pathologic fracture of the vertebral body, intractable pain, failure of nonsurgical treatment, abscess formation, neurological deterioration and progressive deformity are all indications for surgical intervention. The surgical treatment of vertebral osteomyelitis should follow the principles of treatment for infection anywhere in the skeletal system and should include

debridement of the infected unhealthy material and stabilization of the involved segments. This has shown to be effective in both pyogenic and tuberculous vertebral osteomyelitis. [23, 24, 25] The goals of treatment were to eradicate the infection, restore neurologic function, restore spinal stability, and relieve pain.

Surgical debridement of the anterior column, which is necessary to completely treat discitis, results in further loss of stability and it requires anterior reconstruction and fusion. We present a method for providing immediately anterior column support combined with direct local application of antibiotics in the setting of vertebral osteomyelitis.

Our method accomplishes immediate debridement and stabilization, which are essential in the successful treatment of discitis and vertebral osteomyelitis. It also borrows techniques from the successful treatment of chronic osteomyelitis in other parts of the body. It has been well documented that the use of antibiotic impregnated polymethylmethacrylate has been useful in these patients with chronic osteomyelitis which is refractory to conservative medical treatment [26, 27, 28, 29]

In our study, we had six patients that had negative cultures and one patient grew tuberculosis. We realize that the antibiotic which was impregnated in the cement may not have been of great benefit in those cases. However, it did not appear to cause any harm. The wound cultures which were negative could have been a result of an old and granulated osteomyelitis or a result of the pre-operative intravenous antibiotics which some patients received.

Past studies support the use of supplemental posterior instrumentation in cases in which the stability of the spine is in question. [30, 31, 32, 33] By using a transforaminal approach to achieve 360 degree debridement, the spine is destabilized by our approach. Therefore, all patients received posterior stabilization.

Evaluating for an effective "cure" of vertebral osteomyelitis is difficult because any of these patients could have reoccurrence in the distant future because of their comorbidities. However, no patients in this series has had a recurrence on follow-up ranging from 3 to 36 months. There appears to be excellent incorporation of the PMMA and fusion has been achieved in all patients with no instrumentation failure.

Conclusion

This retrospective series demonstrates a novel technique in the treatment of vertebral osteomyelitis. The use of antibiotic impregnated PMMA and pedicle screw fixation following aggressive debridement is safe and effective. It provides immediate stabilization which we believe promotes faster recovery. As we continue to improve our treatment of vertebral osteomyelitis, further prospective studies will be needed.

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Figure 1 : Pedicle screw soaking in Bacitracin

Figure 2: PMMA as the Vancomycin and Gentamice is being added.

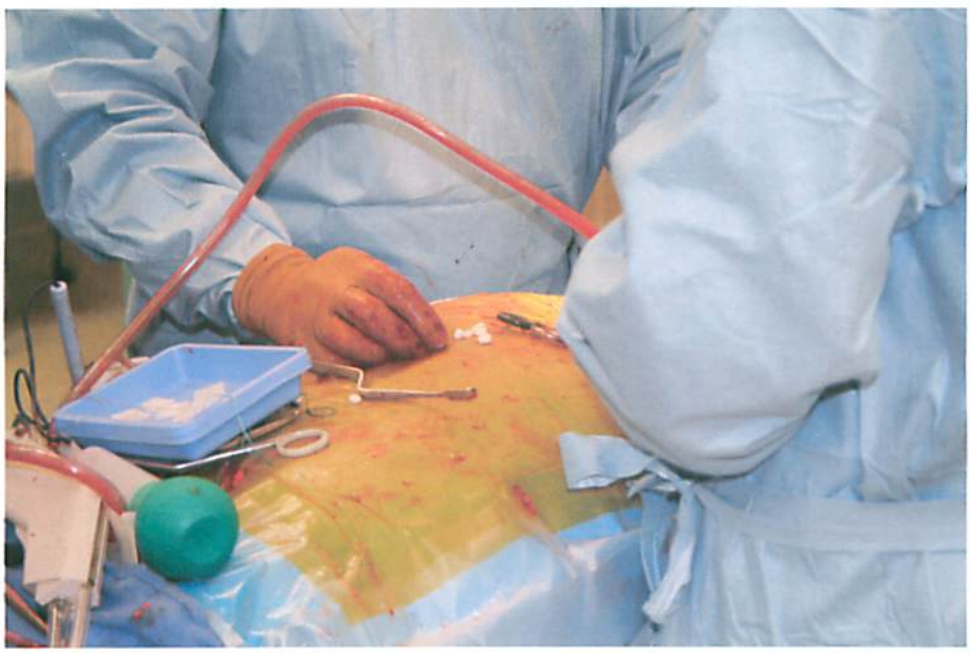

Figure 3: The PMMA has been formed into small 0.5cm diameter balls.

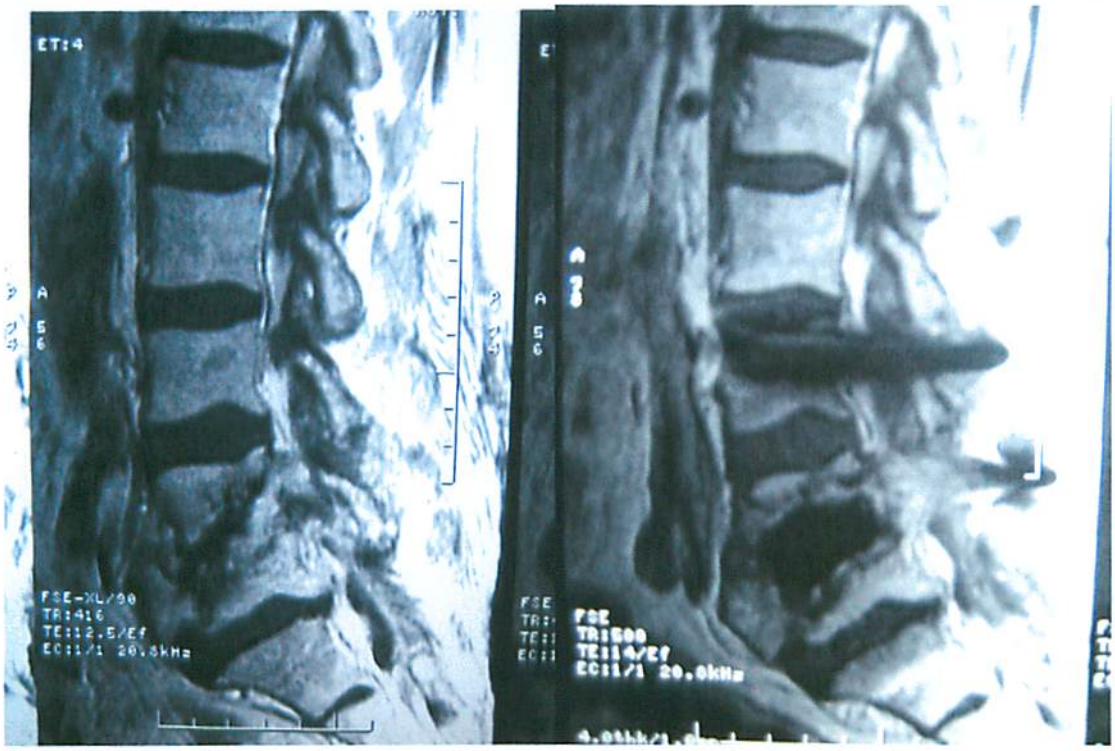

Figure 4: Pre and Postoperative MRI Demonstrating L4-L5 Discitis with Epidural Abscess. The Postoperative MRI *(right)* shows a bony fusion anterior to the disc space and AI-PMMA.

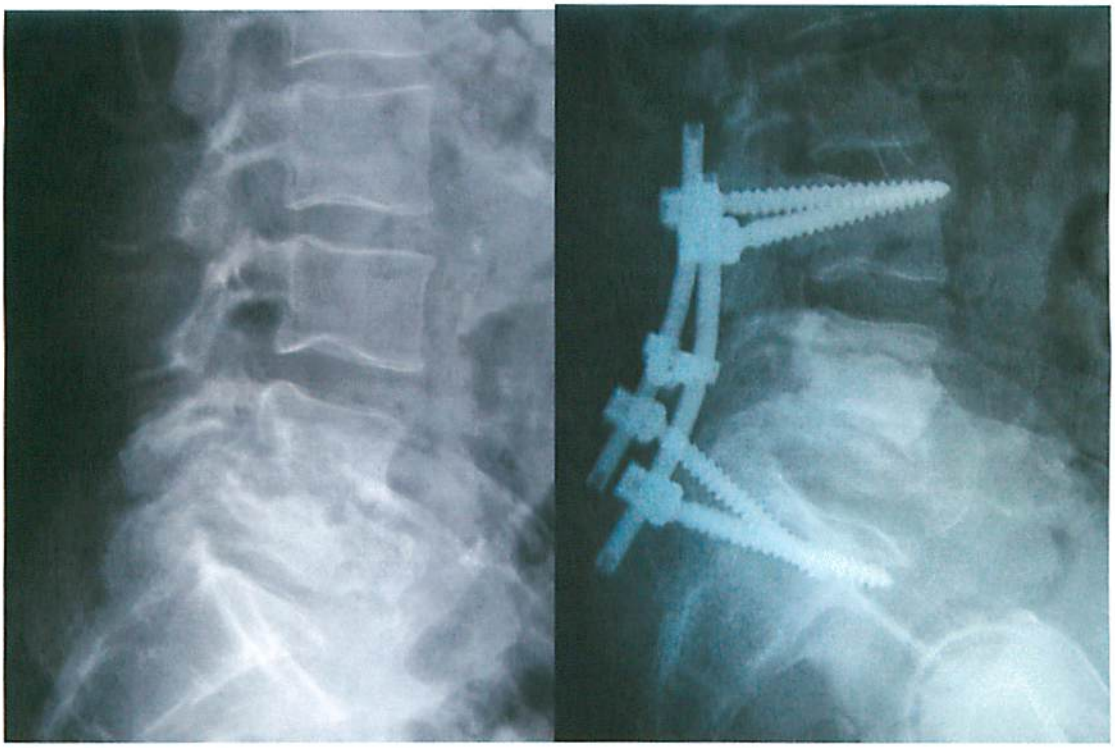

Figure 5: Pre and Post operative X-rays which confirm fusion. The AI-PMMA can be seen in L4-L5 disc space.

A substituted pyrimidine, KP447, reduces mortality and motor pathology in a rodent model of Huntington's disease.

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Abstract

Huntington's disease is a fatal, genetic disorder, characterized by striatal degeneration and extensive motor impairments. Although no effective treatment currently exists, administration of exogenous trophic factors, or drugs that amplify the effects of endogenous trophic factors, such as substituted pyrimidines, show considerable promise as potential therapies. The present study tested the efficacy of the substituted pyrimidine, KP447 [(2-amino-5-(4-chlorophenylthio)-4-(trans-4-hydroxycyclohexylamino) pyrimidine], for treating motor deficits in a quinolinic-acid model of Huntington's disease. Adult, male rats were given daily, oral administration of either vehicle (0.5% methylcellulose) or equivalent volumes of 0.1 mg/kg-, 1.0 mg/kg-, or 10 mg/kg-KP447, beginning three days prior to receiving bilateral intrastriatal injections of either phosphate-buffered saline or quinolinic acid, and continuing throughout the study. A battery of motor tasks, including assessments of balance, clasping, swim speed, and spontaneous motor activity, was undertaken over 28 days, followed by histological examination of the brains. The results indicated that all doses of KP447 decreased mortality, while attenuating deficits in balance, clasping, and swim speed. However, only the highest dose of KP447 attenuated changes in spontaneous motor activity and reduced quinolate-induced striatal atrophy. These results suggest that substituted pyrimidines, such as KP447, have significant potential as pharmacotherapy for Huntington's disease.

Keywords: quinolinic acid; nerve growth factor, striatal atrophy

Introduction

Huntington's disease (HD) is a fatal, autosomal dominant neurodegenerative disorder marked by preferential striatal degeneration, cognitive difficulties, and extensive motor impairments, all of which are progressive in nature [28]. Striatal degeneration is characterized by selective destruction of medium-spiny GABAergic neurons [1], decreases in choline acetyltransferase (ChAT), and the relative sparing of NADPH-diaphorase neurons [5]. Cognitive deficits appear prior to the onset of motor dysfunction, often by as much as ten years. The characteristic motor dysfunction of HD is chorea, most commonly appearing in mid-life and

gradually increases in intensity. This progression is accompanied by bradykinesia, rigidity and lack of mobility in the later stages of the disease. Death finally occurs from secondary causes of immobilization [40].

Although the exact cause of neurodegeneration in HD is not understood, probable mechanisms include excitotoxicity, oxidative stress, and disrupted energy metabolism [15]. Intrastriatal injections of quinolinic acid (QA), an NMDA receptor agonist, mimic HD neuropathology in rodents by inducing toxic levels of calcium influx. The increased level of calcium leads to a cascade of cellular events, including enzyme activation, the production of reactive oxygen species, and subsequent energy impairment [7], eventually leading to the generation of more free radicals, further oxidative damage, and apoptosis [26]. Support for the hypothesis that HD neurodegeneration may result from this cycle of excitotoxicity and impaired energy metabolism [1] is underscored by observation that QA produces a pattern of cell loss similar to that observed in HD [3,4].

In attempts to find viable treatments for HD, researchers have examined several types of neurotrophic factors, which are a class of proteins that are involved in regulating apoptotic events during development and facilitate other forms of neuronal plasticity. Several types of neurotrophic factors have been targeted as potential therapeutic agents for treating neurodegenerative disorders [6,18]. In fact, a prominent neurotrophic factor, nerve growth factor (NGF), has already been shown to be neuroprotective against striatal neurodegeneration [17,32]. Although the mechanisms for this protection are still unknown, it has been suggested that it may involve glutamate receptor function, induction of stress proteins, peroxidative metabolism, or ionic balance [11]. In addition to protecting against excitotoxicity, NGF may also inhibit secondary excitotoxic death through the destruction of oxidative free radicals [29].

It has been shown that NGF can maintain activity in striatal cholinergic neurons *in vitro* [10] and *in vivo* [32], and can protect against QA-induced loss of cholinergic neurons in the striatum [32]. This is particularly relevant because phenotypic symptoms in one transgenic mouse model of HD have been associated with changes in cholinergic striatal neurons [37]. More recently, NGF administration into the striatum has been shown to protect both cholinergic [22] and non-cholinergic neurons [17] from QA-induced neurotoxicity.

