Be Aware of Potential for Significant Platelet Dysfunction in TBI Patients

Platelet Dysfunction and Platelet Transfusion in Traumatic Brain Injury.

Briggs A, Gates JD, et al:


Platelet dysfunction after traumatic brain injury results from both aspirin therapy and the injury itself.

**Background:** Platelet function, which is important for initial coagulation after traumatic brain injury (TBI), may be negatively altered by medication or the injury itself. Platelet transfusion is associated with increased risk of complications and/or death.

**Objective:** To determine if platelet transfusion would improve aspirin-induced, but not trauma-induced platelet dysfunction.

**Design:** Single-institution, prospective, case cohort study.

**Methods:** Patients with intracranial hemorrhage (subdural, epidural, subarachnoid, and/or intraparenchymal) after TBI were assessed with platelet count and hematocrit initially after admission and at the next clinical blood draw after admission. Platelet function was assessed by a Multiplate multiple electrode aggregometer (but clinicians were blinded to results). Patients on anticoagulation therapy other than aspirin or clopidogrel, a history of thrombocytopenia or other coagulopathy, or non-head, neck, or face Abbreviated Injury Scale score >3 were excluded. All patients on pre-injury aspirin therapy were transfused 1 unit of apheresis platelets <4 hours after admission. Patients taking aspirin and given transfusion were compared to those not taking aspirin.

**Results:** Of the 17 patients prospectively enrolled (median admit Glasgow Coma Scale score of 15), 12 were taking aspirin (including 3 also on clopidogrel). Ten were taking aspirin 81 mg and 2 were taking aspirin 325 mg. All 12 received platelet transfusions; none of the 5 non-aspirin patients received transfusions. Aspirin patients were older (median age, 79.5 years) than non-aspirin patients (67 years). All aspirin patients had abnormal arachidonic acid (median, 19 U) and collagen platelet activation (median, 25.5 U), whereas non-aspirin patients had normal arachidonic activation (median, 46 U) but abnormal collagen activation (median, 37.0 U). Platelet count did not vary over time for non-aspirin patients. After platelet transfusion in aspirin patients, arachidonic activation improved (median, 26 U), but collagen activation was unchanged (median, 24 U). Platelet count did not vary over time in aspirin and transfusion patients.

**Conclusions:** Patients with TBI have abnormal platelet function in response to collagen that is not improved with transfusion of 1 unit of apheresis platelets. Patients taking platelets had their abnormal response to arachidonic acid improve with platelet transfusion

**Reviewer’s Comments:** This small study demonstrates that aspirin, as well as brain injury itself, negatively impacts platelet function, and that transfusion of platelets can correct some of these changes. The clinical relevance of these changes is not defined by the study, as subsequent neurological status and CT scans were beyond its scope. Many unanswered questions are left hanging, including impact of severity of brain injury (clinical and radiographic), timing of assessment, optimal amount of platelet transfusion, impact of platelet count, etc. Neurosurgeons should be aware of the potential for significant platelet dysfunction in patients with TBI. (Reviewer-N. Scott Litofsky, MD, FACS).

© 2014, Oakstone Publishing, LLC

Keywords: Traumatic Brain Injury, Aspirin, Platelet Transfusion, Multiple Aggregometry

Print Tag: Refer to original journal article
Prophylactic AED Use in Brain Tumor Surgery -- Yes or No?

Anticonvulsant Prophylaxis for Brain Tumor Surgery: Determining the Current Best Available Evidence.
Sayegh ET, Fakumejad S, et al:

J Neurosurg 2014; (August 29): epub ahead of print

Most meta-analyses examining the use of prophylactic antiepileptic drugs for brain tumor surgery, while flawed, do not show a reduction in seizure occurrence.

Background: Seizures occur commonly in brain tumor surgery patients (15% to 50%). Prophylactic drugs can prevent seizures, but may also be associated with adverse side effects.

Objective: To determine the most appropriate use of prophylactic antiepileptic drugs (AEDs) in patients experiencing brain tumor surgery based on best evidence from the literature.

Design: Quality assessment of multiple meta-analyses on this subject.

Methods: PubMed was searched for English language meta-analyses using the terms anticonvulsants, antiepileptic, prophylaxis, prophylactic, brain tumor, craniotomy, and neurosurgery. Citations of reviewed papers were also scrutinized. Papers reviewing safety and/or efficacy of prophylactic AEDs in patients having surgery for brain tumors were considered. Quality of selected meta-analyses was determined via Quality of Reporting Meta-analyses (QUOROM) and Oxman-Guyatt scoring. Jadad Decision Algorithm was used to assess clinical questions asked, inclusion and exclusion criteria, search strategies, data extraction and pooling, and statistics. Issues, such as rational for prophylactic AED use, mechanisms of AED action, risks of AED prophylaxis, seizure control, and advent of newer AED (such as levetiracetam) were considered.

Results: 6 meta-analyses, including 5 assessing only randomized controlled trials (RCTs), were identified. Five found no reduction in seizure risk with prophylactic AED; 1 showed reduced early risk. Two of 6 meta-analyses reviewed adverse events associated with AEDs. Most adverse events (23.8% of patients in 1 study) were mild. These 6 meta-analyses pulled from between 3 and 6 of a total of 10 RCTs. QUOROM score and Oxman-Guyatt score varied widely, indicating major flaws in 4 of 6 meta-analyses. Three of 6 meta-analyses were limited by the clinical question they considered (including one analyzed to be of the best quality). Four had suboptimal selection criteria. One was limited by using only a single reviewer. Of the 2 meta-analyses considered to be of the best quality, neither showed an improvement in seizure control by prophylactic AEDs.

Conclusions: Best evidence suggests that prophylactic perioperative AEDs should not be used. However, these conclusions do not account for newer agents that are thought to have less adverse side effects.

