Update of Comprehensive Review of the Safety Profile of Bone Morphogenetic Protein in Spine Surgery

To the Editor:

We read with great interest the article by Benglis et al[1] on the safety profile of bone morphogenetic protein (rhBMP) in spine surgery. However, several updates and clarifications are needed to make this important review more up to date and useful.

Benglis et al[1] stated that to the date (the review was submitted on July 11, 2007), no clinically relevant neurological deficits resulting from excess bone formation were reported. We would like to point out the claim of the Haid et al[2] that ectopic bone formation extending outside the disc space and into the spinal canal or neuroforamina (found in 24 of 32 patients treated with rhBMP-2 during posterior lumbar interbody fusion which caused the Federal Food and Drug Administration to halt the trial) did not correlate with a recurrence or an increase in leg pain from the preoperative state, was challenged with findings of Wong et al.[3] Ectopic bone formation in the spinal canal after interbody fusions assisted with rhBMP-2 in their 5 patients, was associated with neural complaints, and finally resulted with demanding revision surgery in three of them.[3] All 3 patients had partial improvement in their corresponding radicular pain postoperatively, suggesting that at least a portion of their root pain was associated with the extrinsic pressure or tethering of the root.

Although the section about neck swelling, hematoma, severe dysphagia, and respiratory failure was well written, we would like to emphasize that diffuse prevertebral soft-tissue swelling in the case report of the Perri et al[4] caused significant narrowing of tracheal opening (less than 5 mm in cross-section) which caused the patient to be intubated and on the ventilator for 24 hours after revision operation.

We have the most objections for the section related to bony resorptions and graft subsidence. The first transient vertebral resorption after clinical application of rhBMPs in proximity of vertebral bodies was reported by Laursen et al[5] back in 1999. Severe resorption of the whole anterior column at the site of the implantation of the rhBMP-7 sponge within the vertebral body was seen at the 3- and 6-months follow-up in 1 of 5 patients with unstable thoracolumbar vertebral fractures treated with transpedicular rhBMP-7 sponge transplantation. Except the reports mentioned by Benglis et al,[6-9] transient resorptions of vertebral end plates and bodies after rhBMP-2 applications during interbody fusions were reported[10-14] or discovered[15] in several other studies as well.

The analysis of published literature revealed that vertebral bone resorptions occurred when larger contact area between by rhBMPs soaked collagen sponges and trabecular bone of vertebral bodies existed.[16] Seeherman and Wozney[17] have shown that the collagen sponge soaked with rhBMP-2 and placed in contact with trabecular bone of distal femoral core defect in nonhuman primates resulted in significant transient bone resorption at 2 weeks after the surgery. This was not the case when they used carrier with slower release of rhBMP (calcium phosphate matrix). The rapid release of rhBMPs at the bone surface which is in contact with the collagen sponge creates favorable conditions for significant osteoclastic reaction prior to the bone formation phase as it is known that rhBMP-2 stimulates osteoclast formation[18] and dentin resorption by osteoclasts in dose depended manner.[19]

The larger the contact surface between the sponge and cancellous bone is, the larger the area under bone resorption will be. This might explain why different degrees of vertebral resorptions between patients in same study, or between the different levels of the same patient, appeared especially after additional rhBMPs sponges were freely placed in the intervertebral space in the study of Vaidya et al.[14] Depending on the size of bone resorption area, additional spinal stabilization, and/or patient's activity during the resorption phase, there will be consequences of vertebral resorptions. If the stability of the spine and fusion device remains adequate, the final result will be complete bone healing at 12 and 24 months. Unless stability remains adequate, surgeons and their patients will be faced with subsidence, loss of correction, graft dislodgment, and failure of spinal fusion.

To conclude, we join the great efforts of Benglis et al[1] at emphasizing the power of this family of molecules and the responsibility of all included in clinical applications of rhBMPs in spinal surgery; pharmaceutical industries, spinal surgeons and patients.