Unfortunately, the clinical utility of NGF is limited because it is unable to pass through the blood-brain barrier in physiologically significant amounts [2,24]. Therefore, delivery of NGF requires surgical implantation or intrathecal injection. Because of this limitation, alternative means of providing NGF therapy have been proposed, such as developing drugs that might enhance the activity of endogenous levels of NGF.

One class of compounds, the substituted pyrimidines, offers significant promise for enhancing the effects of endogenous NGF. Of these compounds, KP544, already has been shown to enhance the effects of NGF *in vitro*, most notably by increasing neurite outgrowth in PC12 cells by two-fold at 2 μM concentration and enhancing ChAT activity in PC12 cells by 3- to 8-fold at 0.12-0.3 μM concentrations [13]. In addition, KP544 readily passes through the blood-brain barrier and can reduce QA-induced behavioral deficits *in vivo* [25]. The

pharmacokinetics and safety profile of KP544 suggests that this drug has considerable promise for clinical trials [25]. Preliminary work with other related compounds, including KP66 [2-amino-5-(4-chlorophenoxy)-4-[2-(2-hydroxyethoxy) ethylamino] pyrimidine hydrochloride] [15] and KP546 [2-amino-5-(4-chorophenoxy)-4-(4-hydroxyanilino) pyrimidine hydrochloride] [21] suggests that other substituted pyrimidines may also reduce behavioral deficits in the QA model of HD, suggesting that this family of compounds offer significant promise as a potential therapy for HD.

The overall goal of the present study was to test the safety and efficacy of one of these substituted pyrimidines, KP447 [(2-amino-5-(4-chlorophenylthio)-4-(trans-4-hydroxycyclohexylamino) pyrimidine] in the QA model of HD. KP447 is a close structural analogue to KP544, with the primary difference being the substitution of a sulfur linker instead of the vinyl linker of the 5-subtituent. Our pilot studies with KP447 suggest that it amplifies the effects of NGF on ChAT activity in PC12 cells at levels that compare favorably with KP544. As such, the primary aim of the present study was to assess the safety and efficacy of KP447 and to test its effects *in vivo*. Specifically, the focus of the present study was to determine if KP447 treatments could reduce motor deficits in a QA model of HD. In the present study, bilateral intrastriatal injections of 200 nmol QA were used because this protocol has been previously shown to produce significant motor deficits in rats [34]. Based on the safety and efficacy profiles obtained from our previous work with KP544 [25], we tested a relatively wide range of doses of KP447 for safety profiles (100 mg/kg, 300 mg/kg, and 1000 mg/kg) and for efficacy profiles (0.1 mg/kg, 1 mg/kg, and 10 mg/kg) with respect to its ability to reduce QA-induced motor deficits.

Materials and Methods

2.1 Compound Synthesis

KP447 (Fig. 1) [(2-amino-5-(4-chlorophenylthio)-4-(trans-4-hydroxycyclohexylamino) pyrimidine] was synthesized according to the procedures previously described [20].

2.2 Concentration of KP447 in Rat Plasma and Brain

Whole brain and plasma were extracted from three groups (n=3) of male Sprague Dawley rats dosed (50 mg/kg) at 2, 3, or 5 hours before sacrifice. Analysis by HPLC for KP447 was conducted using the same procedures previously described for KP544 [25].

2.3 Safety Study

Rats were allocated to 4 groups of 6/sex and given daily oral gavage doses of KP447 suspended in 0.5% methylcellulose at dose levels of 0 (vehicle only), 100, 300, 1000 mg/kg/day for 30 days. At the end of the dosing period, rats were euthanized and necropsied. Throughout the dosing period, rats were observed daily for clinical signs of effect or toxicity, such as abnormal posture, listlessness, lack of grooming, and abnormal changes in body weight. Plasma samples were collected at 1, 2, and 4 hours after the 1^{st} and 27^{th} doses to estimate systemic exposure to KP447. At

necropsy, blood was collected for hematology and clinical chemistry analyses, selected organs were weighed, gross pathological findings were recorded, and tissues were collected, fixed, and subsequently processed and examined for histopathologic findings by a certified veterinary pathologist (J.Dillberger).

2.4 QA Lesion Model

2.4.1 Subjects

Seventy-one, 9-week old, male, Sprague-Dawley (Charles River) rats, weighing approximately 300 grams, were housed individually in wire cages and given water *ad libitum.* The rats were deprived of food for 4 hours before and after KP447 administration. Throughout the experiment, the animals were kept on a 12-hr light/dark cycle (0800-2000 hr). The rats were randomly assigned to one of five groups: (1) Controls (Con; n=11), that received intrastriatal injections of phosphate buffered saline (PBS) and oral treatments of vehicle (0.5% methylcellulose); (2) QA group (n=26), that received intrastriatal injections of QA (200 nmol) and oral treatments of vehicle; (3) 0.1 mg/kg group (n=11), that received intrastriatal injections of QA (200 nmol) and oral treatments of 0.1 mg/kg KP447; (4) 1.0 mg/kg group (n=12), that received intrastriatal injections of QA (200 nmol) and oral treatments of 1.0 mg/kg KP447; or (5) 10 mg/kg group (n=12), that received intrastriatal injections of QA (200 nmol) and oral treatments of 10 mg/kg KP447. Based on our pilot work, which indicated a 50% mortality rate in rats given only QA, a higher number of rats were allocated to the QA-alone group. All animals were gentled 10 minutes per day for three consecutive days prior to any testing. Care and use of the animals was in strict adherence to the National Institutes of Health and Central Michigan University Institute for Animal Care and Use Committee guidelines.

2.4.2 Surgery

All rats were anesthetized with sodium pentobarbital (50 mg/kg, i.p.), following injection of atropine sulfate (0.3 mg/kg, i.p.). Animals were positioned in a David Kopf stereotaxic apparatus and given 1 μL bilateral intrastriatal injections of either QA (200 nmol) or phosphate buffered saline (PBS; pH of 7.2) at the following coordinates: AP = +0.4 mm; ML = $\pm$2.5 mm (both from bregma); and DV = -4.5 mm [31]. A 1 μL Hamilton syringe was used to deliver the injections, which were given over a two-minute period, followed by a 5-minute diffusion period whereby the needle remained stationary. To avoid seepage up the needle tract, the needle was withdrawn slowly over a two-minute period.

2.4.3 Administration of KP447

Rats received KP447 or 0.5% methlycellulose (vehicle) via gavage. Administration began 3 days prior to surgery and continued for 28 days post-surgery. All animals were deprived of food for 4 hours prior to treatment and for 4 hours following treatment, in order to minimize the effect of stomach contents on absorption. KP447 treatments were prepared as vortexed 0.5%

methylcellulose suspensions at concentrations of 0.1, 1.0, or 10.0 mg/ml. QA and PBS control rats were given equivalent amounts of vehicle.

2.4.4 Balance Beam

The balance beam task [35] consisted of a beam (117 x 28.5 x 2 cm), which was suspended 100 cm over a 7 cm thick foam cushion, and contained a goal box (24.5 x 20 x 18 cm) placed at the end of the beam on a table from which the beam was attached. Animals were trained to traverse the 100 cm from the suspended end to the goal box by walking on top of the 2-cm-wide surface of the balance beam. Training sessions were conducted twice daily for three consecutive days prior to surgery, with testing sessions conducted at 1000 hr on the day of surgery (1 hour prior to surgery) and on post-operative days 7 and 28. The dependent variable was the number of footslips, which was operationally defined as a slip of any forepaw or hindpaw past a line drawn 1.5 cm below the surface of the beam. The total number of foot-slips was recorded over a 3-minute period or until the rat traversed the 100-cm length of the beam. The task was considered incomplete if the animal exceeded three minutes, or fell off the beam.

2.4.5 Clasping

The presence of QA-induced clasping response was measured at approximately 1100 hrs on post-operative days 7 and 28. Clasping response has been observed in a transgenic model of HD [33] and was adapted for this QA model of HD. Rats were given three trials on each of the two testing days. During each trial, the rat was lifted by the base of the tail about 5 cm above the surface of a table for 5 seconds, and then placed back down on the table for a 10-second inter-trial interval rest period [13]. In this study, a clasp was operationally defined as a simultaneous withdrawal of both forelimbs to the trunk of the body, as opposed to the rat extending its forelimbs and paws toward the table. Only one clasp per trial was recorded and the number of trials in which a clasp was observed was used as the dependent measure [25].

2.4.6 Open-Field

Spontaneous motor activity in an open-field maze [34] was measured for each rat, using a Hamilton-Kinder open-field monitoring box (40.6 x 40.6 x 38.1 cm; Hamilton-Kinder, Poway, CA). Each animal was monitored for distance traveled and fine motor movements over 12-hr periods (2000-0800 hr) on the evening prior to surgery, and on post-operative days 7 and 28. Fine motor movements were operationally defined, via the Hamilton-Kinder software, as repeated breaks of the same infrared beam in the open-field monitoring box, without registering linear movement of the animal (i.e., without the animal vacating the area it was occupying during such beam breaks).

2.4.7 Swim Speed

The swim speed [33] of each rat was measured at days 7 and 28 post surgery. The dependent measure was the time it took the rat to swim from the starting point at one end of a

plexiglass channel (10 cm wide x 140 cm long x 55 cm high) filled with water to a depth of 30 cm, to a raised platform in the opposite end. Rats were given three trials per testing period, with a five-minute inter-trial interval.

2.4.8 Paw Placement

Each animal was also assessed for sensorimotor abilities using a paw placement task [35] on post-operative days 7 and 28. In this task, the rat was held by its torso and moved at a speed of about 10 cm/sec parallel to the edge of a 1-m-long table. Special care was taken to ensure vibrissae did not come into contact with the edge of the table. The presence or absence of any forepaw placement on the table was the dependent measure for this task. Three trials, with a five-minute inter-trial interval, were performed at each testing session.

2.4.9 Histology

Following behavioral testing each animal was overdosed with sodium pentabarbitol and transcardially perfused with a PBS and 4% paraformaldehyde solution. Each brain was extracted and post-fixed for 1 hr in 4% paraformaldehyde and then placed in 30% sucrose solution until it sank. The brains were then sliced coronally in 40 μm sections on a freezing microtome. Lesion size, lateral ventricle enlargement, and striatal atrophy were assessed using cytocrome-oxidase-(CYO) stained tissue sections at five levels of the neostriatum, corresponding to the following AP coordinates (in mm from bregma): +1.6, +0.7, +0.2, -0.8 and –1.4 [31]. Analysis of the sections was performed using a computerized image analysis system (Sigma Scan Pro, SPSS Science, Chicago, IL). For measurements of the neostriatum, the level of the anterior commissure was used as the ventral border, the lateral ventricles served as the medial border, and the corpus callosum served as the dorsal and lateral borders. Striatal, lesion, and lateral ventricular volumes were estimated by plotting the mean surface areas of the stained sections against the anterior-posterior distances from bregma (in mm) and calculating the surface areas under the resulting curves, following the procedures of Lehéricy et al. [27].

2.4.10 Statistical Analysis

Mixed design analysis of variance (ANOVA) was used to evaluate footslips on the balance beam, number of clasps on the clasping measure, spontaneous activity in the open field task, and swim speed. Analyses of lesion size, striatal volume, and volume of the lateral ventricles were done using one-way ANOVAs. *Post hoc* analyses were conducted using Fisher's protected least significant difference (PLSD) test, when appropriate. A .05 alpha level was used for all analyses.

Results

3.1 Pharmacokinetics

After an oral dose of KP447 (50 mg/kg), KP447 was detectable in both plasma and brain extracts (Table 1). At 2 and 3 hours post dose, the plasma levels were 4 times higher than the brain levels. At 5 hours post dose, the plasma and brain levels were approximately equal.

3.2 Safety Study

Rats tolerated daily oral dosing with KP447 at up to 1000 mg/kg/day for 30 days. The only deaths were due to infection secondary to accidental perforation of the esophagus during dose administration. Because these deaths occurred in all groups including controls, they were considered unrelated to KP447. All rats gained weight during the study. Daily oral doses of KP447 reduced weight gain by approximately 50% in males at 1000 mg/kg/day, but did not affect body weight in other groups. Between-group differences related to KP447 are summarized in Table 2. The only definitive KP447-related in-life and postmortem findings suggestive of toxicity were in liver and kidney at higher dose levels.

3.2.1 Liver-related findings

Bile duct proliferation, without any evidence of cholangitis or portal fibrosis, was observed microscopically at ≥300 mg/kg/day in rats of both sexes, and there was evidence of intrahepatic cholestasis (bile plugs in periportal cannaliculi) at 1000 mg/kg/day in males, but not in females. These liver findings were not accompanied by changes in clinical chemistry parameters for serum measures of aspartate aminotransferase (AST), gamma glutamic transpeptidase (GGTP), or in mean serum concentrations of bilirubin or cholesterol. However, the 1000 mg/kg group did show elevation in serum levels of alanine aminotransferase (ALT), alkaline phosphatase, and albumin for the male rats and alkaline phosphatase for the females.

3.2.2 Kidney-related findings

Renal tubular necrosis and regeneration was observed microscopically at 1000 mg/kg/day in males, but not females. Renal findings were not accompanied by changes in kidney weight or electrolyte measurements of calcium, phosphorus, chloride, and magnesium. However the male 1000 mg/kg group showed significant increase in values of serum measures of the kidney-related clinical chemistry parameters urea nitrogen, and creatinine, with significant decreases in total protein, and potassium. The male 100 mg/kg group was found to have elevated sodium and decreased potassium. For the female rats, the highest two treatments showed decreased total serum protein and increased serum chloride. The 1000 mg/kg group also showed increased sodium. The only other significant change in kidney-related parameter was an increase in serum creatinine in the 100 mg/kg group.

3.3 QA Lesion Study

3.3.1 Survival

Survival data was analyzed using the Mantel-Cox log-rank test and Kaplan-Meier survival curves, following a modification of the procedures used by Ferrante et al [9]. All three

doses of KP447 improved survival (Fig. 2). Treatment with 0.1 mg/kg KP447 increased average survival by 32.5% (0.1 mg/kg KP447: 18.18 ± 3.68 d; QA: 12.27 ± 2.28; $p>0.05$). Treatment with 1.0 mg/kg KP447 increased average survival by 41.6% (1 mg/kg KP447: 20.67 ±3.46 d; QA: 12.27 ± 2.28; $p<0.05$). Treatment with 10 mg/kg KP447 increased average survival by 43.2% (10 mg/kg KP447: 21.58 ± 3.04 d; QA: 12.27 ± 2.28; $p<0.05$). In the QA group, only 8 of 26 rats survived, while 6 of 11 survived in the 0.1 mg/kg group, 8 of 12 survived in the 1.0 mg/kg group, and 8 of 12 survived in the 10 mg/kg group. All 11 rats in the Control group survived through post-operative day 28. Only those rats that completed all testing, which included all rats that survived through post-operative day 28, were used in the subsequent analyses.