Reviewer’s Comments: When I selected this paper, I was hoping to get some closure regarding the use of prophylactic AEDs in patients having brain tumor surgery. In my opinion, this paper illustrates that our best evidence regarding this issue is somewhat flawed and does not consider newer agents, such as levetiracetam (available now for over a decade). As the authors indicate, much of physician choice is based on personal preference. Having had plenty of patients experience seizures in the immediate postoperative period, I prefer any reduction by use of prophylactic AEDs if the side effect profile is minimal. Studies looking at levetiracetam or other newer agents as prophylactic AEDs are warranted. (Reviewer-N. Scott Litofsky, MD, FACS).

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Keywords: Anticonvulsant, Antiepileptic, Prophylaxis, Craniotomy, Brain Tumors, Oncology, Epilepsy

Print Tag: Refer to original journal article
Custom mouthguards significantly reduce traumatic brain injuries as compared with over-the-counter mouthguards.

**Background:** Athletic associations have known for years that mouthguards (MG) help prevent brain injuries. They were added to the mandatory equipment list for the National Federation of State High School Associations in 1962 and the National Collegiate Athletic Association in 1973. The mandatory rule was refined in 2005 to include coverage of the occlusal and labial surfaces, coverage of the posterior teeth with "adequate thickness," and made from a custom impression and stone model. The concept of mouthguards helping prevent mild traumatic brain injuries (MTBI) was first introduced in the literature in 1964. The concept was re-introduced in 2001, and multiple studies since then have looked at how mouthguards slow the acceleration of the condyle toward the glenoid fossa during blunt force to the head and jaw. Unfortunately, no studies exist to compare the benefits of custom laboratory fabricated MGs (injection-molded, vacuum-formed, and pressure-laminated (LM) to over-the-counter (OTC) MGs.

**Objective:** To examine the role of custom-made, properly fitted LM MGs compared to OTC MGs, and to assess their effects on MTBI/concussion incidence in high school football players.

**Design/Methods:** This was a randomized prospective study of 412 high school football players. The participants were randomly divided into 2 groups: group 1 consisted of 22 players who wore a custom LM MG; group 2 consisted of 192 players who wore an over-the-counter MG. The custom LM MGs were made with polyvinyl acetate copolymer from an alginate impression taken by a dentist, and seated by the author. The posterior thicknesses at the occlusal surfaces were measured and recorded for each participant. Group 2 participants self-selected and fitted their OTC MGs, and posterior thicknesses were measured and recorded for each participant before each practice. When an MTBI/concussion occurred during the season, the mouthguard was measured and recorded in the posterior occlusal areas by 2 independent evaluators. A chi-square test compared the data.

**Results:** The average thickness of the LM MGs was 3.50 mm in the posteriors, while the average thickness of the OTC MGs was 1.65 mm. In total, 23 participants suffered from an MTBI/concussion, of whom 8 were wearing an LM MG and 13 were wearing an OTC MG. Participants wearing the OTC MG had an 8% incidence of MTBI, while those wearing an LM MG had a 4% incidence.

**Conclusions:** According to the authors, wearing custom-made, properly fitted LM MGs with ≥3 mm thicknesses in the posterior occlusal area statistically reduced the incidence of MTBI/concussion injury when compared to OTC MGs.

**Reviewer's Comments:** This was an interesting study that showed how custom mouthguards with appropriate thickness can help prevent traumatic brain injuries. The authors point out that more research should be conducted in this field. (Reviewer-Kelly A. Halligan, DDS, PC).

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Keywords: Mouthguards, Concussion Injuries, Football Athletes, Mild Traumatic Brain Injuries

Print Tag: Refer to original journal article
Knowledge of Risk Model Can Help Radiologist Suggest Possibility of TON

Traumatic Optic Neuropathy Prediction After Blunt Facial Trauma: Derivation of a Risk Score Based on Facial CT Findings at Admission.

Bodanapally UK, Van der Byl G, et al:

Radiology 2014; 272 (September): 824-831

Certain CT imaging findings of facial and orbital injury can help predict the possibility of traumatic optic neuropathy.

Objective: To determine the CT findings that can be used to predict presence of traumatic optic neuropathy (TON) in patients with blunt facial trauma.

Design/Participants: Retrospective review of facial CT examinations in 637 patients (479 men and 158 women; mean age, 40.4 years) who experienced facial trauma between May 2008 and December 2009.

Methods: CT variables were related to intraorbital soft-tissue injuries, and craniofacial fractures were selected for image analysis by 3 experienced trauma radiologists with 7, 21, and 25 years experience in trauma imaging. On the basis of their clinical experience, the most commonly seen CT findings related to blunt facial trauma, and the variables described previously in the literature that are related to TON were included for analysis. The selected variables were facial fractures (orbital and mid-facial fractures), extraconal hematoma, intraconal hematoma, hematoma along the optic nerve, hematoma along the posterior globe, extraconal emphysema, intraconal emphysema, optic canal fracture, and optic canal fracture impinging the nerve. A prediction model was derived by using regression analysis, followed by receiver operating characteristic analysis to assess the diagnostic performance. To examine the degree of overfitting of the prediction model, a k-fold cross-validation procedure (k = 5) was performed. The ability of the cross-validated model to allow prediction of TON was examined by comparing the mean area under the receiver operating characteristic curve (AUC) from cross-validations with that obtained from the observations used to create the model.

Results: The 5 CT variables with significance as predictors were intraconal hematoma (OR, 12.73; 95%, 5.16, 31.42; P <0.001), intraconal emphysema (OR, 5.21; 95% CI, 2.03, 13.36; P =0.001), optic canal fracture (OR, 4.45; 95% CI, 1.91, 10.35; P =0.001), hematoma along the posterior globe (OR, 0.326; 95% CI, 0.111, 0.958; P =0.041), and extraconal hematoma (OR, 2.36; 95% CI, 1.03, 5.41; P =0.042). The AUC was 0.818 (95% CI, 0.734, 0.902) for the proposed model based on the observations used to create the model and 0.812 (95% CI, 0.723, 0.9) after cross-validation, excluding substantial overfitting of the model.