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1. Benglis D, Wang MY, Levi AD. A comprehensive review of the safety profile of bone morphogenetic protein in spine surgery. *Neurosurgery*. 2008;62:ONS423-431; discussion ONS431.
2. Haid RW Jr, Branch CL Jr, Alexander JT, Burkus JK. Posterior lumbar interbody fusion using recombinant human bone morphogenetic protein type 2 with cylindrical interbody cages. *Spine J.* 2004;4:527-538; discussion 538-529.
3. Wong DA, Kumar A, Jatana S, Ghiselli G, Wong K. Neurologic impairment from ectopic bone in the lumbar canal: a potential complication of off-label PLIF/TLIF use of bone morphogenetic protein-2 (BMP-2). *Spine J*. 2008;8:1011-1018, 2008.
4. Perri B, Cooper M, Lauryssen C, Anand N. Adverse swelling associated with use of rh-BMP-2 in anterior cervical discectomy and fusion: a case study. *Spine J*. 2007;7:235-239.
5. Laursen M, Hoy K, Hansen ES, Gelineck J, Christensen FB, Bunger CE. Recombinant bone morphogenetic protein-7 as an intracorporal bone growth stimulator in unstable thoracolumbar burst fractures in humans: preliminary results. *Eur Spine J.* 1999;8:485-490.
6. Caixeta T, Park P, La Marca F. Early focal demineralization following the use of BMP-2 in transverse lumbar interbody fusion. Presented at Joint Section on Disorders of the Spine and Peripheral Nerves (AANS/CNS), 23nd Annual Meeting, Phoenix, AZ, March 7–10, 2007.
7. Lewandrowski KU, Nanson C, Calderon R. Vertebral osteolysis after posterior interbody lumbar fusion with recombinant human bone morphogenetic protein 2: a report of five cases. *Spine J*. 2007;7:609-614.

8. McClellan JW, Mulconrey DS, Forbes RJ, Fullmer N. Vertebral bone resorption after transforaminal lumbar interbody fusion with bone morphogenetic protein (rhBMP-2). *J Spinal Disord Tech.* 2006;19:483-486.
9. Pradhan BB, Bae HW, Dawson EG, Patel VV, Delamarter RB. Graft resorption with the use of bone morphogenetic protein: lessons from anterior lumbar interbody fusion using femoral ring allografts and recombinant human bone morphogenetic protein-2. *Spine.* 2006;31:E277-284.
10. Burkus JK, Sandhu HS, Gornet MF, Longley MC. Use of rhBMP-2 in combination with structural cortical allografts: clinical and radiographic outcomes in anterior lumbar spinal surgery. *J Bone Joint Surg Am*. 2005;87:1205-1212.
11. Hansen SM, Sasso RC. Resorptive response of rhBMP2 simulating infection in an anterior lumbar interbody fusion with a femoral ring. *J Spinal Disord Tech*. 2006;19:130-134.
12. Kuklo TR, Rosner MK, Polly DW Jr. Computerized tomography evaluation of a resorbable implant after transforaminal lumbar interbody fusion. *Neurosurg Focus*. 2004;16:E10.
13. Vaidya R, Carp J, Sethi A, Bartol S, Craig J, Les CM. Complications of anterior cervical discectomy and fusion using recombinant human bone morphogenetic protein-2. *Eur Spine J.* 2007;16:1257-1265.
14. Vaidya R, Weir R, Sethi A, Meisterling S, Hakeos W, Wybo CD. Interbody fusion with allograft and rhBMP-2 leads to consistent fusion but early subsidence. *J Bone Joint Surg Br*. 2007;89:342-345.
15. Smoljanovic T, Pecina M. Re: Burkus JK, Transfeldt EE, Kitchel SH, et al. Clinical and radiographic outcomes of anterior lumbar interbody fusion using recombinant human bone morphogenetic protein-2. *Spine.* 2002;27:2396-2408. *Spine*. 2008;33:224 (letter).
16. Smoljanovic T, Grgurevic L, Jelic M, et al. Regeneration of the skeleton by recombinant human bone morphogenetic proteins. *Coll Antropol*. 2007;31:923-932.
17. Seeherman H, Wozney JM. Delivery of bone morphogenetic proteins for orthopedic tissue regeneration. *Cytokine Growth Factor Rev*. 2005;16:329-345.
18. Wutzl A, Brozek W, Lernbass I, et al. Bone morphogenetic proteins 5 and 6 stimulate osteoclast generation. J Biomed Mater Res 2006;77:75-83.
19. Miyaji H, Sugaya T, Kato K, Kawamura N, Tsuji H, Kawanami M. Dentin resorption and cementum-like tissue formation by bone morphogenetic protein application. *J Periodontal Res*. 2006;41:311-315.