3.3.2 Balance Beam

Footslips on the balance beam task were examined using a 5 (treatment) x 3 (time) mixed design ANOVA. This analysis indicated that effects of time [$F(1, 36)=12.16$, $p<.05$], treatment [$F(4, 36)=8.19$, $p<.01$] and treatment x time interaction [$F(4, 36)=8.97$, $p<.01$], were significant. Post hoc analysis indicated that all doses of KP447 reduced QA-induced footslips to saline-control levels on the balance beam task, at 7 days (Con: 0.54 ± 0.31; 0.1 mg/kg KP447: 0.0 ± 0.0; 1 mg/kg KP447: 1.75 ± 0.85; 10 mg/kg KP447: 2.50 ± 1.32; QA: 7.0 ± 2.75; $p<0.05$) and 28 days (Con: 0.54 ± 0.20; 0.1 mg/kg KP447: 1.33 ± 0.88; 1 mg/kg KP447: 0.80 ± 0.49; 10 mg/kg KP447: 0.66 ± 0.49; QA: 9.33 ± 4.04; $p<0.05$) post-surgery (Fig. 3).

3.3.3 Clasping

The number of clasps was analyzed using a 5 (treatment) x 2 (time) mixed design ANOVA. The effect of treatment [$F(4, 36)=9.83$, $p<.001$] was significant, whereas the effect of time [$F(1, 36)=4.05$, $p>.05$] was not. The treatment x time interaction was significant [$F(4, 36)=2.97$, $p<.05$]. Post hoc analysis showed that all doses of KP447 significantly reduced QA-induced clasping at days 7 (Con: 0.09 ± 0.09; 0.1 mg/kg KP447: 1.0 ± 0.36; 1 mg/kg KP447: 0.12 ± 0.12; 10 mg/kg KP447: 0.88 ± 0.29; QA: 2.13 ± 0.29; $p<0.05$) and 28 (Con: 0.36 ± 0.20; 0.1 mg/kg KP447: 0.17 ± 0.17; 1 mg/kg KP447: 0.50 ± 0.27; 10 mg/kg KP447: 0.25 ± 0.16; QA: 1.37 ± 0.49; $p<0.05$) post-surgery (Fig 4).

3.3.4 Open Field

Distance traveled and fine motor movements in the open field are summarized in Table 4. A 5 (treatment) x 3 (time) mixed design ANOVA revealed significance for time [$F(1, 36)=73.75$, $p<.001$] and treatment group [$F(4, 36)=3.51$, $p<.05$], but not on treatment x time interaction [$F(4, 36)=1.14$, $p>.05$] for distance traveled. Similarly, significance was observed for time [$F(1, 36)=65.21$, $p<.001$] and for treatment group [$F(4, 36)=3.36$, $p<.05$], but not for treatment x time interaction [$F(4, 36)=1.09$, $p>.05$] for fine motor movements.

Post hoc analysis revealed that at postoperative day 7, only rats receiving the 10 mg/kg dose of KP447 were protected from QA-induced hypoactivity, as measured by decreases in distance traveled (Con: 24.82 ± 1.49; 0.1 mg/kg KP447: 12.25 ± 1.41; 1 mg/kg KP447: 10.87 ± 2.78; 10 mg/kg KP447: 21.99 ± 4.84; QA: 16.55 ± 1.92; $p<0.05$; measurements in meters) and the number of fine motor movements (Con: 17.0 ± 0.95; 0.1 mg/kg KP447: 8.44 ± 1.19; 1 mg/kg KP447: 7.42 ± 1.93; 10 mg/kg KP447: 14.53 ± 3.06; QA: 11.42 ± 1.58; $p<0.05$; measurements are in thousand movements). No significant differences were noted on postoperative day 28 for measures of distance traveled (Con: 18.36 ± 1.46; 0.1 mg/kg KP447: 17.82 ± 2.29; 1 mg/kg KP447: 17.19 ± 1.74; 10 mg/kg KP447: 15.85 ± 1.16; QA: 18.85 ± 2.16; $p>0.05$; measurements in meters) or fine motor movements (Con: 12.31 ± 0.94; 0.1 mg/kg KP447: 12.09 ± 1.81; 1 mg/kg KP447: 11.89 ± 2.97; 10 mg/kg KP447: 10.33 ± 0.79; QA: 13.03 ± 1.29; $p>0.05$; measurements are in thousand movements).

3.3.5 Swim Speed

Swim speed was assessed at days 7 and 28 post-surgery using a 5 (treatment) x 2 (time) mixed design ANOVA. The effect of treatment [$F(4, 36)=8.24$, $p<.001$] and time [$F(1, 36)=39.57$, $p<.001$] were significant, whereas the treatment x time interaction was not significant [$F(4, 36)=1.46$, $p>.05$]. Post hoc analysis showed that the QA group, the 0.1 mg/kg KP447 group, and the 1.0 mg/kg KP447 group all had significantly slower swim speeds than the saline controls at postoperative day 7 (Con: 3.27 ± 0.11; 0.1 mg/kg KP447: 4.35 ± 0.22; 1 mg/kg KP447: 4.16 ± 0.17; 10 mg/kg KP447: 3.86 ± 0.34; QA: 4.45 ± 0.30; $p<0.05$). However, this QA-induced decrease in swim speed was not present in the 10 mg/kg KP447 group. At day 28 post-surgery, the QA group still exhibited significantly slower swim speeds than controls, while all KP447 treated groups were performing at control levels (Con: 2.49 ± 0.16; 0.1 mg/kg KP447: 3.18 ± 0.49; 1 mg/kg KP447: 2.91 ± 0.27; 10 mg/kg KP447: 2.55 ± 0.06; QA: 4.12 ± 0.37; $p<0.05$; Fig. 5).

3.3.6 Paw Placement

All rats were able to place their paws on the table during each trial of the paw- placement test. This indicated that basic sensorimotor function was intact for all rats.

3.3.7 Histological Analysis

Histological analysis was completed on all surviving animals except for one untreated control rat whose brain was improperly fixed. All groups receiving QA administration had comparable lesions (0.1 mg/kg KP447: 36.20 ± 2.66; 1 mg/kg KP447: 33.99 ± 1.95; 10 mg/kg KP447: 33.23 ± 3.55; QA: 38.54 ± 1.79; Mean ± SEM in mm^3), with no between-group differences in lesion volume [$F(3, 26)=0.90$, $p>.05$]. Measures of striatal volume revealed a significant QA-induced shrinkage [$F(4, 35)=12.67$, $p<.05$].. Post hoc analysis indicated that rats given the 10 mg/kg dose, of KP447 had significantly less atrophy than other QA-treated groups (PBS Controls: 66.23 ± 1.78; 0.1 mg/kg KP447: 52.83 ± 1.81; 1 mg/kg KP447: 50.68 ± 1.53; 10

mg/kg KP447: 56.63 ± 1.40; QA: 49.46 ± 3.10; Mean ± SEM in mm^3) (Fig. 6). Although there was a significant QA-induced enlargement of the lateral ventricles [$F(4, 35)=3.84$, $p<.05$], none of the KP447-treated groups differed significantly from the QA-alone group (PBS Controls: 7.82 ± 0.80; 0.1 mg/kg KP447: 11.36 ± 0.91; 1 mg/kg KP447: 14.53 ± 2.17; 10 mg/kg KP447: 13.20 ± 1.73; QA: 14.25 ± 0.77; Mean ± SEM in mm^3).

Discussion

The major findings of this study are that KP447 has a favorable safety profile and, at 0.1-, 1.0-, and 10- mg/kg doses, it reduced abnormalities in balance and clasping caused by intrastriatal injections of QA. In addition the 10 mg/kg dose reduced deficits in the swim task, hypoactivity in the open-field test, and striatal atrophy induced by intrastriatal injections of QA. Collectively, these results suggest that KP447 may be a potentially safe and effective treatment for the motor symptoms in HD.

Brain/Plasma Concentrations and Safety Profile of KP447

Our measures of blood plasma and brain levels of male rats given 50 mg/kg oral dosing of KP447 indicated that the drug was readily absorbed and entered the brain by 2 hours post-dosing. Although it is possible that peak absorption occurred earlier, it appears to have peaked by at least two hours post-dosing, as both the plasma and brain levels were reduced by about 33% at 3 hours post-dosing and by an additional 87% and 50% for plasma and brain levels, respectively, at 5 hours post-dosing. However, unlike the closely-related substituted pyrimidine, KP544, which had a four-fold increase in brain-to-plasma level concentration at 2 hours post-dosing, the concentration of KP447 in the brain was only about 23% of that found in the plasma at 2 hours post-dosing. This brain-to-plasma ratio remained the same at 3 hours post-dosing, but the concentration of KP447 in the brain and plasma were nearly identical (0.10 and 0.12 µM, respectively) at 5 hours post-dosing.

KP447 was well tolerated by rats of both sexes given daily doses up to 1000 mg/kg for 30 days. Several differences among groups were likely related to KP447 but were not considered to be adverse findings indicative of toxicity (Table 2). Hepatocellular hypertrophy, with an associated increase in liver weight, occurred at all dose levels. Hepatocellular hypertrophy is a commonly observed effect in rats given high dose levels of xenobiotics, which reflects the induction of xenobiotic-metabolizing enzymes, and is often considered to be an adaptive rather than an adverse response [39]. Myocardial atrophy was observed microscopically at ≥300 mg/kg/day, without any evidence of inflammatory or degenerative changes and unaccompanied by any differences in heart weight or serum creatine phosphokinase (CPK) activity. The underlying cause of the myocardial atrophy was undetermined, although it may have been an adaptive response to reduced cardiac workload. Because myocardial atrophy was unaccompanied by any in-life or postmortem signs suggesting impaired cardiac function, it was not considered to be an adverse finding. Adrenal cortical hypertrophy, seen in all rats at 1000 mg/kg/day and a few rats at lower dose levels, was considered to be a nonspecific response

to stress and not a primary effect of KP447, although the stress response appears to occur more readily in rats receiving the highest dose of KP447.

The results do indicate that KP447 may have some toxic effects at high doses, though. This is indicated by the serum hepatic and renal markers examined in the safety study. The elevation of ALT and alkaline phosphotase seen in the male 1000 mg/kg group suggested that at this high dose of KP447 may have some detrimental effects on liver functioning. This may be less in females however, since only an elevation in alkaline phosphotase was seen in the liver enzymes of the 1000 mg/kg group. This elevation in the females may indicate early congestion of the biliary tree or slowed emptying of the cystic duct, which has yet to cause enzyme elevation. It should be noted though that these changes were only seen at the highest level.

Examination of serum levels of kidney-related markers and electrolytes indicate that at high levels, KP447 may also affect kidney filtration and functioning. This is suggested by the increase in serum urea nitrogen and creatinine along with the decrease in serum protein and potassium seen in the male 1000 mg/kg group. Once again these effects may be lessened in females since the 1000 mg/kg group showed only a decrease in serum protein and an increase in sodium and chloride. This might indicate less damage and rather some urinary loss of protein with accompanied reabsorption of sodium and chloride in an attempt to replace loses in serum osmolality. The other point that was seen in the safety study was a few significant makers at levels other than the 1000 mg/kg dose. The 100 mg/kg dose did show increase serum creatinine for both males and females. However no increase was seen in the 300 mg/kg group for either sex or the 1000 mg/kg female group. This suggests that the increase in serum creatinine might be either coincidental or transient in nature. While the 100 mg/kg male group does also show variations in the sodium/potassium balance, neither electrolyte is extremely varied there may be some filtration changes related to the elevated creatinine or it may too be coincidental in nature. In either case, the signs of toxicity seem to exist most in the highest doses with the lower doses seeming far safer. Such that the 10 mg/kg high dose used in this study was likely be far low enough to avoid any toxic effects.

Based on the results of the 1-month toxicity study, it was concluded that rats would tolerate daily oral doses of KP447 at 100 mg/kg/day without toxicity, which is 10 times the highest dose used in our efficacy study. The only effect expected at this dose level was slight hepatocellular hypertrophy, probably due to metabolic enzyme induction, which might lead to slightly lower systemic exposure to KP447 with repeated dosing.

Efficacy of KP447 in the QA model of HD

Perhaps the most impressive beneficial effect from the KP447 was the increase in survival. Treatments of KP544 reduced mortality rates and increased survival time in a dose-dependent manner. The mortality rate was reduced by 26% in the 0.1 mg/kg group, 38% in the 1.0 mg/kg and 10 mg/kg groups, with survival times being increased by 32.5%, 41.6%, and 43.2%, respectively.

In addition to reducing mortality, the high (10 mg/kg) dose of KP447 provided some protection against QA-induced striatal atrophy, despite having no effect on lesion volume. The precise degree of KP447 protection against QA-induced cell loss could not be accurately measured because of the high mortality rate of the rats given QA without KP447. In other words, it is possible that many of the QA-alone rats that died before the study was finished may have had significantly larger lesions than the surviving rats in this group. However, since histological measures were made on only those rats that completed the behavioral testing, the beneficial effects of KP447 on cell survival may have been underestimated. Nonetheless, there was a significant decrease in striatal atrophy in rats receiving the 10 mg/kg dose of KP447.

Despite the evidence of some neuroprotective benefit from the high dose of KP447, it is difficult to reconcile the findings of significant behavioral sparing and recovery in the absence of evidence for neuroprotection by the two lower doses of KP447. The finding of a significant correlation between lesion volume and performance on all of the motor tasks on post-operative day 7, but none on post-operative day 28 suggests that subtle reductions in lesion size by KP447 may have contributed to the observed behavioral sparing, but cannot account for the observed recovery on some measures. All doses of KP447 prevented QA-induced deficits on the balance-beam and clasping measures, but only rats receiving the high dose showed behavioral sparing on all of the motor tasks. Interestingly, rats in the 0.1 mg/kg and 1.0 mg/kg groups showed recovery of the QA-induced decreases in both swim speed and spontaneous motor activity when levels at postoperative day 7 are compared with those on postoperative day 28. However, close inspection of Table 4 indicates that the recovery observed for distance traveled and fine motor movements in the open-field was due to a combination of some increases in activity levels of all those QA-treated groups that showed a deficit at postoperative day 7 and a decrease in activity levels, likely due to habituation, for the two groups (10 mg/kg and Controls) that did not show this initial hypoactivity. Conversely, close inspection of Figure 5 suggests behavioral recovery on measures of swim speed for all rats receiving the KP447. Surprisingly, this recovery does not correlate with lesion or striatal volume (see Table 5), and only the 10 mg/kg dose significantly reduced striatal atrophy.