Conclusions: Knowledge of the described risk model can help radiologists suggest the possibility of TON.

Reviewer’s Comments: I agree with the authors in that familiarity with certain CT imaging findings of facial and orbital injury can help predict possibility of TON. More robust studies are needed, however, to validate these findings. (Reviewer-Sebastian Sadowski, MD).

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Keywords: Traumatic Optic Neuropathy, Facial Trauma

Print Tag: Refer to original journal article
Are Dry Lungs Happier Than Wet Ones During Weaning?

Ventilator-Associated Pneumonia During Weaning From Mechanical Ventilation: Role of Fluid Management.
Mekontso Dessap A, Katsahian S, et al:

Chest 2014; 146 (July): 58-65

Fluid depletion (driven by brain natriuretic peptide levels) during weaning from mechanical ventilation reduces ventilator-associated pneumonia and increases successful liberation from mechanical ventilation.

**Background:** Ventilator-associated conditions (VAC) and ventilator-associated pneumonia (VAP) are costly to patients and our health care systems.

**Objective:** To determine if diuresis and fluid restriction during weaning from mechanical ventilation reduce risks of VAC and VAP.

**Participants:** 304 mechanically ventilated patients in 9 ICUs located in South America and Europe who were already enrolled in the prospective, randomized controlled B-type Natriuretic Peptide (BNP) for the Fluid Management of Weaning (BMW) study.

**Methods:** Patients already assigned to an automated weaning strategy were randomized to receive usual care or daily BNP levels. When BNP levels were ≥200 pg/mL, patients in the treatment arm were fluid-restricted and administered furosemide to achieve a urine output of 5 to 9 mL/kg. Main outcomes included VAC and VAP, diagnosed by standard criteria. Competing risks analysis was completed to assure that outcomes were independent of each other.

**Results:** Patients in the treatment arm received greater amount of diuretics and were extubated sooner (42.4 vs 58.6 hours; \( P = 0.03 \)) than those patients in the control arm. Compared to controls, patients who received diuretics had lower rates of VAC (8.6% vs 17.8%; \( P = 0.02 \)) and VAP (9.2% vs 17.8%; \( P = 0.03 \)), even when accounting for their shorter times on the ventilator.

**Conclusions:** Patients who received diuretics during weaning from mechanical ventilation had lower rates of VAP and faster rates of extubation than those who did not receive diuretics.

**Reviewer's Comments:** Elevating the head of the bed, comprehensive oral care, and spontaneous awakening and breathing trials are just a few of the solutions we have sought to reduce VAP. This trial offers another weapon: diuresis directed by BNP level. Diuresis during weaning is not a new idea, and its cardiovascular and respiratory benefits during weaning were shown 25 years ago. In this study, 70% of the patients in the usual care arm received diuretics. But, guidance by BNP levels resulted in more patients receiving diuretics, higher diuretic doses, and a more negative fluid balance. While it's logical that those liberated faster would have less VAP, the authors performed a competing risks statistical analysis to show that lower rates of VAP were not merely attributable to shorter ventilation. There are a few limitations to this study that deserve mention. First, the initial study was conducted from 2007 to 2009 and did not control for other VAP prevention strategies, like spontaneous awakening. Second, patients were enrolled 5 days after mechanical ventilation was initiated, so fluid balance prior to study entry might have impacted outcome. Patients were weaned using an automated weaning strategy, which is not widely used. Finally, one author had a potential conflict of interest with that ventilator weaning strategy. (Reviewer-Alison S. Clay, MD).

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Keywords: Ventilator-Associated Pneumonia, Mechanical Ventilation, Weaning, Diuresis

Print Tag: Refer to original journal article
Most Cases of END After IV tPA Are Unexplained

**Unexplained Early Neurological Deterioration After Intravenous Thrombolysis: Incidence, Predictors, and Associated Factors.**

Seners P, Turc G, et al:

*Stroke 2014; 45 (July): 2004-2009*

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Most cases of early neurologic deterioration (END) after intravenous tissue plasminogen activator therapy for middle cerebral artery strokes are unexplained. Unexplained END is associated with a poor outcome at 3 months.

**Objective:** To identify the incidence of early neurologic deterioration (END) in patients who received intravenous (IV) tissue plasminogen activator (tPA) for middle cerebral artery (MCA) strokes, and to identify mechanisms and risk factors for unexplained END (END-u) after IV thrombolysis with tPA.  
**Design:** Retrospective cohort study.  
**Participants:** 309 patients with MCA ischemic strokes who received IV tPA within 4.5 hours of onset were included. Patients were excluded if they underwent endovascular therapy.  
**Methods:** A poor outcome was defined as a modified Rankin Scale score >2 at 3 months. END was defined as an increase of ≥4 points in the National Institutes of Health Stroke Scale (NIHSS) score. The definition of symptomatic intracerebral hemorrhage (sICH) used the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) criteria of "parenchymal hemorrhage type 2." END-u was defined as END that was not attributable to intracerebral hemorrhage, infarct in a new territory, early brain edema, extension of original infarct, or other causes, such as seizures or metabolic disturbances.  
**Results:** At presentation, the median NIHSS score was 15, and the mean age was approximately 69 years. All were treated with IV tPA, and most had MCA occlusions, with about 1 in 5 patients having tandem ICA-MCA occlusion. Inexplicably, 11% were recorded as having "no MCA occlusion." END occurred in 33 patients, which was attributed to sICH in 6 and to edema in 4. Of the remaining 23 patients with END-u, 2 improved and then worsened. The timing of END-u was scattered throughout the first 24 hours after IV tPA, with some concentration in the first 6 hours. END-u was associated with a poor outcome at 3 months. Statistically significant predictors of END-u included a history of not using antiplatelet drugs before presentation, a lower NIHSS score at presentation, and increased blood glucose levels at presentation. The lower NIHSS score may be an artifact, because in a large MCA stroke with an NIHSS score in the 20s, there is not much room for the NIHSS score to worsen by ≥4 points unless there is a contralateral infarct, especially if the original stroke was in the dominant hemisphere.  
**Conclusions:** END-u accounts for most cases of END after IV tPA. Recognizing predictors and associated factors will be important for understanding mechanisms and developing ways of preventing this discouraging turn of events.  
**Reviewer’s Comments:** END of any sort in the patient with acute ischemic stroke who has or has not been given any type of intervention remains a vexing subject. Our ability to study this is limited by the number of looks we can take at a complex pathophysiology. (Reviewer-James Warne Schmidley, MD).