10.1227/NEU.0B013E3181D8CCCD

In Reply:

We thank Smoljanovic et al for their comments on our review article entitled "A Comprehensive Review of the Safety Profile of Bone Morphogenetic Protein (BMP) in Spine Surgery."[1]

In our review, we attempted to cover the current reported adverse events in the literature with the 2 most widely-utilized BMPs in spine surgery: rh-BMP-2 (Medtronic Spinal and Biologics, Memphis, TN) and rhOP-1/rhBMP-7 (Stryker Corp., Kalamazoo, MI).

Smolijanovic et al in their letter present a series of papers which support the concepts raised in our paper. Some of these reports cited were printed after our original article was submitted in July 2007.

With regards to the case report on dysphagia and neck swelling, we felt that the 5 studies (n = 280 patients), the table, and our documented experience at the University of Miami as cited in our review article was sufficient information covering this topic. We do not believe that the addition of the case report by Perri et al was necessary.[2]

The authors state that in a newly published study by Wong et al[3]—findings suggest a potential link of bone overgrowth with neurologic sensory complaints challenging the previous claim from the FDA sponsored trial.[3-5] In this small retrospective series by Wong et al[3] (n = 5) of TLIFs and PLIFs, the use of BMP-2 resulted in ectopic bone formation within the spinal canal causing radicular pain, which improved following revision surgery, suggesting that not only can BMP induce ectopic bone formation but that the new bone can result in a delayed onset of radiculopathy. While their observations are interesting, the study was retrospective and contains a small number of patients of which only 3 of 5 underwent revision surgery. In some of the patients, leg pain was a prominent finding even prior to the presence of ectopic bone formation. As suggested by Villavicencio et al[6] and cited in our paper; we would also recommend anterior placement of the BMP with in the disc space.

With respect to the issue of bony resorption, graft subsidence and the use of rh-BMP we cited 10 recent articles spanning 1995 to 2007 on this topic and we do not believe the addition of the 7 papers cited by Smolijanovic add a substantial amount of further information on this subject.[7-13]

Other points made by Smolijanovic et al include the recognition of previously published literature that may suggest a potential link to the area of the bone-sponge interface and speed of rh-BMP-2 release in regards to the degree of boney resorption.[14,15] The current human spinal literature cited by Smolijanovic et al suggests that osteolysis, when observed, is typically proximal to the site of contact of the BMP sponge on the endplate.[3,8-10,16-18]

These reports however do not support a direct link between the size of the contact area and the amount of boney resorption. We must also view a link between the rates of BMP release and the amount of osteolysis with caution as the report by Seeherman et al documented greater osteolysis with a collagen sponge carrier vs a calcium phosphate carrier in femoral bones of non-human primates, not in an experimental spinal model.[14]

In closing we all agree that bone morphogenetic proteins have changed the face of modern spine surgery. There are still many unanswered questions concerning these molecules, and hopefully some of those questions raised will be answered over time as future studies are developed.

We thank Smoljanovic et al again for their comments concerning our recent review article.

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1. Benglis D, Wang MY, Levi AD. A comprehensive review of the safety profile of bone morphogenetic protein in spine surgery. *Neurosurgery* 2008;62:ONS423-431; discussion ONS431.
2. Perri B, Cooper M, Lauryssen C, Anand N. Adverse swelling associated with use of rh-BMP-2 in anterior cervical discectomy and fusion: a case study. *Spine J*. 2007;7:235-239.
3. Wong DA, Kumar A, Jatana S, Ghiselli G, Wong K. Neurologic impairment from ectopic bone in the lumbar canal: a potential complication of off-label PLIF/TLIF use of bone morphogenetic protein-2 (BMP-2). *Spine J*. 2008;8:1011-1018.
4. Alexander J, Branch CL, RW H. An analysis of the use of rhBMP-2 in PLIF constructs: Clinical and radiographic outcomes. In 18th Annual Meeting of the AANS and CNS Section of Disorders of the Spine and Peripheral Nerves. Orlando, FL; February-March 2002.