Although the behavioral sparing observed in the rats given the high dose of KP447 and the recovery observed in the other KP447-treated rats may have been due to a stimulatory effect of KP447, some of the findings in the present study argue against this hypothesis. For example, the finding that rats given the high dose of KP447 were the only ones that showed behavioral sparing on all behavioral measures and was the only group that was spared from significant QA-induced striatal atrophy suggests that a neuroprotective effect of KP447 is a more likely explanation underlying the behavioral sparing and recovery observed in the present study. This explanation is underscored by the finding that rats in the 10 mg/kg group that did not show initial QA-induced hypoactivity in the open-field on post-operative day 7, showed significant decreases in distance traveled and fine motor movements on post-operative day 28, when levels on post-operative day 28 in these rats are compared with those on post-operative day 7. Although this does not rule out the possibility that a stimulatory effect of KP447 underlies the observed

normalized spontaneous motor activity observed in this study, it would appear to be unlikely that only the rats receiving the high dose became habituated to a stimulatory effect of the KP447.

Although mechanisms of KP447-induced behavioral sparing are currently unknown, the indications from *in vitro* work with a close structural analogue, KP544 [13], suggest that substituted pyrimidines may be potentiating the effects of endogenous NGF. An elevation of endogenous level of NGF by substituted pyrimidines may be akin to the widespread effects of *ex vivo* gene transfer or grafted cells with a transfected gene for producing NGF, which has been hypothesized to protect the functioning of both cholinergic and non-cholinergic cell populations, perhaps through the dispersion of free radical scavenger such as catalase [23]. Although KP447 may have been unable to protect striatal cells from the initial toxic QA insult, it may have been able to more quickly restore functioning in traumatized neurons outside the area of primary neuronal death. This could be mediated by protecting sodium/potassium ATPase levels and or the generation of antioxidant enzymes [30]. The finding in the present study that some beneficial behavioral effects of KP447 were observed at all doses, and only the high dose attenuated the QA-induced striatal atrophy, suggests that the hypothesis that KP447 treatments can exert their effects by preserving the functioning of some of the compromised neurons, or by enhancing the functioning of other spared neurons suggests this hypothesis is worthy of further exploration. Research using electrophysiological measures of neuronal functioning, following treatments with KP447 and/or other substituted pyrimidines in HD models are being planned to address this possibility. Clearly, further research is needed to elucidate NGF-mediated recovery mechanisms in general, as well as the specific mechanisms underlying the protective effects of substituted pyrimidines in this HD model.

Substituted Pyrimidines as Potential Treatments for HD

Despite the lack of a clear mechanistic explanation for the ameliorative effects of KP447 in the QA model of HD, the present study provides further evidence that substituted pyrimidines, such as KP447 and KP544 [13], have considerable therapeutic potential for treating HD. Although the present study was not designed to compare, directly, the effects of KP447 and KP544, some critically important similarities and differences between the two related compounds can be ascertained when the results of this study are evaluated in light of the findings in the KP544 study. Comparisons of the plasma/brain levels of the two compounds suggests that KP544 may be entering the brain more readily than KP447 at two hours post-treatment (brain/plasma ratios of 4.35 vs. 0.23, respectively), although the peak effects may have occurred before two hours and the potencies of the two drugs may differ, so it is difficult to make definitive conclusions as to which compound has the most favorable profile. In terms of safety profiles, KP447 was tolerated at doses up to 1000 mg/kg, a dose level that was lethal to rats given KP544 [13]. However, KP447 produced significant elevations in liver-to-body, without affecting the kidney-to-body ratios at 100 mg/kg/d, whereas the same treatments with KP544 did not produce increases in either of these measures [13].

In terms of efficacy for motor tasks, the present study provides the first indication of ameliorative effects of substituted pyrimidines for countering QA-induced deficits on a balance-beam task, spontaneous motor activity, and swim speeds. Previous attempts at assessing the behavioral effects of KP544 following bilateral intrastriatal injections of QA used a 150 nmol concentration, instead of the 200 nmol concentration used in the present study, which did not produce significant deficits for assessing treatment effects on balance, spontaneous motor activity, or swim speeds [13]. The previous study with KP544 did show a reduction in QA-induced learning deficits in a radial-arm-water-maze task and in measures for clasping and almost an identical reduction in the number of clasps as observed with KP447. The use of the higher QA concentration in the present study produced significant motor deficits on all tasks, which allowed for a more comprehensive assessment of the efficacy of substituted pyrimidines in treating QA-induced motor deficits, as well as their effects on survival. Although use of a lower concentration of QA or use of a unilateral model can provide useful information on motor asymmetries [8], it would not have allowed an accurate assessment of the motor tasks used in the present experiment. For example, rats with a unilateral lesion have difficulty swimming in a straight line, or walking in a straight line on the balance beam and in the open-field.

Conclusion

In summary, our study indicates that KP447, like the related substituted pyrimidine, KP544, offers significant promise as a potential treatment for some of the behavioral deficits that occur in HD. It also suggests that these types of compounds may possess some ability to decrease striatal damage and increase survival in this model of HD. Future studies into the underlying mechanisms of the beneficial effects of substituted pyrimidines may provide further insights into designing drugs that may provide an effective treatment for the debilitating motor deficits observed in HD.

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Table 1

KP447 is Adsorbed and Enters the Brain after Oral Administration to Rats

Fasted male Sprague Dawley rats (300 g) were dosed by gavage with a suspension of KP447 (50 mg/kg) in 0.5% methylcellulose (values are in mean±SEM).

Hours (post-dosing)	micromolar KP447	
	Plasma	Brain
2	1.40 ± 0.70	0.32 ± 0.10
3	0.89 ± 0.20	0.20 ± 0.10
5	0.12 ± 0.10	0.10 ± 0.06

Table 2

Summary of Noteworthy Findings from 1-Month Toxicity Study

	Males				Females			
Dose (mg/kg/d) =	**0**	**100**	**300**	**1000**	**0**	**100**	**300**	**1000**
Non-Adverse								
Hepatocellular hypertrophy (n)*	0/6	6/6	4/4	5/5	0/5	1/5	5/5	1/3
Liver weight (g)	11.9	13.3	13.1	14.2	7.3	8.3	8.4	9.9
Liver weight (% body weight)	3.7	3.9	4.5	6.0	3.5	4.0	4.5	5.3
Myocardial atrophy (n)*	0/6	0/6	2/4	5/5	0/5	0/5	0/5	2/3
Adrenal cortical hypertrophy (n)*	0/6	1/6	2/4	5/5	0/5	1/5	1/5	3/3
Adverse Effects—Liver								
Bile duct proliferation (n)*	0/6	0/6	3/4	5/5	0/5	0/5	2/5	3/3
Intrahepatic cholestasis (n)*	0/6	0/6	0/4	5/5	0/5	0/5	0/5	0/3
Adverse Effects—Kidney								
Renal tubular necrosis/regeneration (n)*	0/6	0/6	0/4	4/5	0/5	0/5	0/5	0/3
Nonspecific Effects								
Body weight at end of study (g)	323	338	317	253	208	219	190	195
Weight gain over the study (%)	+69 %	+85 %	+71 %	+34 %	+30 %	+36 %	+27 %	+28 %

* (n) = number of affected rats over total number of rats examined.

Table 3

Summary Serum Values from 1-Month Toxicity Study

	Males				Females			
Dose (mg/kg/d) =	**0**	**100**	**300**	**1000**	**0**	**100**	**300**	**1000**
Liver-related measures								
ALT (μ/L)	**45(3)**	**61(6)**	**75(13)**	**118(31)***	**49(5)**	**50(5)**	**52(5)**	**67(8)**

AST (µ/L)	**148(13)**	**154(26)**	**196(50)**	**243(37)**	**202(23)**	**202(48)**	**257(42)**	**277(70)**
Alkaline phosphatase (µ/L)	**44(18)**	**114(23)**	**111(38)**	**278(92)***	**3(1)**	**4(2)**	**17(6)**	**58(38)***
GGTP (µ/L)	**9(3)**	**2(0)**	**4(1)**	**7(3)**	**2(0)**	**2(.4)**	**7(5)**	**2(0)**
Bilirubin (mg/dL)	**.3(.07)**	**.13(.03)**	**.2(.05)**	**.22(.05)**	**.3(.04)**	**.22(.06)**	**.2(.03)**	**.2(.06)**
Albumin (g/dL)	**4.7(.2)**	**4.5(.07)**	**4.6(.12)**	**3.7(.29)***	**5.1(.17)**	**5.7(.13)**	**4.6(.36)**	**4.5(.2)**
Cholesterol (mg/dL)	**123(6)**	**123(9)**	**124(11)**	**143(19)**	**134(10)**	**145(11)**	**149(10)**	**140(7)**
Kidney-related measures								
Urea nitrogen (mg/dL)	**17(1)**	**21(1)**	**18(1)**	**32(5)***	**19(1)**	**17(1)**	**18(1)**	**22(2)**
Creatinine (mg/dL)	**.6(.03)**	**.83(.06)***	**.68(.05)**	**.8(.05)***	**.76(.05)**	**.92(.02)***	**.74(.04)**	**.9(.1)**
Total protein (g/dL)	**7(.15)**	**7(.1)**	**7(.15)**	**6(.5)***	**8(.2)**	**8(.3)**	**7(.4)***	**7(.1)***
Electrolytes								
Calcium (mg/dL)	**11(.5)**	**12(.5)**	**11(.4)**	**12(.5)**	**11(.5)**	**13(.8)**	**11(.6)**	**11(.8)**
Phosphorous (mg/dL)	**30(1.8)**	**30(1.5)**	**28(.45)**	**28(.23)**	**27(.44)**	**29(1.7)**	**26(.61)**	**27(.75)**
Sodium (meq/L)	**137(1)**	**143(1)***	**140(1)**	**140(1)**	**137(2)**	**138(1)**	**140(2)**	**144(.3)***
Potassium (meq/L)	**25(1)**	**21(1)***	**23(1)**	**21(1)***	**21(1)**	**20(1)**	**19(1)**	**19(.4)**
Chloride (meq/L)	**88(.6)**	**87(.3)**	**89(.6)**	**89(.5)**	**87(.7)**	**87(.8)**	**91(.7)***	**91(.3)***
Magnesium (meq/L)	**4(.1)**	**4(.1)**	**4(.1)**	**3(1)**	**4(.1)**	**4(.1)**	**4(.1)**	**4(.1)**

*p<.05 compared to 0 mg/kg group of the same sex

Table 4

The 10 mg/kg Dose of KP447 Alleviated QA-Induced Hypoactivity in the Open Field Task on Post-Operative Day 7

	Distance Traveled (m)			Fine Motor Movements (in 1000's)		
Treatment	PreSurg	Day 7	Day 28	PreSurg	Day 7	Day 28
Con	23.1 (1.6)	24.9 (1.4)	18.0 (1.4)	15.9 (1.1)	17.1 (0.9)	12.1 (0.9)
QA	24.6 (2.1)	16.5 (1.9)*	17.6 (1.8)	16.7 (1.4)	11.4 (1.0)*	12.2 (1.1)
0.1 mg/kg	27.1 (2.0)	12.5 (1.0)*	19.0 (3.7)	18.2 (1.3)	8.5 (1.9)*	12.9 (1.0)
1 mg/kg	21.6 (1.7)	12.1 (2.0)*	16.2 (1.4)	14.8 (1.1)	8.3 (0.9)*	11.3 (2.5)
10 mg/kg	25.8 (1.1)	23.5 (3.7)	16.3 (0.9)	17.5 (0.6)	15.6 (2.3)	10.6 (0.6)

Values are means (± SEM) *p<.05 compared with Con Group

Table 5

Lesion volume correlated significantly with slower swim speeds, decreases in distance traveled and fine movements in the open field (OF), and increases in clasping and footslips on the balance beam, while striatal volume correlated with increases clasping on post-operative day 7.

	Lesion Volume		Striatal Volume	
Behavioral Measure	Day 7	Day 28	Day 7	Day 28
Swim Speed	r=-.469*	r=-.292	r=-.147	r=-.280
Clasping Responses	r=.421*	r=.115	r=-.378*	r=-.185
Balance Beam Footslips	r=.440*	r=.286	r=-.214	r=-.283
OF Distance Traveled	r=-.384*	r=-.210	r=.242	r=.343
OF Fine Movements	r=-.456*	r=-.108	r=.276	r=.097

Values are Pearson R Correlations *p<.05

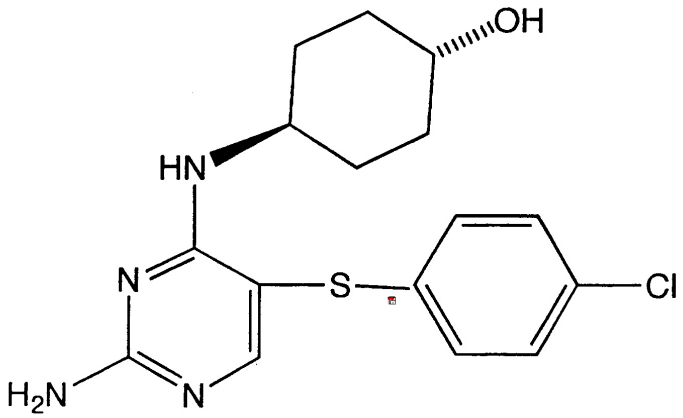

Figure 1. The structure of KP447 [(2-amino-5-(4-chlorophenylthio)-4-(trans-4-hydroxycyclohexylamino)pyrimidine].