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Keywords: Intravenous Thrombolytic Therapy, Complications, Early Neurologic Deterioration

Print Tag: Refer to original journal article
Does Gadolinium Enhancement Have Prognostic Significance in Pediatric Medulloblastoma?

Differences in Vascular Endothelial Growth Factor Receptor Expression and Correlation With the Degree of Enhancement in Medulloblastoma.

Hervey-Jumper SL, Garton HJL, et al:

J Neurosurg Pediatr 2014; 14 (August): 121-128

Prognosis does not correlate with gadolinium enhancement, but such enhancement may be used as a treatment target.

Background: The incidence of medulloblastoma is 0.6 per 100,000 in children who are aged <16 years. The tumor represents 20% of pediatric CNS tumors and 40% of posterior fossa brain tumors. Approximately 35% of medulloblastomas enhance minimally with gadolinium administration. However, the correlation between enhancement and vascular endothelial growth factor (VEGF) has never been closely studied. Major prognostic factors for medulloblastoma include VEGF, VEGF receptor (VEGFR), basic fibroblast growth factor, angiopoietin, integrins, matrix metalloproteinases, and CD 31. Gadolinium enhancement has recently been shown to have a strong correlation with prognosis.

Objective: To review prognosis predictability between VEGF and gadolinium enhancement of medulloblastoma.

Design: Single-institution retrospective review.

Methods: A medical record review was performed at the University of Michigan; 58 children treated for medulloblastoma between 1991 and 2010 were identified. Three pediatric neurosurgeons and 1 pediatric radiologist reviewed the cases independently. Tumors were classified as enhancing (>50% enhancement), partially enhancing (<50% enhancement), or non-enhancing (absence of enhancement). Patients with residual tumor >1.5 cm², age <3 years, or distant metastasis at diagnosis were considered to be high risk. Tumor volume was determined by the tumor's greatest diameter multiplied by width of tumor perpendicular to diameter multiplied by number of slices on MRI divided by 2. A cohort of 3 enhancing and 3 nonenhancing tumors was chosen for analysis of VEGFR, CD31, and microvessel density.

Results: Gadolinium enhancement and expression of VEGFR1/2 immunofluorescence showed strong correlation. Medulloblastoma with strong enhancement demonstrated strong VEGF expression. Enhancing medulloblastoma had approximately 3.6 times higher VEGFR1/2-positive cells per high powered field than nonenhancing tumors. mRNA VEGFR level was 1.8 times higher with enhancement. CD31 was expressed 5.5 times higher in enhanced tumors. Microvessel density was >2.8 times higher with enhanced tumors. In the cohort, 58.6% were male, and the mean age at diagnosis was 6.9 years. No significant differences in sex, age, or histological subtype were present. Enhancing tumors were larger (39 cm³ vs 27 cm³) and had higher rates of hydrocephalus (89.1% vs 66.7%) than nonenhancing tumors, but these were not significant. Overall survival rate for nonenhancing tumors was 12.3 years compared to 9.2 years with enhancing tumors, but this difference was not significantly different.

Conclusions: Gadolinium contrast-enhancement in pediatric medulloblastoma tumors could be targeted with antiangiogenetic therapies to benefit patient outcome.

Reviewer's Comments: Gadolinium enhancement and VEGFR expression had some correlation in medulloblastoma, but no statistical advantage to survival with these characteristics has been observed. However, these features may be able to be used to target treatment. Audio review recorded by N. Scott Litofsky, MD, FACS. (Reviewer-Tomoko Tanaka, MD).

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Keywords: Medulloblastoma, Tumor Enhancement, VEGF, CD31, Oncology

Print Tag: Refer to original journal article
New Insights Into Cripto-1 Growth Factor Expression in Glioblastoma

Cripto-1 Expression in Glioblastoma Multiforme.

Pilgaard L, Mortensen JH, et al:

Brain Pathol 2014; 24 (July): 360-370

Most patients with glioblastoma have elevated levels of the growth factor Cripto-1 in the plasma and in the tumor itself.

**Background:** Human glioblastoma multiforme (GBM) is an aggressive cancer with a poor prognosis. Human Cripto-1 (CR-1) is known to regulate essential steps in early embryogenesis, and it plays a key regulatory role in cell migration, stem cell maintenance, and angiogenesis. In adult tissue, re-expression of CR-1 has been correlated to malignant progression in solid cancers of non-neuronal origin. CR-1 expression has yet to be described in cerebral cancer.

**Objective:** To investigate the association of CR-1 with GBM in the context of brain tumors.

**Methods:** Blood and tissue samples from 28 GBM and 4 low-grade glioma patients were submitted for enzyme-linked immunosorbent assay (ELISA), Western blot, polymerase chain reaction (PCR), and immunohistochemical staining for CR-1.