5. Haid RW, Jr, Branch CL, Jr, Alexander JT, Burkus JK. Posterior lumbar interbody fusion using recombinant human bone morphogenetic protein type 2 with cylindrical interbody cages. *Spine J*. 2004;4:527-538; discussion 538-529.
6. Villavicencio AT, Burneikiene S, Nelson EL, Bulsara KR, Favors M, Thramann J. Safety of transforaminal lumbar interbody fusion and intervertebral recombinant human bone morphogenetic protein-2. *J Neurosurg Spine*. 2005;3:436-443.
7. Burkus JK, Sandhu HS, Gornet MF, Longley MC. Use of rhBMP-2 in combination with structural cortical allografts: clinical and radiographic outcomes in anterior lumbar spinal surgery. *J Bone Joint Surg Am*. 2005;87:1205-1212.
8. Hansen SM, Sasso RC. Resorptive response of rhBMP2 simulating infection in an anterior lumbar interbody fusion with a femoral ring. *J Spinal Disord Tech*. 2006;19:130-134.
9. Kuklo TR, Rosner MK, Polly DW Jr. Computerized tomography evaluation of a resorbable implant after transforaminal lumbar interbody fusion. *Neurosurg Focus.* 2004;16:E10.
10. Laursen M, Hoy K, Hansen ES, Gelineck J, Christensen FB, Bunger CE. Recombinant bone morphogenetic protein-7 as an intracorporal bone growth stimulator in unstable thoracolumbar burst fractures in humans: preliminary results. *Eur Spine J*. 1999;8:485-490.
11. Smoljanovic T, Pecina M. Re: Burkus JK, Transfeldt EE, Kitchel SH, et al. Clinical and radiographic outcomes of anterior lumbar interbody fusion using recombinant human bone morphogenetic protein-2. *Spine.* 2002;27:2396-408. *Spine*. 2008;33:224
12. Vaidya R, Carp J, Sethi A, Bartol S, Craig J, Les CM. Complications of anterior cervical discectomy and fusion using recombinant human bone morphogenetic protein-2. *Eur Spine J*. 2007;16:1257-1265.
13. Vaidya R, Weir R, Sethi A, Meisterling S, Hakeos W, Wybo CD. Interbody fusion with allograft and rhBMP-2 leads to consistent fusion but early subsidence. *J Bone Joint Surg Br*. 2007;89:342-345
14. Seeherman H, Wozney JM. Delivery of bone morphogenetic proteins for orthopedic tissue regeneration. *Cytokine Growth Factor Rev*. 2005;16:329-345.
15. Smoljanovic T, Grgurevic L, Jelic M, et al. Regeneration of the skeleton by recombinant human bone morphogenetic proteins. *Coll Antropol.* 2007;31:923-932.
16. Burkus JK, Sandhu HS, Gornet MF. Influence of rhBMP-2 on the healing patterns associated with allograft interbody constructs in comparison with autograft. *Spine*. 2006;31:775-781.
17. McClellan JW, Mulconrey DS, Forbes RJ, Fullmer N. Vertebral bone resorption after transforaminal lumbar interbody fusion with bone morphogenetic protein (rhBMP-2). *J Spinal Disord Tech*. 2006;19:483-486.
18. Pradhan BB, Bae HW, Dawson EG, Patel VV, Delamarter RB. Graft resorption with the use of bone morphogenetic protein: lessons from anterior lumbar interbody fusion using femoral ring allografts and recombinant human bone morphogenetic protein-2. *Spine*. 2006;31:E277-284.