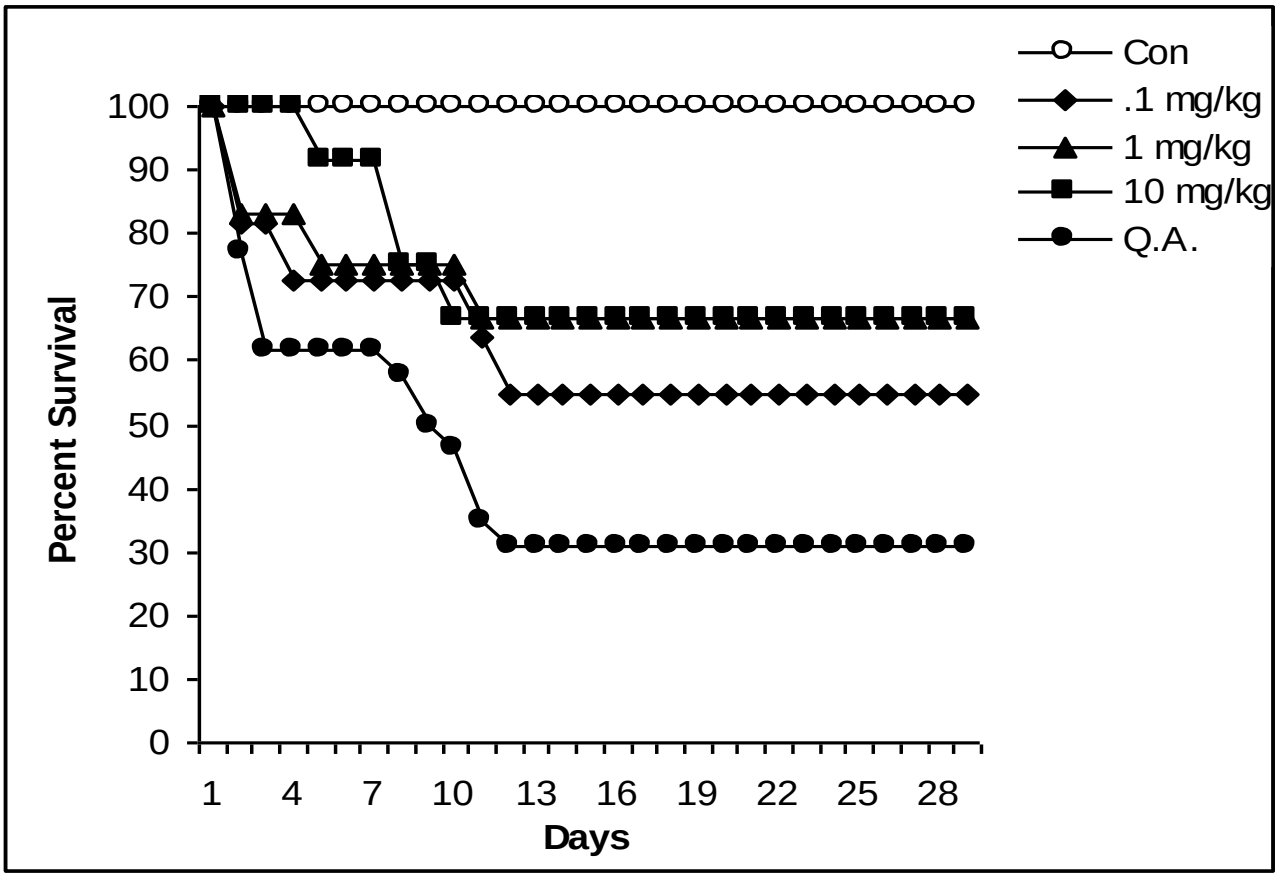
Con
.1 mg/kg
1 mg/kg
10 mg/kg
Q.A.
Percent Survival
100
90
80
70
60
50
40
30
20
10
0
1
4
7
10
13
16
19
22
25
28
Days

Figure 2. The 0.1 mg/kg dose of KP447 reduced QA-induced mortality from 69.2% to 45.5% while the 1.0- and 10 mg/kg doses reduced mortality to 33.3%.

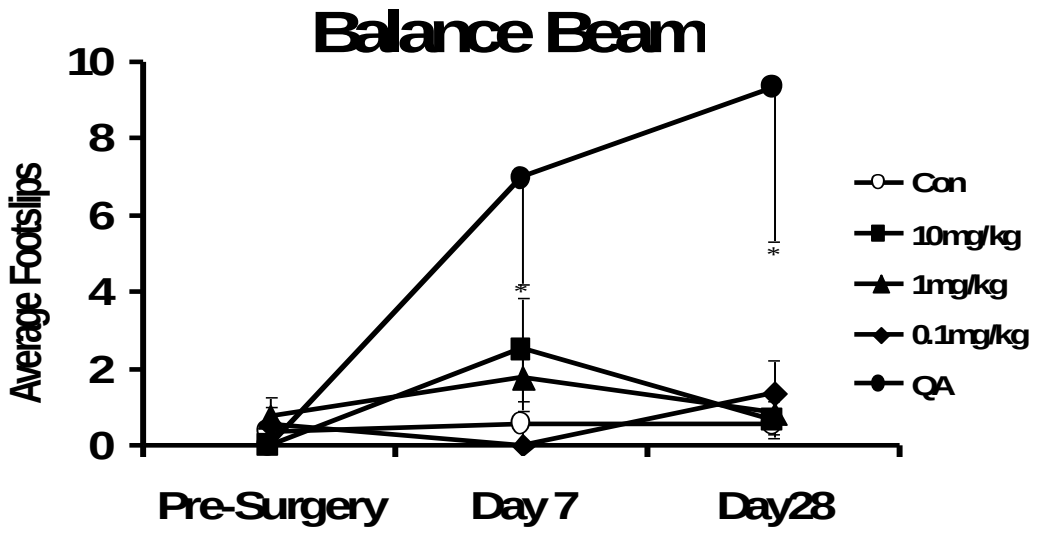

Figure 3. Rats that received only QA had

significantly more footslips on the balance-beam task on postoperative days 7 and 28. All rats receiving KP447 performed at control levels. Values are in means ± SEM (error bars); *p<.05, compared to controls.

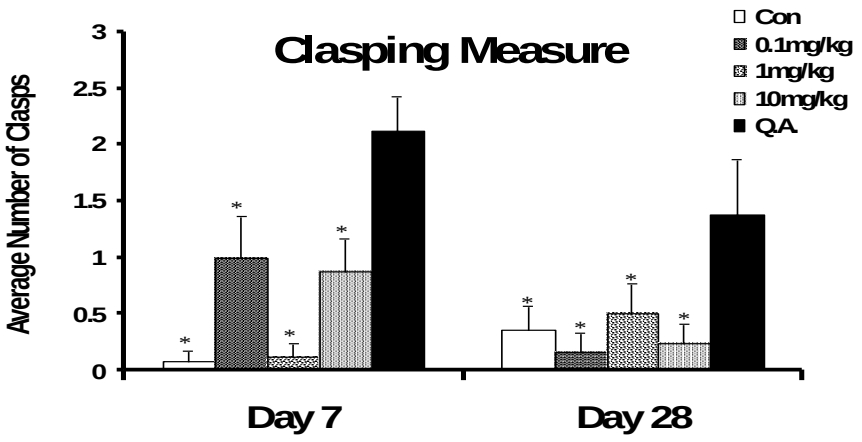

Figure 4. All KP447 groups exhibited significantly fewer clasps than QA controls on postoperative days 7 and 28. Values are in means ± SEM (error bars); *p<.05, compared to QA controls.

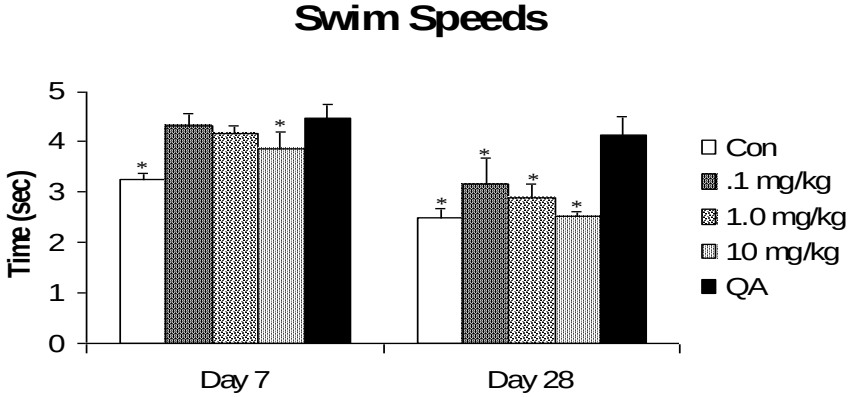

Figure 5. By postoperative day 7, the 10 mg/kg KP447 group was the only QA-treated group that had significantly faster swim speeds than the QA group. All groups were significantly faster than the QA group by postoperative day 28. Values are in means ± SEM (error bars); *p<.05, compared to QA controls.

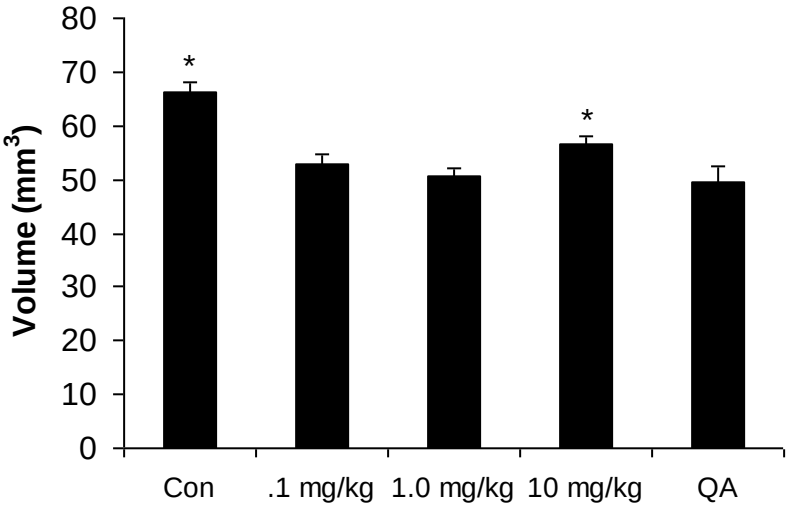

Figure 6. The 10 mg/kg dose of KP447 significantly reduced striatal atrophy, without reducing lesion volume or reducing QA-induced enlargements of the lateral ventricles. Values are in means ± SEM (error bars); *$p<.05$, compared to QA controls.

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Neurosurgery Residency Program
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Statement of contribution:
Type of paper: Original manuscript
The study: "A substituted pyrimidine, KP447, reduces mortality and motor pathology in a rodent model of Huntington's disease." The study was conducted with the Central Michigan University Neuroscience Department.

The purpose: The field of functional neurosurgery has in recent years become increasingly involved with the treatment of various movement disorders many of which are related to degenerative neurologic diseases. And yet, despite the advances we have made in understanding many diseases involving the basal ganglia system there are still some disorders, such as Huntington's disease for which there are no notable treatments, surgical or otherwise.

This study was designed to test the effectiveness and possible application of a new drug in the class of compounds call substituted pyrimidines in a rodent model of Huntington's disease. These compounds are unique in that they have been shown to enhance the effectiveness of endogenous Nerve Growth Factor (NGF) in neuronal cells in vitro. NGF has been shown previously to be neuroprotective in striatal cell death. Krenitsky Pharmaceuticals provided the compound.

Methods: The exact methods are explained in detailed in the paper, but in summary, rats were assigned to a lesion or a non-lesion group. The non-lesion group was given a benign placebo while the lesion rats were either given a placebo or one of three treatment doses, for 28 days. All the rats were tested on motor tasks while receiving treatment. The brains were then extracted and examined histologically.

Results: The higher doses of the compound were found to both increase survival and improve motor functioning in rats that had received the striatal lesions.

Conclusion: These results suggest that this class of compounds and in particular KP447 may have potential in treating some of the devastating effects of neurodegenerative and traumatic brain injuries.

Resident contribution: My involvement included helping to conceptualize and design the

study as well as perform the data analysis and write the manuscript. For much of the study's conduction, the in vitro work, and toxicology aspects, I was assisted greatly by the co-authors listed. A great deal of thanks must also be attributed to Dr Gary Dunbar at Central Michigan University who helped oversee the project and in whose laboratory the experiment was conducted.

X-STOP: An evaluation of a potentially minimal invasive treatment for symptomatic spondylolisthesis.

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Abstract

Objective: to evaluate the X-STOP interspinous implantation as a potential new, minimal invasive method to treat symptomatic spondylolisthesis.

Method: 28 patients underwent decompressive X-STOP interspinous implantation for lumbar stenosis using 14mm titanium spacers, between July 21, 2006 and May 30, 2008 at our desert facility. 39% of these patients (N=11) had an underlined grade 1 spondylolisthesis at the treaded levels. Anterior-posterior and lateral x-rays were taken pre and post-operative. Spondylotic offsets were measured before and after the X-STOP interspinous decompressive implantation, to see whether this minimal invasive treatment could be used solely for symptomatic spondylolisthesis. A reduction in spondylolisthesis of 50% or greater would be considered significant. Correlations with age and gender were compared.

Results: 18.2% (N=2) of our patients had significant realignment of the vertebral body after the X-STOP interspinous decompressive implantation. 100% restoration of the vertebral alignment was never achieved; 63% improvement in one and 53.4% improvement in the other. Over all correction of the spondylolisthesis was not significant. Average correction was 26.5% with a mean correction of 28%. Our figures ranged from 0.6% to 63.8% in least to greatest prospectively. Women (N=6) had better results than men (N=5), 29% to 23% improvement. One from each gender group had significant realignment as mentioned above. Age had no significant factor.

Conclusion: X-STOP interspinous decompression implantation is not significantly effective in correcting spondylolisthesis as a sole treatment. Our patients had a 26.6% reduction in lumbar grade 1 spondylolisthesis, which is radiographicly visible, but insignificant for the treatment of spondylolisthesis. We do not recommend it as a sole treatment unstable symptomatic spondylolisthesis of any grade.

Key words: X-Stop, Interspinous implantation, Minimal invasive lumbar decompression, Spondylolisthesis, Grade 1 Spondylolisthesis, Lumbar stenosis

Introduction

This is a prospective analysis of the X-STOP Interspinous Process Decompression (IPD) systems ("X-STOP") for Lumbar stenosis caused by spondylolisthesis. The objective was to evaluate the

X-Stop interspinous process decompressive implant for its affects on spondylolisthesis. The current treatment for symptomatic spondylolisthesis include; laminectomy, discectomy with fusion, interbody fusion, Pedicle screws and rod fixation, etc, depending on the degree of spondylolisthesis. The X STOP Interspinous Process Decompression systems was not marketed or approved for symptomatic spondylolisthesis. We have noted on several of our post-operative imaging, that re-approximation of spinal column was achieved with the X-STOP interspinous process implants. We aim to look more closely at the percentage of correction of the original spondylolisthesis following interspinous process implant (s) using S-STOP's titanium alloy implant. If our hypothesis is correct, this may yield a potentially minimal invasive treatment for symptomatic spondylolisthesis.