**Results:** Variable expression of CR-1 was detected using Western blot analysis and ELISA, showing expected bands between 25 and 37 kDa and protein concentrations ranging from 0.6 to 14.3 ng/mL. In GBM patient blood samples, CR-1 protein concentrations were >4-fold higher compared with average levels detected in healthy control subjects and in patients with low-grade glioma. More than 70% of newly diagnosed GBM patients presented with higher CR-1 plasma levels compared with controls. By immunohistochemistry, CR-1 expression was seen in association with endothelial cells, glomeruloid microvessels, and at the edge of areas of palisading tumor necrosis.

**Conclusions:** In most cases, CR-1 levels are significantly increased in patients with GBM. CR-1 may have utility as a prognostic biomarker for GBM with the potential of being a therapeutic target.

**Reviewer’s Comments:** Interestingly, CR-1 levels tend to have variable expression within normal human brain tissue, such that tissue from the temporal and parietal lobes generally has higher CR-1 expression than tissue from the occipital lobe. (Reviewer-T. David Bourne, MD).

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Keywords: Cripto-1, Endothelial Proliferation, Glioblastoma Multiforme, Microvasculature, Plasma Biomarker, Tumor Niche

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Survival Longer for IESM Than for LM

Intradural Extramedullary Spinal Metastases of Non-Neurogenic Origin: A Distinct Clinical Entity or a Subtype of Leptomeningeal Metastasis? A Case-Control Study.

Knafo S, Pallud J, et al:

Neurosurgery 2013; 73 (December): 923-932

Patients with intradural extramedullary spinal metastases survive significantly longer than patients with leptomeningeal metastases, suggesting that these are 2 fundamentally different diseases.

**Background:** Leptomeningeal metastasis (LM) is a diffuse process. Intradural extramedullary spinal metastasis (IESM) presents as a focal mass between the dura and the spinal cord, which is usually considered a bulky variant of LM.

**Objective:** To determine whether LM and IESM are different presentations of the same disease.

**Design:** Retrospective, multicenter case-control study.

**Participants:** 11 cases of solitary IESM and 11 controls with LM were included. The cases and controls were matched for age, gender, performance status, and primary cancer.

**Methods:** The authors performed a medical record review of study participants. Primary end point was overall survival; secondary end points were diagnostic criteria and prognostic factors.

**Results:** The median age of the patients with IESM was 59 years, and they had a good performance status. Six patients presented with back pain or sciatica and had no neurologic signs, while the remaining 3 patients presented with a spinal cord or cauda equina syndrome. The location of the IESM was more often thoracic or lumbar (n=5 each) than cervical (n=1). The lung (n=4) and kidney (n=2) were the most common locations of primary tumors. Spine MRI showed an enhancing, nodular tumor attached to the inner surface of the cervical or thoracic spinal dura. Tumors in the lumbar spine were attached to cauda equina roots, which also enhanced near the tumor but not diffusely, as is seen in LM. No patient with IESM had evidence of LM, such as tumor cells in the CSF and/or MRI contrast enhancement of the craniospinal meninges distant from the tumor. Of the 9 IESM patients who underwent surgical excision of the tumor and postoperative radiotherapy or chemotherapy, 7 improved. None developed LM during follow-up. All patients with LM had intrathecal chemotherapy, and 5 improved. Survival was much longer in the patients with IESM (2 years) than in those with LM (2 months, \( P <0.0002 \)). For IESM, multivariate analysis showed preoperative neurological deficit to be a significant predictor of shorter survival, whereas neurological improvement after surgery predicted longer survival.

**Conclusions:** Patients with IESM survive significantly longer than do patients with LM; this finding suggests that IESM and LM are fundamentally different diseases. Unlike LM, IESM should be treated focally, with surgery followed by radiotherapy or radiotherapy alone.

**Reviewer's Comments:** Another point indicating that IESM is not a variant presentation of LM is that none of the IESM patients developed LM during follow-up. All of the authors’ cases had solitary IESM, so it is not surprising that they did well with surgery. What would the authors have done with multiple IESM? Would they have treated them with surgery, multifocal radiotherapy, or chemotherapy? The situation is similar to the problem of the treatment of solitary versus multiple brain metastases. (Reviewer-Marc David Winkelman, MD).

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Keywords: Intradural Extramedullary Spinal Metastasis, Leptomeningeal Metastasis

Print Tag: Refer to original journal article
For lateral lumbar interbody fusion, insertion of lateral cage supplemented with lateral plate and spinous process plate results in comparable rigidity compared to bilateral pedicle screw fixation.

**Background:** Lumbar interbody fusions are well-accepted surgical treatment for degenerative diseases such as symptomatic lumbar stenosis and spondylolisthesis. There are a number of methods one can use to achieve interbody fusion. These include laterally or posteriorly inserted interbody cages supplemented with lateral plates, spinous process plates, or posterior pedicle screws. Currently there are no biomechanical studies to support the beneficial effect of one over the others. This paper attempts to establish biomechanical data for different approaches in lumbar interbody fusion.

**Objective:** To investigate the structural stability of the interbody cage and fixations in an in vitro environment.

**Design:** Biomechanical study.

**Methods:** A total of 10 lumbar spine cadaveric specimens were subjected to spine stimulator with nondestructive moments (±7.5 N·m) with multi degrees-of-freedom. Intervertebral motions were measured optoelectronically. Specimens at the L3-4 level with intact; interbody cage alone; cage supplemented with lateral plate; cage supplemented with ipsilateral pedicle screws; cage supplemented with bilateral pedicle screws; cage supplemented with spinous process plate; and cage supplemented with a combination of lateral plate and spinous process plate were evaluated. Subsequently, rotations were calculated and range of motion (ROM) data were normalized to the intact ROM data.

**Results:** In general, all surgical methods used for lumbar interbody fusion resulted in rigid fixation when it compared to intact specimen. Laterally inserted stand-alone interbody cage significantly reduced ROM with respect to the intact state in flexion-extension (31.6% intact ROM; \( P < 0.001 \)), lateral bending (32.5%; \( P < 0.001 \)), and axial rotation (69.4%; \( P = 0.002 \)). Addition of lateral plate to the interbody cage only affected lateral bending and axial rotation (\( P < 0.001 \)). However, laterally inserted cage with lateral plate fixation was not significantly different than laterally inserted cage supplemented with ipsilateral pedicle screws, bilateral pedicle screws, or a spinous process plate.