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Carotid Versus Coronary Disease Plaque Morphology

To the Editor:

The article by Virmani et al "Histopathology of carotid atherosclerotic disease" is well written and very interesting.[1]

One of its main conclusions is that "the ulcerated plaque, which is rare in the coronary artery circulation, is relatively common in the carotid and other elastic arteries." They further explain that "ulcerated plaque is a term used when the thrombus and a portion of the plaque have embolized, leaving an excavation in the remaining lesion."

It is well known that carotid endarterectomy is accompanied by many small embolizations, some gaseous and some which can increase the number of the remaining ulcerated plaques. Transcranial Doppler ultrasonography intraoperatively detects emboli in one-third of the cases.[2]

The problem is that the authors compare the results of coronary disease from a necrotomic study[3] with those of carotid disease obtained almost entirely after carotid endarterectomy.[4-8]

It is possible that these results are not comparable concerning the number of ulcerated plaques and that part of the difference is due to the different populations involved.

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1. Virmani R, Ladich E, Burke A, Kolodgie F. Histopathology of carotid atherosclerotic disease. *Neurosurgery*. 2006;59(5 Suppl):S219-S227.
2. Bailes JE, Medary MB. Carotid endarterectomy. In: Winn HR, ed. *Youmans Neurological Surgery*, 5th Ed. Saunders, Philadelphia; 2004, pp 1621-1649.
3. Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lessons from Sudden Coronary Death. *Arterioscler Thromb Vasc Biol*. 2000;20:1262-1275.
4. Bassiouny HS, Davis H, Massawa N, Gewertz BL, Glagov S, Zarins CK. Critical carotid stenoses: morphologic and chemical similarity between symptomatic and asymptomatic plaques. *J Vasc Surg*. 19899(2):202-212.
5. Carr S, Farb A, Pearce WH, Virmani R, Yao JS. Atherosclerotic plaque rupture in symptomatic carotid artery stenosis. *J Vasc Surg*. 1996;23(5):755-765.
6. Golledge J, Greenhalgh RM, Davies AH. The Symptomatic Carotid Plaque. *Stroke*. 2000;31:774-781.
7. Redgrave JNE, Lovett JK, Gallagher PJ, Rothwell PM. Histological Assessment of 526 Symptomatic Carotid Plaques in Relation to the Nature and Timing of Ischemic Symptoms. *Circulation*. 2006;113:2320-2328.
8. Spagnoli LG, Mauriello A, Sangiorgi G, et al. Extracranial Thrombotically Active Carotid Plaque as a Risk Factor for Ischemic Stroke. *JAMA*. 2004;292:1845-1852.

10.1227/01.NEU.0000371387.29124.8C

A new aneurysm therapy: Neucrylate AN

To the Editor:

The next quantum change in the treatment of cerebral berry aneurysm is likely to be the development and clinical application of a liquid embolic agent that can rapidly and effectively fill an aneurysm completely.

Liquids have the desired property of conforming to irregular aneurysm shapes, and more importantly, can be contoured around a balloon interface at the neck. That smooth interface would then recreate normal nonturbulent blood flow dynamics past the area that was previously the aneurysm neck.

We have recently experimented in the laboratory with such a device (Neucrylate AN™, VALOR Medical Inc., San Diego, CA), and having received institutional approval and, following all local human use guidelines, have used it to treat a patient with an anterior communicating artery aneurysm.

A 59-year-old male suffered significant subarachnoid hemorrhage, recovered, and 10 days later presented to University Hospital Tehran for definitive treatment. At the time of admission, he was completely neurologically normal, and had no risk factors. Under general anesthesia, catheter cerebral angiography demonstrated a broad neck anterior communicating aneurysm that filled from both anterior cerebral arteries (Figure 1).

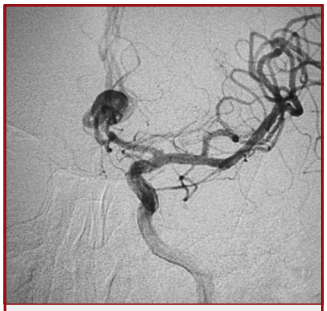

FIGURE 1.