Background:

The X-STOP Interspinous Process Decompression (IPD) systems ("X-STOP") is a titanium alloy implant that was approved by the FDA in November 2005 as the first and only non-fusion treatment to improve symptoms and function of patients with lumbar spine stenosis[1]. X-STOP interspinous decompression has been available in Europe and Japan since 2001[4,5]. More than 7,000 X-STOP procedures have been preformed worldwide before its migration to the United States[4,5]. The X-STOP procedure fills a gap in the continuum of care for lumbar spine stenosis sufferers that, until now, required patients to leap from conservative therapies, such as analgesics and injections, straight to laminectomy. In the last 2 ½ years hundreds of X-STOP interspinous process implants have been performed and with efficacious results.

General terms:

Lumbar spondylolisthesis is a condition in which one vertebral body becomes progressively out of alignment with another in a front-to-rear orientation (Subluxation). Spondylolisthesis can be a progressively acquired spinal deformity occurring in the context of severe degenerative arthritis or it can occur as a result of a (usually hidden) birth abnormality of the spine. Both forms usually develop slowly over the course of many years and a person might not have any symptoms he considers abnormal until the process has been well established. Many people have no neurological symptoms and some even have few mechanical symptoms other than what they have come to know as "muscular pains".

Degenerative spondylolisthesis can be described as a deformity of the facet joints which normally prevent forward sliding of one vertebral body on another. The bone structure slowly yields to forces producing mal-alignment and is remolded. Many individuals will be found to have no instability or change in alignment during spinal movement but some will be unstable.

Occasionally, the upper vertebral body involved in the mal-alignment is displaced to the rear rather than toward the front, a condition sometimes called "retrolisthesis
Spondylolisthesis is most often seen at L5 on S1 occasionally on L4 on L5. 11 percent of men and 25 percent of women develop degenerative spondylolisthesis over their lifetime[8,9,10].

Lumbar stenosis is the narrowing of the AP dimensions of the spinal canal and lateral recess in the lumbar region. The reduction in canal size causes local nerve root compression and compromise of the blood supply to the spinal cord or cauda equina. Spinal stenosis can be congenital as in the achondroplastic dwarf, acquired, or most commonly acquired superimposed on congenital[8,9].

Spondylosis is a non-specific degenerative process of the spine that leads spinal stenosis. Facet hypertrophy, osteophytic changes, ligamental hypertrophy/calcification, disc herniation and or spondylolisthesis may add to and already congenital narrowed canal. L4/5 is the most common area of lumbar stenosis, followed by L4/3 and L2/3 respectively[9,10,19].

Neurogenic claudication, aka *pseudoclaudication* is unilateral or bilateral buttock, hip, thigh, or leg discomfort that is precipitated by standing or walking and characteristically relieved by a change in posture to sitting, squatting or recumbency[1,7,8].
This is not to be confused with vascular claudication aka intermittent claudication which results from ischemic change on exercised muscles causing similar symptoms but relieved my just resting. Neurogenic claudication is believed to arise from ischemic changes on Lumbosacral nerve roots due to compression of these nerve roots by surrounding structures[8,9]. Neurogenic claudication is specific for lumbar spine stenosis. Patients with neurogenic claudication develop the “anthropoid Posture”. Anthropoid posture is an exaggerated waist flexion. These are the classically elderly hunched forward as they walk, or resting their forearms on a shopping cart as the walk. The lumbar flexion allows for improved lumbar canal stenosis, and decreasing radiculopathy associated with lumbar spine stenosis[8,9,24,27].

Grade	**Amount of subluxation**
I	< 25%
II	25-50%

III	50-75%
IV	75-100%

Table 1: Grading of spondylolisthesis

Figure 1: Titanium alloy implant that varies in diameter from 6mm-16 mm

Figure 2: Illustration of X-STOP Interspinous Process Decompression (IPD) systems implant. Central core spacer separates spinous processes and two wings retain it in place

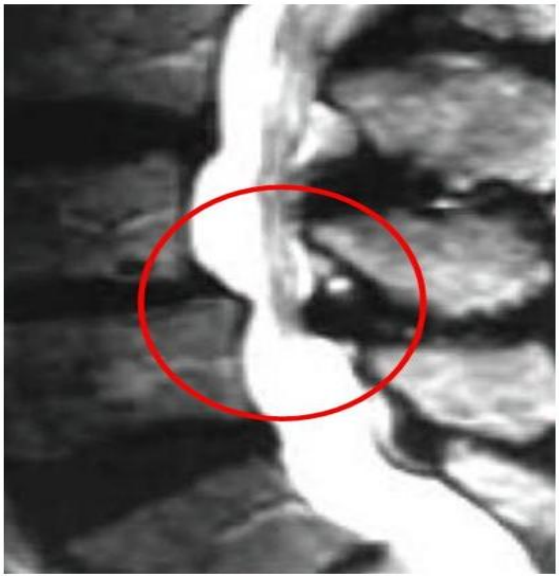

Figure 3: Lumbar stenosis due to grade 1 spondylolisthesis and facet disease (Inside red circle)

Materials and Methods:
Our Facility has performed a total of 37 X-STOP lumbar interspinous process decompression surgeries with various spacers from 10 mm to 14mm. The company (Kyphon) advocates a 16mm spacer, but none had been available for clinical use. Our study is limited to 28 patients who underwent X-STOP interspinous implantation for lumbar stenosis using 14mm titanium spacers, between July 21, 2006 and May 30, 2008 at our desert facility. We would have preferred the largest 16 mm spacer over the 14 mm spacer for optimal results. We did not include 10mm or 12mm spacers on our study. 39 percent of our 28 patient group (N=11) had an underlined grade 1 spondylolisthesis at the treaded levels. We did not include spondylolisthesis outside our surgical site(s). Pre and Post-operative lumbar x-rays were taken with an Anterior-posterior and lateral views. Spondylotic offsets were measured before and after the X-STOP interspinous decompressive implantation. Measurement of the Spondylotic offset pre-operative (Spndy) were compared to post-operative offset (PO spdy). The difference (Sdy Chg) multiplied by 100 percent, lead to percent improvement (% improve). A reduction in spondylolisthesis offset by 50% or greater would be considered significant. Correlations with age and gender were compared.

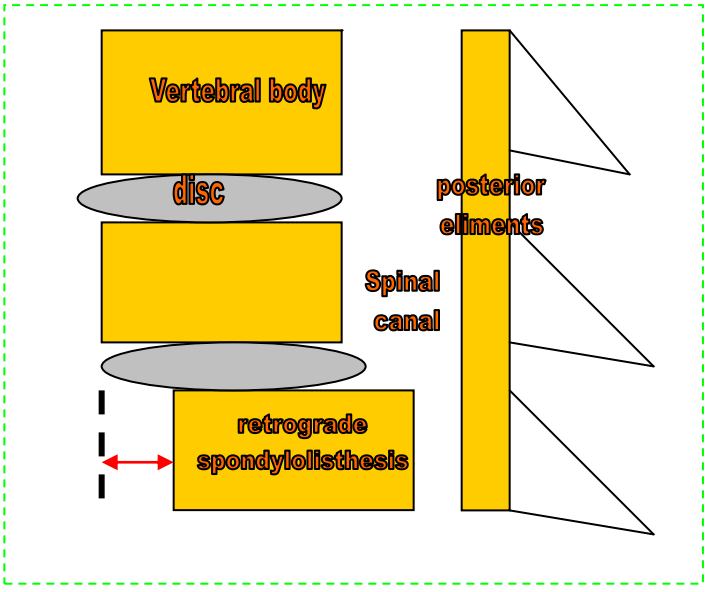

Figure 4: Diagrammatic representation of lumbar stenosis via retrograde spondylolisthesis and spondylotic offset (Red Arrow)

Results

Age	Sex	DOS	Levels	Spndy	PO Spdy	Spd Chg	% improve

62	F	4/18/2008	**L4/5**	7.39mm	5.13mm	2.26mm	30.6
83	F	4/18/2008	L3/4 **L4/5**	3.53	2.58	0.97	27.5
79	F	4/16/2008	**L4/5** L5/S1	8.25	6.03	2.22	26.9
78	M	2/23/2008	L3/4 **L4/5**	7.05	4.2	3.75	53.4
70	M	2/1/2008	**L3/4** L4/5	11.9	11.2	0.7	5.9
72	M	2/1/2008	**L4/5** L5/L6	4.57	4	0.57	12.5
62	F	9/28/2007	L3/4 **L4/5**	7.13	2.58	4.55	63.8
68	M	5/25/2007	L2/3 **L4/5**	11.7	11.5	0.2	1.7
75	F	5/18/2007	L1/2 **L4/5**	8.7	6.5	2.2	25.3
82	M	5/18/2007	**L4/5** L5/S1	10.9	6.01	4.89	44.9
66	F	4/27/2007	L2/3 **L4/5**	8.85	8.9	0.05	0.6

Table 2: Patients with spondylolisthesis, age, sex, date of surgery, Level(s) of implants (Spondylolisthetic level in bold), Spondylotic offset (Spndy), Post-Operative spondylotic offset (PO Spdy), difference in offset (Spd Chg), and Percent improvement (% improve)

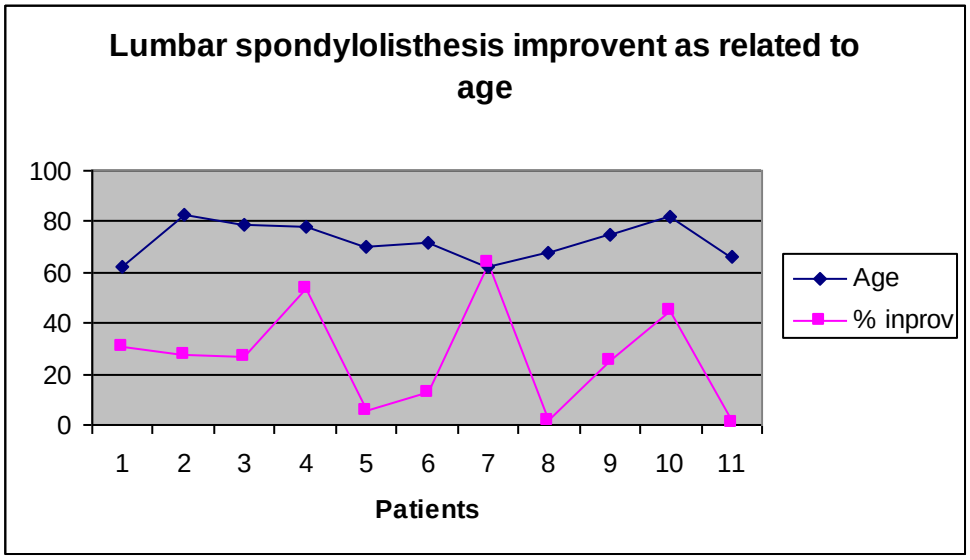

Figure 5: Post-operative Lumbar spondylolisthesis improvement as it relates to age

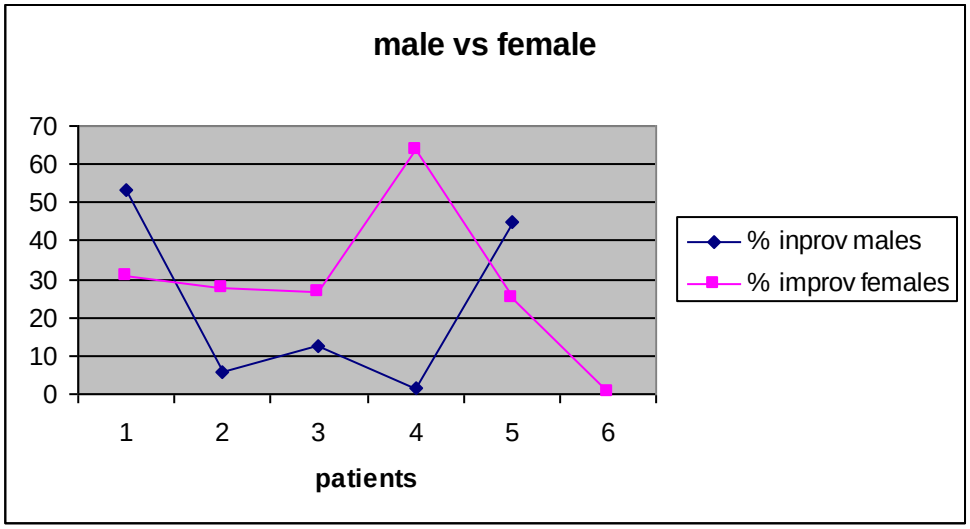

Figure 6: Spondylolisthesis improvement status post X-STOP interspinous implant, male compared to female

Of the 28 patients who underwent decompressive X-STOP interspinous implantation for lumbar stenosis using 14mm titanium spacers, 39% of these patients (N=11) had an underlined grade 1 spondylolisthesis at the treaded levels. 18.2% (N=2) of our patients had significant realignment of the vertebral body after the X-STOP interspinous decompressive implantation. 100% restoration of the vertebral alignment was never achieved; 63% improvement in one and 53.4%

improvement in the other. Over all correction of the spondylolisthesis was not significant. Average correction was 26.5% with a mean correction of 28%. Our figures ranged from 0.6% to 63.8% in least to greatest. Women (N=6) had better results than men (N=5), 29% to 23% improvement overall. As it relates to significant improvement, there were no differences in gender. Age had no significant influence.