**Conclusions:** For lumbar interbody fusion, laterally inserted plate supplemented with lateral plate and spinous process plate fixation has comparable biomechanical rigidity in all motions compared to that in laterally inserted cage supplemented with ipsilateral or bilateral pedicle screws.

**Reviewer’s Comments:** Lumbar spine fusion continues to have numerous imperfections secondary to a lack of objective data. In this study, authors attempted to generate an objective biomechanical study supporting the idea of minimum hardware utilization for lateral interbody fusions. The study supports the idea that the lateral interbody fusion with insertion of lateral cage supplemented with a lateral plate and spinous process plate has adequate rigidity compared to laterally inserted cage with bilateral pedicle. (Reviewer-Fassil B. Mesfin, MD, PhD).
No Permanent Deficit in the Vast Majority of VAI

Vertebral Artery Injuries in Cervical Spine Surgery.
Lunardini DJ, Eskander MS, et al:
Spine J 2014; 14 (August 1): 1520-1525

Two-thirds of vertebral artery injuries occur during procedures other than C1-C2 posterior instrumentation.

**Background:** Vertebral artery injuries (VAI) are more likely to occur with C1-C2 fusion or during a corpectomy. An abnormal course of the vertebral artery puts patients at greater risk.

**Objective:** Given that the current data are based on small series, the authors collected data from a larger group of patients to re-assess the epidemiology of VAI.

**Design:** Retrospective trial.

**Methods:** A web-based survey was sent to the members of the Cervical Spine Research Society (CSRS).

**Results:** 72% of the 195 members of the CSRS reported their vascular complications. The rate of VAI was 0.07% for 163,324 cervical spine surgeries. One-third of these VAI occurred during posterior instrumentation of C1-C2, one-fourth during an anterior corpectomy, and more than 10% during posterior exposures of the spine. ACDFs, laminectomies, posterior foraminectomies, and anterior instrumentations of C1-C2 were less frequently associated with VAI. In 20% of all cases, the vertebral artery had an atypical course. In most instances, the VAI was managed by direct tamponade. In total, 90.0% of patients had no long-term neurologic deficits, while 5.5% had a permanent deficit and 4.5% died as a direct result of the vertebral injury. More experienced surgeons had a lower incidence of VAI.

**Conclusions:** VAI occurs mostly during posterior instrumentation of C1-C2, anterior corpectomy, and posterior exposure of the cervical spine.

**Reviewer’s Comments:** The incidence of 0.07% described here appears low compared to the 1.4% reported by Rampersaud (Spine 2006;31:1503-1510). A description of the variation in anatomy of vertebral artery should have been discussed. For instance, 5% of patients have an abnormal V3 segment, which either enters the spinal canal under C1 or duplicates after exiting from the transverse foramen of C2 (Hong et al: J Neurosurg Spine 2008;8:230-236). The suggestion that tamponade is a good treatment was unexpected. One would think that a better approach would be to directly repair the vessel with a small Prolene suture. Finally, keep in mind that when the vertebral is ligated, if there is no good retrograde flow, an immediate bypass surgery is probably needed. (Reviewer-Luc Jasmin, MD, PhD, FRCS (C), FACS, FAANS).

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Keywords: Complication, Spine Surgery, Vertebral Arteries, Instrumentation, Corpectomy, Bleeding,

Print Tag: Refer to original journal article
Knowledge of Postoperative Imaging Appearance Critical


Petscavage-Thomas JM, Ha AS:

AJR Am J Roentgenol 2014; 203 (August): 394-405

Given the 10-fold increase in cervical spine fusion procedures and advances in surgical technique in the past decade, knowledge of the postoperative imaging appearance is critical.

Background: Spinal fusion procedures have increased >10-fold from 1992 to 2003, with marked innovations in surgical technique happening in the past decade as well.

Objective: To review the postoperative imaging appearance of recent advances in cervical spine procedures and complications. Discussion: Radiographs can be used as initial assessment for hardware placement, MRI for fluid collections and possible epidural communication as well as hardware assessment with MARS protocol, and CT for osteolysis, fluid collections, and subtle fractures. Recent advances in cervical fusion techniques have resulted in new routes, less invasive hardware, and radiolucent graft material. To review, the purpose of spinal fusion is to maintain disk height and normal cervical lordosis and decrease neural foraminal stenosis. Traditionally, while cage implants have been titanium with bone graft or stainless steel, recent devices have been made of polyetheretherketone (PEEK) with autologous bone graft. Complications include subsidence with rates being similar to that for metal cages, reported at 25% for >2 mm, and nonunion with lack of osseous incorporation at 6 months after surgery. Osteolysis can also result from particle wear or breakdown of recombinant human bone morphogenic protein. Because up to two-thirds of patients may experience dysphagia after fusion, the Zero-P device was designed, which consists of an interbody spacer made of PEEK with a radiolucent plate that is held in place with locking screws. Total disk replacement (TDR) was designed to decrease rates of adjacent segment degeneration. Candidates for TDR must have at least 4 mm of residual disk height, a lack of significant endplate degenerative changes to anchor the prosthesis, and discogenic pain without nerve root involvement. Complications include subsidence, osteolysis, fracture, and heterotopic ossification. Compression fractures have been treated with vertebroplasty and kyphoplasty. Both involve injection of barium-impregnated polymethylmethacrylate into the vertebral body to restore height; however, kyphoplasty differs with the addition of balloon inflation and is recommended for patients with kyphosis. The major complication for both is extrusion of cement into the epidural venous plexus, spinal canal, disk, or neural foramina.