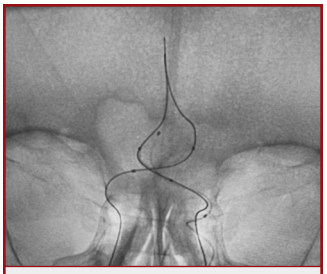

FIGURE 2.

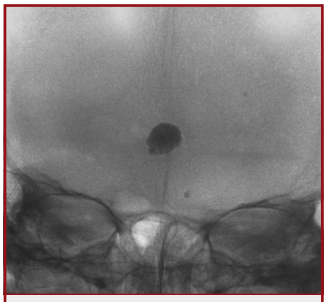

FIGURE 3.

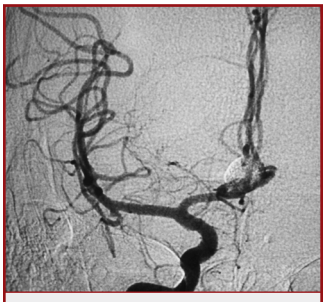

FIGURE 4.

A single balloon microcatheter did not cover the neck to our satisfaction, so 2 balloons were placed across the anterior communicating arteries into the contralateral A2 segments. A microcatheter was then guided into the mid portion of the aneurysm (Figure 2), and the Neucrylate was introduced using real-time fluoroscopic visualization control. Introduction and polymerization of the device took less than 1 minute (Figure 3). The microcatheter was then removed, the balloons were deflated, and a follow-up angiogram was performed (Figure 4). All cranial vessels filled normally.

Our only technical complication was to allow a micro drop of the device to leak from the microcatheter after it had been withdrawn from the aneurysm. That small deposit remained adherent to the left internal carotid artery and caused no symptoms.

The treatment was carried out under mild systemic heparinization (4000 units given as a single bolus at the beginning of the insertion of the balloon microcatheters), and with platelet inhibition (aspirin 325 mg and clopidogrel 75 mg daily for 3 days prior to the procedure.)

The patient is now 6 weeks postop and remains symptom-free. He will return at 6 months for the protocol mandated follow-up angiogram.

As the full battery of required FDA toxicology tests and animal and implant studies have been completed, this first clinical success may be the beginning a new treatment paradigm, a technique to give surgeons a more rapid and effective treatment for cerebral berry aneurysms, as not only does the liquid Neucrylate fill aneurysms of irregular shape, but it also presents a smooth surface to blood flowing past the prior aneurysm neck.

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Microsurgical and Angiographic Anatomy of Middle Cerebral Artery Aneurysm

To the Editor:

We have read with great interest the recent report of Ulm et al.[1] As stated, surprisingly few (the authors' literature search has not been very extensive), reports deal with such a common aneurysm site as the middle cerebral artery (MCA), and especially the overall management outcome of this specific group of patients.

They conclude on their retrospective review of 125 patients that, the majority of MCA aneurysms arose along the M1 segment proximal to the M1 bifurcation.[1] This conclusion and distribution of the MCA aneurysms in their Figure 6 is contrary not only to our own rather extensive surgical experience on treating MCA aneurysms, to a former[2] and recent scrutiny MCA aneurysms[3-5] (Table 1), contrary to experience of generations of neurosurgeons treating these aneurysms.

According to their site, MCA aneurysms (MCAAs) can be divided into 3 groups: proximal, bifurcation, and distal. Proximal MCAAs make up 14% of MCAAs, and their presence often indicates other associated aneurysms. Typically, proximal MCAAs are located at the origin of the first branch of the main trunk, and are pointing downward, or are at the origin of lenticulostriatal perforators and pointing upward (rare). A common feature among proximal MCAAs is that the neck is often wide and partially incorporated with the small efferent vessel, making clipping and coiling of these more tricky. Most of the MCAAs (>80%) are located at the bi/trifurcation, usually pointing laterally and inferiorly. Distal MCAAs are less frequent, in our series 5% of MCAAs were

TABLE 1. Patients With MCA Aneurysm in a Consecutive Population-Based Series of 3005 Patients With 4253 Intracranial Aneurysms From 1977 to 2005 in the Kuopio Cerebral Aneurysm Database (Adapted From 2-4)