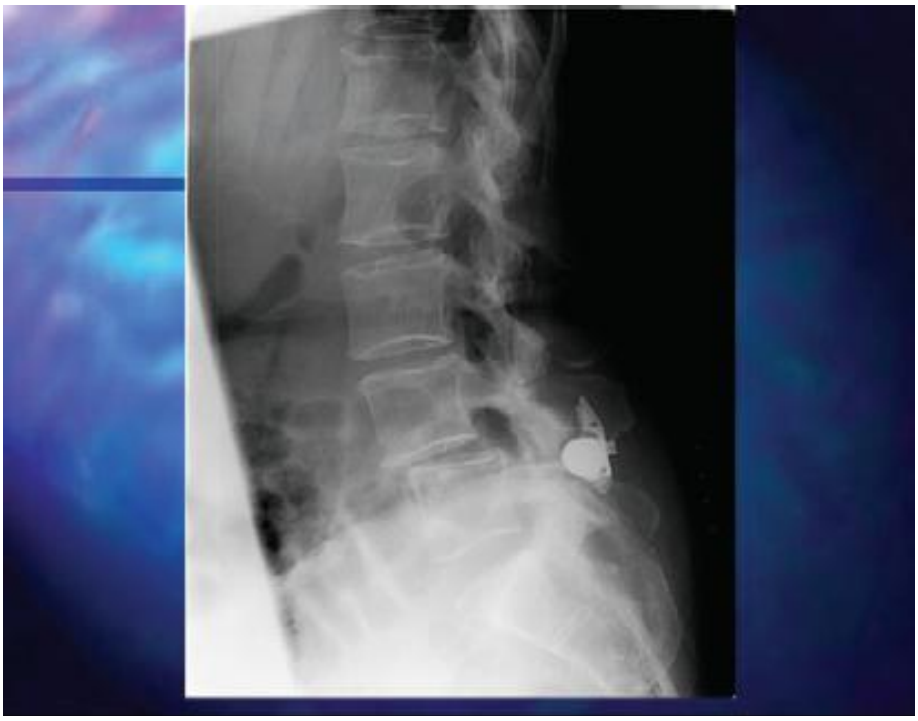

Figure 7: Post-operative x-ray showing X-STOP implant with the L4/5 interspinous space. The 14 mm implant improved the vertebral alignment, but not significantly

Discussion

Even though our sample size was small, our results were constant. The majority of patients (91%) had two levels implants. All had 14 mm spacer. Our result varied from 0.6% improvement to 63% improvement. The lack of improvement may be attributed to facet disease, osteophytic, etc, that are stronger inhibitors of motion, despite spacer size. The greater improvements maybe explained by soft tissue inhibitors of motion, i.e. disc, ligaments, scare tissue, etc. Age had not significance. All the patients were elderly and results varied. When it came to gender, females had an obvious constant improvement compared to males. This again can be explained with flexibility of women over man and the degree of calcium deposits as it relates to gender. Our study didn't not yield any significant result, but our goal was met. We have evaluated the X-STOP interspinous implantation as a potential new, minimal invasive method to treat symptomatic spondylolisthesis, and discovered that it is not efficacious. In the future, if the 16 mm spacer becomes available a re-evaluation should be indicated.

Conclusion

X-STOP interspinous decompression implantation is not significantly effective in correcting spondylolisthesis as a sole treatment. Our patients had a 26.6% reduction in lumbar grade 1 spondylolisthesis, which is radiographicly visible, but insignificant for the treatment of spondylolisthesis. We do not recommend it as a sole treatment unstable symptomatic spondylolisthesis of any grade.

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Current Treatment of Intracranial Germinomas: An Evidence-Based Review

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Abstract
Objective. The aim of this study is to determine the current recommendations for management of intracranial germinomas, based on the existing literature.
Methods. A detailed search of the medical literature was performed using Medline and the Cochrane library database. The quality of evidence was analyzed according to the categories of evidence as defined by the U.S. Preventative Task Force.
Results. A total of 48 studies were included. The majority were retrospective reviews, with six studies being randomized trials or prospective studies. However, due to the rarity of the disease, a true randomized, controlled clinical trial is difficult to implement. Therefore, most of the literature consists of retrospective series examining the benefits of radiation and chemotherapy, following surgical biopsy or resection.
Conclusions. The evidence suggests that treatment strategies are varied, with combination chemotherapy and reduced-dose irradiation being common. Further investigation is warranted.

Key words: germinoma, treatment, radiation, chemotherapy, intracranial

Introduction

Intracranial germ cell tumors are relatively rare in the United States, accounting for approximately 2-3% of all pediatric central nervous system tumors. They are found more commonly in Eastern countries, comprising 15-18% of pediatric brain tumors in Japan, Taiwan, and Korea. They tend to present in the second to third decade and are located in the pineal region (45%), suprasellar region (35%), both areas (10%), and other locations (5%)[8,10,44].

Germ cell neoplasms can be divided into two classifications: germinoma or non-germinomatous germ cell tumors. Choriocarcinoma, endodermal sinus or yolk sac tumor, embryonal carcinoma, and mixed tumors comprise the non-germinomatous germ cell group. Management varies based on this classification[10].

The diagnosis of germinoma is multifactorial and institution-dependent. CSF is sent for tumor markers (alpha-fetoprotein and beta-human chorionic gonadotropin) to exclude yolk sac tumor or choriocarcinoma. Typically, pathology is obtained via surgical biopsy or resection. Biopsy may be open or stereotactic, usually based on whether there is eloquent cortex or major vasculature in proximity to the lesion. Similarly, resection may be total, subtotal (>95%), or partial, based on the initial pathology and ease of resection. For example, surgical procedures for

germinomas are usually only biopsies, since they are exquisitely radiosensitive. The following review will evaluate the modern literature and summarize the current treatment trends for germinomas[6,8,10].

Materials and Methods

A detailed search of the medical literature was performed searching Medline and the Cochrane library database using search term of "treatment of intracranial germinoma". A total of 334 results returned and only those studies pertaining to the treatment of intracranial germinomas were selected. Those studies not published in the English language were excluded. Germinomas were limited to the pineal and third-ventricle region. The search included intracranial germ cell tumors, but excluded non-germinomatous tumors. The quality of evidence was assessed according to the categories of evidence as defined by the Agency for Healthcare Research and Quality, U.S. Preventive Service Task Force (Fig 1, Table I)[30].

Figure 1

Category of Study Design	Type of Study Design
I	Evidence obtained from at least 1 properly randomized clinical trial
II-1	Evidence obtained from well-designed studies without randomization (eg. concurrent cohort studies)
II-2	Evidence obtained from well-designed retrospective cohort or case-control studies
II-3	Evidence obtained from multiple time series with vs. without the intervention, or dramatic result in uncontrolled experiments
III	Opinions of respected authorities based on clinical experience, descriptive studies, and care reports, or reports of expert comittees

Adapted from: Riegelman RK (2005) Studying a study & testing a test. Lippincott Williams & Wilkins, Washington DC

Results

The search returned 337 citations, with 48 qualifying for further analysis. The majority of the reports consisted of retrospective reviews or case-studies. Again, due to the rarity of the disease, prospective randomized clinical trials were rare. Six studies were randomized trials or prospective studies[1,4,5,18,36,37]. A total of 47 articles discussed treatment responses to radiation therapy [2-12,14-22,24-29,31-41,43-52], most also addressing chemotherapy.

The predominant treatment for germinomas consisted of radiotherapy after biopsy or surgical resection, with survival rates of 90-100%[11]. Biopsy may be open, stereotactic, and/or endoscopic, depending on the anatomy of the tumor and presence of eloquent surrounding tissue. Chernov et al recently reported a series of neurofiberscopic biopsies with simultaneous third ventriculostomy for tumors of the pineal gland and posterior third ventricle. Indications given for the biopsy included necessity for histological diagnosis, decompression of tumor associated cyst, and management of triventricular obstructive hydrocephalus. The neuroendoscopic procedure provides numerous possibilities for removal of tumor, opening and fenestrating an associated cyst, management of hydrocephalus by endoscopic third ventriculostomy, as well as direct visual control, with presumptive decrease in morbidity and mortality associated with open biopsy and better management of intraoperative tumoral hemorrhage[6].

Following histological diagnosis, cranial irradiation is normally given. Due to varied reports of unfavorable neurologic outcomes with radiation therapy, alternative forms of treatment have been explored, mainly chemotherapy. Attempts at chemotherapy as the primary treatment have been abandoned as the relapse rate is high (48-49% in 3-5 years)[11,22]. The initial response rate to chemotherapy (77%) is also lower than to radiation therapy[10]. Combination therapy with radiation and chemotherapy has shown promising results[1,2,5,6,8,10,11,13,18,20,22,24,25,28,35,36,38,39,42-45,47,49,51].

Discussion

Historically, the treatment for intracranial germinomas has consisted of radiotherapy after histological confirmation of the diagnosis, with survival rates of 90-100%[11]. However, cranial irradiation has traditionally been associated with intellectual deterioration, growth retardation, endocrine dysfunction, hearing loss and radiation-induced tumors[10]. Recent studies have been more encouraging about the long-term effects of cranial irradiation: Ogawa et al reported no apparent neurocognitive effects at <55Gy. In the MAKEI 83/86/89 German Cooperative Prospective Trials severe and permanent neurological deficits were all tumor and/or surgery-related. No patient in either series developed a new endocrine abnormality after radiation therapy[4,27].

Due to the traditional reports of unfavorable outcomes with radiation therapy, alternative forms of treatment have been explored, mainly chemotherapy. Attempts at utilizing chemotherapy as the primary treatment have been abandoned due to the high relapse rate (48-49% in 3-5 years [11,22]). The response rate to chemotherapy initially is also lower than to radiation therapy (77%)[10]. As pointed out by Shim et al, the long term effects of chemotherapy are also unknown; renal or gonadal effects are possible with a potential leukemogenic risk[39]. Choi et al have described an alternative approach to diagnosis, in which the decision whether to operate at all is made after a trial of chemotherapy. The patient population, MR characteristics

of the tumor, presence of tumor markers, and response to chemotherapy are used to make a presumptive diagnosis and predict outcome without histological verification[8]. This approach is reminiscent of the practice of irradiating tumors without surgical biopsy in areas where germinoma is endemic, such as Asian countries. Since germinoma is not as prevalent in the United States, this approach should be justified by a randomized, prospective trial.

Combination therapy with radiation and chemotherapy has been successfully utilized. Chemotherapy regimens are based on combinations of platinum-therapy based around carboplatin and cisplatin, with the goal of titrating down the radiation therapy[11,22]. Yoshida et al presented a cooperative study in 1993 showing the effectiveness of chemotherapy with cisplatin and etoposide[51]. The French Society of Pediatric Oncology reported on 29 germinomas treated with two cycles of carboplatin, etoposide and ifosfamine followed by a dose of 40 Gy having an overall survival rate 100% with event-free survival 93.3% at 32 months[39]. Allen et al in 1985 reviews chemotherapy trials and concluded high doses of cyclophosphamide and cisplatin as well as VAB 6 has definite activity in germinomas[1].

There is a lack of standardization of radiation therapy in regards to field size and dose[44]. Most series recommend doses of 50-54 Gy to the tumor bed with craniospinal dosing ranging from 20-30 Gy. However, with adjuvant chemotherapy, it may be reasonable to consider a reduction in field size to the primary tumor, along with a margin treated with a reduced dose for non-disseminated disease. Craniospinal irradiation is not routinely given[44]. In one recent multi-institutional Phase II study, pure germinomas received CARB-VP (carboplatin-etoposide) or PE (cisplatin-etoposide) with 24 Gy to tumor site[23]. The rate of complete response was 83-6 % with chemotherapy alone. Tumor-free rate after chemotherapy and radiation was 92%, with a recurrence rate of 12%. The authors believed that the elevated recurrence rate was secondary to the limited radiation field of less than 1cm margin[22]. In Aoyama's phase II study treating germinomas with etoposide and cisplatin, disease-related, overall and relapse-free survival rates at 5 years were 100%, 100%, and 86%, respectively. One patient out of 16 total experienced relapse, and was free of disease after salvage therapy. These authors concluded that the prognosis of intracranial germinoma was excellent after etoposide and cisplatin treatment, followed by 24 Gy radiotherapy[2]. Cisplatin alone has also been used, followed by reduced-dose irradiation[11]. The target volume in this regimen includes parenchymal margins of 0.5-1.5 cm and ventricular margins of 1-2cm with dosing of 30 and 36 Gy. A survival rate of 100% was reported at 57 months, with 2 eventual relapses (out of 8 patients). The failures were retreated with chemotherapy, followed by cranial- spinal irradiation of 19.8 and 21.6 Gy, with tumor boosts of 36 months. Both patients had no evidence of recurrent disease at 29 and 51 months from time of recurrence. Douglas further comments on large European trials showing a predominance of ventricular subependymal dissemination as the primary source of failure, causing the study group to consider including the entire ventricular system in their initial treatment plan. These studies suggest that current regimens of chemotherapy are unable to clear

the ventricular CSF of tumor cells in 10-15% of patients and that these patients may require further treatment. At this time, the effects of boost irradiation are unknown. However, survival rates still remain excellent with reduced dose irradiation[11]. There are two experimental treatment plans under consideration for a prospective North American trial, both of which involve less than whole-brain radiotherapy. The options include radiation alone using ventricular irradiation followed by a boost to the tumor, or chemotherapy followed by irradiation of the involved fields[31].

Conclusion

Germinomomas are rare intracranial tumors that are very radiosensitive. Current methods of diagnosis include biopsy (open, stereotactic, neuroendoscopic), MR imaging, CSF markers, and response to empiric chemotherapy. The evidence suggests that treatment strategies are varied, with radiation alone or combination chemotherapy and reduced-dose irradiation being most common. Further investigation is warranted to compare the risks of boost irradiation associated with recurrences after reduced-dose radiotherapy versus higher-dose initial radiotherapy. The side effects of chemotherapy need to be weighed against those of radiotherapy, as well. Prospective studies of sufficient size are now needed to create evidence-based guidelines for management of these rare tumors.

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Table 1

Reference	Evidence type	Description
Shim 2007[39]	II-3	Retrospective study comparing radiation (40-45Gy) alone, chemotherapy alone, and combined (N=117). 10 year overall and relapse-free survival rates with 97/93% in radiation alone, 87/67% in chemotherapy alone group, and 92/92% in combined. Conclusions: radiation therapy alone with dose less than 40 Gy should be compared to chemo protocols with low-dose irradiation
Osuka 2007[28]	II-3	Retrospective study looking at outcome (N=19). Consider at least 24 Gy of radiotherapy to the whole ventricle is essential and elective use of combination chemotherapy and/or local boost radiotherapy to prevent recurrence.
Nguyen 2006[26]	II-3	Retrospective review of series of patients receiving craniospinal irradiation and focal irradiation (N=21). Focal techniques of irradiation tend to be associated with increased failure rates. Local control rates for focal irradiation 59% versus CSI 100%.
Nakamura 2006[25]	II-3	Retrospective review of reduced radiation volume and combined chemotherapy (N=52). Concluded in combination with chemotherapy, the delivery of irradiation covering the ventricles (24 Gy) effectively reduced recurrence
Douglas 2006[11]	II-3	Retrospective review with treatment with platinum-based chemotherapy and focal, reduced dose irradiation (N=8). 57 months follow-up- 100% survival rates with treatment of 30.6-36Gy. 5 year actuarial CNS control rate 71.4% (2 failures), both treated with chemotherapy and irradiation and no further complications. Recommend reduction in dose and volume retains excellent survival rates.
Chitapanarux 2006[7]	II-3	Retrospective study evaluate local control and overall survival after radiotherapy (N=32). Concluded that definitive radiation therapy is effective in controlling germinoma with excellent cure rates 83.1-90%.
Schoenfeld 2006[33]	II-3	Retrospective review low-dose CSI (21Gy) with boost to ventricular system (9Gy) and primary site (19.5Gy) (N=29). 94% disease free.
Strojan 2006[45]	III	Review of radiotherapy (tumor bed, whole brain, CNS) and adjuvant cyclophosphamide (N=9). 6 pt alive 19 years from diagnosis. Results confirm efficacy and relative safety of limited-field and reduced-dose radiotherapy with adjuvant chemotherapy.