Conclusions: Given the 10-fold increase in cervical spine fusion procedures and advances in surgical technique in the past decade, knowledge of the postoperative imaging appearance is critical.

Reviewer’s Comments: This is an excellent review article on the postoperative imaging appearance of the cervical spine. The importance and prevalence was clearly delineated, the article was well structured, and images were provided of the major devices as well as complications. (Reviewer-Uma Thakur, MD, MSK).

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Keywords: Degenerative Disease, Spine Hardware, Fracture Fixation

Print Tag: Refer to original journal article
Knowledge of Post-Imaging Appearance of Lumbar Spine Critical for Accurate Assessment

Imaging of Current Spinal Hardware: Lumbar Spine.

Ha AS, Petscavage-Thomas JM:

AJR Am J Roentgenol 2014; 203 (September): 573-581

The knowledge of updates in lumbar surgical fusion procedures is critical for accurate postoperative imaging assessment.

**Background:** Given the increasing geriatric population, lumbar spinal stenosis due to degenerative disease has resulted in one of the fastest growing reasons for spinal fusion surgery.

**Objective:** To review indications for posterior spinal fusion in the lumbar spine, appropriateness of imaging modalities, postoperative imaging appearance, and complications. **Discussion:** Basic spinal fusion involves laminectomies and placement of graft material and an interbody disk spacer. The radiopaque marker for the disk spacer should be at least 2 mm anterior to the posterior margin of the vertebral body, and the posterior pedicle screws should not protrude beyond the anterior margin of the vertebral body. Complications related to dural rupture have motivated the development of less invasive surgical techniques, one of which is extreme lateral interbody fusion in which the disk space is approached from a far lateral approach, avoiding penetration of the peritoneum. An anterior approach can be used when pain is diskogenic and posterior decompression is not needed. Dynamic posterior stabilization was designed to avoid the common complication of adjacent segment degeneration with the goal of distributing stress more evenly throughout the lumbar spine. The most common device used is the Dynesys device in which titanium alloy pedicle screws and spacers connected by cords are placed under tension. Complications include hardware loosening and infection. Lumbar disk replacement was also designed to decrease the rate of adjacent segment degeneration. Complications include subsidence, particle disease, facet degeneration, compression fracture, and hardware migration. An anterior surgical approach necessitating violation of the peritoneum is required for these procedures. Interspinous distraction devices were developed for patients with intermittent position-dependent claudication related to spinal stenosis. The device places the patient in slight flexion, as flexion is said to relieve epidural pressure and open the neural foramina and spinal canal. The procedure is done with local anesthesia, and while there are fewer complications from the initial surgery, higher revision rates have been noted. Complications include spinous process resorption along the implant.

**Conclusions:** The knowledge of updates in lumbar surgical fusion procedures is critical for accurate postoperative imaging assessment.

**Reviewer's Comments:** This is an excellent article given the prevalence of lumbar fusion surgeries and the recent advances. The authors provide a structured review and fulfill their objectives. They provide a thorough, but relevant table of complications related to lumbar spine instrumentation, which I found particularly useful. They also provide 15 figures nicely depicting the various types of instrumentation mentioned as well as complications. (Reviewer-Uma Thakur, MD, MSK).

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Keywords: Spinal Hardware, Degenerative Disease

Print Tag: Refer to original journal article
Watchful Waiting Okay for Asymptomatic Spondylolisthesis

Patient Outcomes in the Operative and Nonoperative Management of High-Grade Spondylolisthesis in Children.

Lundine KM, Lewis SJ, et al:

J Pediatr Orthop 2014; 34 (July-August): 483-489

Pediatric patients with asymptomatic high-grade spondylolisthesis may not require surgical intervention.

Background: In children with spondylolisthesis, high-grade slips (>50%) are a relatively rare condition, while low-grade slips are considered to be clinically benign. Standard recommendations have been for the surgical management of patients with a slip >33% to 50%. However, the risk of surgical complications has been ≥10% in recent surveys.

Objective: To determine whether conservative monitoring is a safe approach to managing high-grade spondylolisthesis in asymptomatic pediatric patients.

Participants: All patients aged <18 years with idiopathic spondylolisthesis of grade 3, 4, or 5 who had a minimum 2-year follow-up.

Methods: The study was conducted at the Hospital for Sick Children, Toronto, which has a large practice in spinal deformity. A 92% rate of follow-up was achieved, which represented 49 patients. Patients were studied via radiographs, the SRS-30 score, and a study-specific questionnaire. Patients chose whether they wished to have conservative or operative treatment for their slips.

Results: The operative group had 24 patients, and the nonoperative group had 25. Mean age at enrollment was 12.6 years, and mean duration of follow-up was 7.5 years. The groups were evenly matched. Although the operative group had slightly more severe slips, the difference in distribution was not statistically significant. Before treatment, the operative group had slightly higher pain scores and missed more school than did the nonoperative group. The surgical treatments varied, including a Bohlman procedure in some patients and posterior uninstrumented fusion in situ in a few others. Surgery did not cause any permanent neurological deficits. The outcome trends were the same from both groups, and the complication rates were not significantly different for the 2 groups. The operative group improved their preoperative SRS-30 scores. The overall rate of complications included 1 deep and 1 superficial procedure, which is appropriate for the sample size. Ten patients converted from nonsurgical to surgical intervention for unstated reasons. The slip angle was significantly higher in patients who converted late to surgery (24°) compared to those who completed a nonoperative course (3°).

Conclusions: Patients with high-grade spondylolisthesis who chose to have surgery seemed to have higher slip angles, and the nonoperative patients who then converted to surgical management revealed higher slip angles than did those who stayed with the nonoperative strategy. The authors state that patients who have asymptomatic slips may be treated conservatively if they so desire, which results in satisfactory clinical outcomes.

Reviewer's Comments: This was an interesting study. However, the patients need to be followed up for a much longer period. I think that, once they outgrow adolescence, greater difficulty in recovering from surgery will be experienced. I agree that it is better to go into the surgery with a clinical reason in mind given that the complication rate associated with instrumented surgery is approximately 10%. (Reviewer-Paul D. Sponseller, MS, MD, MBA).

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Keywords: Pediatric Spondylolisthesis, Spine Fusion, Outcomes

Print Tag: Refer to original journal article
Among surgeons performing adolescent idiopathic scoliosis surgery, younger surgeons perform the surgery more slowly than more experienced surgeons, but their complication rates are not higher.

**Background:** Adolescent idiopathic scoliosis (AIS) surgery is associated with both high reward and high risk. The surgeon must perform the surgery efficiently and safely and in a manner that results in a low postoperative infection rate.

**Objective:** To review the largest series of operative scoliosis patients to determine whether a surgeon’s overall experience affects the operative process or the outcome of AIS surgery.

**Participants/Methods:** 165 patients with AIS who underwent surgery during a 1-year study interval by members of the Harms Study group were studied. The surgeons performing the surgery were subdivided into 2 groups: young surgeons (<5 years of experience; n=4) and experienced surgeons (≥5 years of experience; n=5). In both groups, patients had similar ages, Cobb angles, and preoperative Scoliosis Research Society 22 (SRS-22) scores.

**Results:** The younger surgeons had inferior scores in the process of surgery: the estimated blood loss was 2063 mL for younger surgeons versus 1013 mL for experienced surgeons. The surgical time was nearly twice as long for younger surgeons (458 minutes) than for experienced surgeons (263 minutes). The hospital stay was half a day longer for those treated by the younger surgeons than for those treated by experienced surgeons. The improvement in the SRS-22 scores was significantly better with the experienced surgeons than with the younger surgeons. The 2-year postoperative Cobb-angle correction was equal in both groups, as was the complication rate. The younger surgeons performed only 17 surgeries on patients with AIS during this time, while the experienced surgeons performed 148 surgeries.

**Conclusions:** There is a significant learning curve to scoliosis surgery. These results may lead to the development of optimal ways of simulating the training to improve performance for young surgeons.

**Reviewer’s Comments:** I enjoyed this article, and I agree with the conclusions. It requires a lot of practice to gain the physical skills to perform the surgery smoothly and efficiently. As Keith Bridwell, MD, noted in his accompanying commentary on this article, the younger surgeons may also get the less experienced teams to work with, including nursing, anesthesia, and first assistant. They also may be working with patients and families who are more stressed at intake and follow-up. However, the younger surgeons may perform more high-intensity procedures, such as osteotomies. Regardless, AIS surgery is a very specialized area that demands experience and care. It would be interesting to determine how many cases are required to achieve a learning plateau. (Reviewer-Paul D. Sponser, MS, MD, MBA).

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**Keywords:** Adolescent Idiopathic Scoliosis, Surgery, Surgeon Experience vs Outcomes

**Print Tag:** Refer to original journal article
In one report, olfactory mucosal stem cells implanted at the site of spinal cord injury grew into a spinal mass. We still do not have a complete understanding of stem cell behavior in a pathological environment.

**Background:** Olfactory ensheathing cells and olfactory mucosal stem cells may induce or aid the repair of an injured spinal cord.

**Objective:** To describe a unique occurrence of a mass found at the site of a prior olfactory mucosal cell implant intended to restore neural function after a severe spinal cord injury. **Case Report:** About 11 years after sustaining a fracture dislocation at T10-T11, with complete loss of motor function in the legs and a sensory level at T-11, a 29-year-old woman presented to the authors with gradually worsening back pain at the site of the injury. Eight years earlier (about 3 years after the original injury), she had undergone experimental therapy consisting of intraspinal olfactory mucosal cell transplantation at the site of injury. The authors of the current paper were not involved in this treatment, which involved endonasal harvesting of autologous olfactory mucosa from the olfactory groove, and implantation at the site of cord damage after laminectomy. When the patient presented to the authors, exam disclosed no identifiable interval clinical improvement. MRIs revealed an enhancing intramedullary mass at T10-T11. Because of concern for a tumor, surgery was performed, which revealed an expanded cord with a heterogeneous fibrous-walled multicystic mass containing white material. Postoperatively, there were no complications and the pain improved. **Histology:** H&E sections showed multiple cysts lined by respiratory mucosa with underlying submucosal glands and a few goblet cells, identical to that seen in normal nasal mucosa. In addition, in connective tissue beneath the respiratory mucosa, many neurofilament and S100 protein-staining nerve twigs with perineurium and the appearance of sprouting or regenerating nerve fibers were seen. Glial nerve tissue that stained positive for glial fibrillary acidic protein was noted adjacent to the respiratory mucosa and was focally lined by respiratory epithelium. The overall histology of this lesion resembled olfactory mucosa; the mucus-like contents suggesting that secretory function continued after transplantation. There was no evidence of malignant transformation. The origin of nerve fibers in the tissue could not be determined.

**Conclusions:** The events described should not inhibit further carefully conducted stem cell research, but they should remind physicians and scientists that what we still do not know may surprise us, especially when it comes to the behavior of cells in a pathological environment.

**Reviewer’s Comments:** A boy with ataxia-telangiectasia has been reported with multiple extra-axial masses after receiving cerebellar and cerebrospinal fluid injections of human fetal neural stem cells. In this boy, the mass that was biopsied: (1) was of non-host origin, (2) contained glial, neuronal, and ependymal elements, (3) appeared benign on histological examination, and (4) had a very low proliferative index. Recall that patients with ataxia-telangiectasia have impaired immune surveillance and are prone to develop lymphomas spontaneously. (Reviewer-James Warne Schmidley, MD).

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Keywords: Spinal Cord Injury, Stem Cell Transplantation, Olfactory Mucosa, Complications

Print Tag: Refer to original journal article