Endo 2005[12]	III	Case report of germinoma treated with gamma knife (10-12 Gy) followed by whole ventricular irradiation (24Gy) (N=3). All patients had complete response to the combined radiotherapy.
Rogers 2005[32]	III	Review of radiotherapy from publications since 1988. Recurrence rate after whole-brain/whole-ventricular radiotherapy plus boost with 7.6%, compared with 3.8% after SCI with no predilection for isolated spinal relapses (2.9 vs 1.2%). Challenge consensus that SCI is the best treatment for germinomas and conclude that reduced-volume radiotherapy plus boost should replace CSI when radiotherapy only approach is used.
Shikama 2005[38]	II-2/3	Retrospective multi-institutional review of patients with germinomas treated with radiotherapy and/or chemotherapy (N=180). Over all survival rate was 91% and event-free survival rate was 89%. Concluded that spinal irradiation did not contribute to a favorable event-free survival.
Silvani 2005[43]	III	Single institution reporting on radiation therapy (30Gy) after neoadjuvant therapy, cisplatin-vinplastin and bleomycin combination (N=20, 18 germinoma, 2 germinomas with STGC). Mean 55 month follow-up, 18 pt alive without recurrence (germinomas).
Roberge 2005[31]	II-3	Retrospective study on theoretical impact of selecting different target volumes and treatment techniques with radiation (N=5). Conclusions: the substitution of whole-ventricular irradiation for whole-brain irradiation can spare a significant amount of normal tissues, ventricular irradiation is best achieved with at least 4-field 3D configuration, and exclusion of 4^{th} ventricle in the target volume had only a minimal impact on normal tissue doses.
Shirato 2004[40]	II-3	Reanalysis of previously published report and examined target volume margin (N=27). 6 relapses were seen in 18 patients with solitary tumors and were treated with minimum margin of 1.5 cm or less. No relapses seen in 9 patients treated with whole ventricle or whole CNS field. Recommend that whole ventricle is the smallest target volume for germinoma after induction therapy.
Kellie 2004[18]	I/II-1	Trial enrolled 19 patients to determine whether intensive cisplatin and cyclophosphamide based chemotherapy without radiotherapy was effective in patients with CNS germinoma. 5 year event-free survival was 0.47 and 5 year overall survival 0.68. Concluded intensive cisplatin and cyclophosphamide-based chemotherapy was effective in achieving remissions, but long-tern outcome is unsatisfactory.
Smith 2004[44]	II-3	Analysis of experience and review of literature (N=17, germinoma=7). Chemotherapy regimen:

		carboplatin, etoposide, bleomycin and radiation treatment 24-36 Gy, CSI in 2 patients. Concluded: little evidence that CSI is necessary in non-metastatic germinomas.
Maity 2004[21]	II-3	Retrospective review of CSI (N=39). Radiation therapy consisted of: median doses to whole brain- 36Gy, primary site- 50.4 Gy and spine- 36Gy. Mean follow-up 7.1 years with no documented relapses.
Ogawa 2004[27]	II-2/3	Multi-institutional study to evaluate long-term results of RT in intracranial germinomas. 10 year overall survival 90%, cause-specific survival rate 95%. No in-field relapses at primary sites in 72 patients treated with total doses 40-50Gy. Incidence of spinal relapses was 4% for patients treated with spinal irradiation and 3% for those without spinal irradiation. No patients treated with total doses <55Gy developed apparent neurocognitive dysfunctions or other complications after RT.
Tseng 2003[47]	II-3	Retrospective review of RT for germinomas (N=30). Whole axis (N=10) received 30.6Gy, whole brain (N=8) received 30.6Gy, and local tumor site (N=12) received 50.4 Gy. 9 received chemotherapy. 7/30 had treatment failure- 5/12 with partial RT vs 2/18 whole brain. Concluded partial RT associated with higher probability of intracranial relapse and sparing spinal RT would not result in more spinal failure, whole brain RT is sufficient for tumor control on primary CNS germinoma.
Haas-Kogan 2003[15]	II-2/III	Multicenter review to assess CSI on patterns of relapse, progression-free survival (PFS), and overall survival (OS) (N=93, germinomas= 49). 5 year PFS and OS for germinomas were 88 and 93%. Out of 41 localized germinomas 6 received CSI, 35 did not and no spinal cord relapses occurred. 21/41 didn't receive either CSI or whole brain radiation, only ventricular radiation, and none relapsed. Concluded: CSI is not indicated in treatment of localized germinomas, and recommend ventricular irradiation followed by primary tumor books to a total of 45-50 Gy if treated by radiation alone.
Aoyama 2002[2]	I/II-1	Results from phase II study to address the outcome of chemotherapy (etoposide and cisplatin) followed by low-dose radiotherapy (24Gy) (N=16). 5 year disease-related survival rate 100%, overall survival 100% and relapse-free 86%. No decline in full-scale, verbal, or performance intelligence quotient in 11 patients. Recommended that dose and volume can be reduced to 24Gy in 12 fractions.

Zissiadis 2001[52]	III	Series evaluation stereotactic radiotherapy (N=18, germinoma=13, tumors=23). Boost using stereotactic radiotherapy delivered to patients receiving whole brain and CSI. Median doses for whole brain 25.2Gy, spinal field 21.6 Gy and stereotactic boost dose 26 Gy. 40 months follow up, no local or marginal recurrences in germinoma patients.
Shibamato 2001[36]	I/II-1	Prospective study to evaluate if germinomas can be cured with radiation doses less than 50 Gy and determine 10 year follow up (N=38). Radiation doses to tumor site were: 36Gy after total removal, 40Gy for tumors < 2.5 cm, 45Gy 2.5-4.0cm, and 50 Gy >4.0cm with 1.6-1.8 Gy daily fractions and 24 Gy to cerebrospinal axis depending on diagnosis. 10 year overall and relapse-free survival rates 91 and 95%. Conclusions: all tumor volume-based radiation doses were effective. 4cm or else can be cured with doses 40-45 Gy.
Matsutani 2001[22]	II-3	Review of clinical studies performed in Japan (N=75). Pure germinomas received CARB-VP (carboplatin-etoposide) or PE (cisplatin-etoposide) with 24 Gy to tumor site. The rate of complete response was 83-6 % with chemotherapy alone. Tumor free rate after chemotherapy and radiation was 92% with recurrence rate of 12%. The authors state that the elevated recurrence rate is secondary to having a limited radiation field of less than 1cm margin and state they now use a more generous field and different protocol.
Farng 1999[13]	II-3	Retrospective review on treatment of germinomas with chemotherapy (vinplastin, bleomycin, cisplatin, and etoposide-VBPE) alone (N=11). 11 achieved complete response with 6 patients having relapses but achieved a second complete response after salvage focal radiotherapy.
Shibamoto 1999[35]	III	Report on salvage radiation therapy after failure following primary chemotherapy (N=5). Tumor site radiation with dose range 39.6-47.0. No further recurrence 61-129 months follow-up.
Sutton 1999[46]	III	Study examining quality of life after whole-neuraxis irradiation for marker-negative germinoma (N=22). Concluded QOL is generally good status post prophylactic whole-neuraxis irradiation.
Diez 1999[10]	II-3/III	Review of most recent advances in CNS germ cell therapy.
Bamburg 1999[4]	I/II-1	Multicenter prospective trial to assess outcome after treatment with radiotherapy alone (craniospinal axis/local boost) at reduced doses (N=60). MAKEI 83/86- 11 patients received 36 GY to CSA, 14 Gy to tumor region. MAKEI 89- 49 patients received 30 Gy to CSA and 15 Gy to tumor region. Complete remission in all patients. No relapses in 83/86, 1 CNS relapse in 89

		(4 outside CNS). Conclusions: radiotherapy directed toward CSA or tumor site alone at decreased dose levels is effective.
Bouffet 1999[5]	I	Randomized controlled multicenter clinical trial evaluating combining chemotherapy (carboplatin-etoposide and etoposide-ifosfamide) with 40Gy local irradiation (N=57). The estimated 3 year survival probability and event-free survival is 98 and96.4% respectively. Conclusions: excellent survival rates in combining chemotherapy and local radiotherapy with non-metastatic intracranial germinomas.
Regine 1998[29]	III	Case report on treatment with radiosurgery alone (N=1). The patient received single dose of 14Gy. No residual disease 2 years out.
Merchant 1998[24]	II-3	Retrospective radiation therapy as salvage therapy after relapsing with primary chemotherapy (PEB) (N=8). At time relapse, patients received high-dose cyclophosphamide with CSI (25.2-36Gy) and boost to site of recurrent disease (45-54Gy). No failures 32 months follow up.
Choi 1998[8]	II-3	Retrospective review of treatment of germ cell tumors (N=107, germinomas= 39). Propose new treatment protocol.
Haddock 1997[16]	II-3	Retrospective review of radiation therapy (N=48).12 were treated with CSI, 11 received whole-brain without CSI, and 24 underwent partial-brain irradiation. Median dose to the primary tumor 44Gy. Increased failures with partial-brain irradiation. Concluded whole-brain or CSI results in fewer failures and doses >40Gy to tumor is associated with better control.
Shirato 1997[41]	II-3	Study to determine appropriate treatment policy (N=51). 16 whole CNS treated, 9 whole brain, 21 whole ventricle, and 5 localized field smaller than whole ventricle. 4 relapses- 2 spinal canal, none with 40Gy treatment. Concluded 40Gy whole-ventricular irradiation using precise three-dimensional treatment planning is appropriate as a standard treatment for most intracranial 0germinoma.
Huh 1996[17]	II-3	Review of radiotherapy for intracranial germinomas (N=32). 29 patients underwent CSI- 54Gy to tumor bed, 36Gy to whole brain, and 24Gy to spinal axis. 5 and 10 year survival rates 96.9 and 96.9%.
Wolden 1995[49]	II-3	Review to define role of prophylactic craniospinal irradiation and chemotherapy (N=48, germinoma=24). 91% disease free survival in germinomas with doses of 50-54Gy to local tumor

		site with or without whole brain or whole-ventricular irradiation. Routine prophylactic cranio-spinal axis irradiation was not give with a spinal failure rate of 2%. Concluded with complete diagnostic craniospinal evaluation, spinal irradiation is not necessary.
Xu 1995[50]	II-3	Review of germinomas receiving radiotherapy (N=31). Clinical symptoms improved in 93.55 of patients and consider that the initial treatment with radiotherapy may be appropriate.
Shibamoto 1994[37]	I/II-1	Prospective study evaluating the reduction of radiation dose (N=84). 5 and 10 year survival rate 88 and 83%, relapse-free survival rate 88 and 85%. 31 patients received 19-47 Gy (10 year relapse-free survival 88%), 28 patients received 48-52Gy (92%), and 25 patients received 54-62Gy (83%). There was no significant difference among the three groups. In field recurrence only developed in one patient who received 40Gy and one who received 60Gy. Concluded can treat germinomas $\leq$4cm can be cured with 40-45Gy of radiation.
Yoshida 1993[51]	I/II-1	Co-operative study to analyze patients with intracranial germ cell tumors and the effectiveness of Cisplatin/Etoposide (CDDP/VP-16) (N=46, germinoma=13). 16 received chemotherapy alone, 30 were treated with combination of surgery and/or radiation in addition to chemotherapy. 10/13 showed complete response, 1/13 partial response to CDDP/V-16 chemotherapy. 88% 2 year survival rate for germinomas.
Aydin 1992 [3]	III	Case study reporting pathologic data of a pineal germinoma treated 8 days with radiation (total 16Gy) with no viable tumor cells on histological sections. Concluded germinomas can be treated with much smaller dose of radiation.
Dattoli 1990[9]	II-3	Retrospective analysis on limited volume irradiation (N=30, germinoma=13). 12/13 were treated with partial brain fields: 10 were tumor plus margin, 2 were entire ventricular system plus tumor boost. 12/13 received 49-55Gy to the primary target and remained free of disease 81 months out. 1/13 received 39.6Gy suffered from local and spine relapse. Concluded irradiation of partial brain is sufficient.
Linstadt 1988[19]	II-3	Retrospective study looking at radiation therapy (N=33). All patients were treated with total dose between 40-55Gy. 2 treated with prophylactic spinal irradiation. No initial or adjuvant chemotherapy was given. Concluded risk of spinal metastases is too low to warrant routine spinal irradiation.
Shibamoto 1988[34]	II-3	Results of treatment of intracranial germinoma as a function of the irradiated volume (N=70).

		Target of radiation was primary tumor site in 34 cases (group A), entire neuraxis in 22 (B), whole brain in 4 (C), and ventricles plus spine in 6 (D). Average dose was 50-55Gy to tumor, 30Gy to whole brain, and 24Gy to spinal axis. Survival and relapse-free survival did not differ significantly between the 4 groups. Concluded for cytology-negative cases without metastasis, irradiation of the tumor plus a wide margin is usually sufficient but craniospinal irradiation should be considered when the disease extends along the ventricular walls or is present pineal and suprasellar.
Fields 1987[14]	III	Series report on patients treated with varying doses of radiation dosing (N=9). Entire craniospinal axis was irradiated with median doses of 45.6 to tumor volume, 31.6Gy to whole brain and 25.2Gy to spinal cord. No recurrence among 7 patients, 2 died without evidence of tumor. Recommend that 45Gy may be sufficient if tumor volume is adequate.
Allen 1985[1]	II-2/II-3	Chemotherapy trials in recurrent primary intracranial germ cell tumors (N=8, germinoma=4). Concluded high doses of single chemotherapy agents like cyclophosphamide and cisplatin as well as VAB 6(vinblastine, bleomycin, cyclophosphamide, actinomycin-d, cisplatin) regimen have definite activity in recurrent CNS germ cell tumors, especially germinoma.
Siegal 1983[42]	III	Case report showing disappearance of germinoma to combination of cis-platinum, bleomycin, and vinblastine.
Waga 1979[48]	III	Report on result of germinoma treatment with radiation (N=62). 5 year survival rates was 61% and 10 year 55%.