	No. of Patients	No. of Aneurysms
Whole series	3005	4253
MCA aneurysms	1456	1704
M1As	221 (15%)	241 (14%)
MbifAs	1166 (80%)	1385 (81%)
MdistAs	69 (5%)	78 (5%)

located distally (Table 1). Distal aneurysms may be fusiform or mycotic, but true saccular aneurysms are found in even most distal parts of MCA. Common to all types of distal aneurysms is that they are difficult to find during surgery, made easier today by more accurate neuronavigation systems. Most of the proximal MCAAs were in patients with multiple intracranial aneurysms, and a patient with a proximal MCAA has an almost 3× higher risk for associated aneurysms than patients with bifurcation or distal MCAAs. Typically, Finnish patients have a higher frequency of MCAAs than reported in other series.

Consequently, we have had a unique opportunity to treat and scrutinize a large group of patients with these particular aneurysms (nowadays united Kuopio and Helsinki experience exceeds 7000 patients with MCAAs) and in our experience the MbifAs remain the most common MCA aneurysm, even in unruptured and ruptured cases.

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1. Ulm AJ, Fautheree GL, Tanriover N, et al. Microsurgical and angiographic anatomy of middle cerebral artery aneurysms: prevalence and significance of early branch aneurysms. *Neurosurgery*. 2008;62:ONS344-352; discussion ONS352-353.
2. Rinne J, Hernesniemi J, Niskanen M, Vapalahti M. Analysis of 561 patients with 690 middle cerebral artery aneurysms: anatomic and clinical features as correlated to management outcome. *Neurosurgery*. 1996;38:2-11.
3. Dashti R, Hernesniemi J, Niemelä M, et al. Microneurosurgical management of distal middle cerebral artery aneurysms. *Surg Neurol*. 2007;67:553-563.
4. Dashti R, Hernesniemi J, Niemelä M, et al. Microneurosurgical management of middle cerebral artery bifurcation aneurysms. *Surg Neurol*. 2007;67:441-456.
5. Dashti R, Rinne J, Hernesniemi J, et al. Microneurosurgical management of proximal middle cerebral artery aneurysms. *Surg Neurol*. 2007;67:6-14.

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Radiotherapy and Radiosurgery for Hormone Secreting Pituitary Adenomas

To the Editor:

Pollock et al suggest that prolactinomas have a significantly worse remission rate outcome than other hormone secreting adenomas, after gamma knife radiosurgery.[1]

This is a very interesting and rather novel finding. Its cause is difficult to understand. As one of the commentators points out, somatotroph and lactotroph cells derive from the same precursor cell type.

The authors discuss the importance of the small number of patients studied, the inconsistency of definitions of biochemical remission and the effect of the possible role of hypothalamic damage from radiosurgery, leading to higher prolactin levels.

We would like to suggest another possibility. We suspect that patients with prolactinomas treated with radiosurgery are highly selected. The usual and very effective treatment of prolactinomas is medical management with prolactin agonists. Their surgical treatment is also very effective.[3] We suppose that the patients with prolactinomas treated with radiosurgery had biologically aggressive adenomas, not responding well to other forms of treatment.

On the other hand, medical and surgical treatment of growth hormone and adrenocorticotropin-secreting adenomas is not as effective and consequently the selection is not so strong.

Series of prolactinomas treated primary with radiotherapy before the availability of dopamine agonists report hormone normalization of 63-70%,[2,5] similar to that of other hormone secreting adenomas. Some series reporting higher remission rate of prolactinomas after radiosurgery have not been referenced by the authors.[5]

We would like finally to remark that the reported difference in remission rate between prolactinomas and other hormone-secreting adenomas is extreme even between the referenced series. This could possibly be explained by the practice of the authors to exclude all patients taking pituitary suppressive medications at the time of radiosurgery. Even if this practice is adequately explained by the authors and leads to greater homogeneity of the populations, we cannot forget that the excluded medications are more effective in prolactinomas than in other types of adenomas.

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1. Ma ZM, Qiu B, Hou YH, Liu YS. Gamma knife treatment for pituitary prolactinomas [in Chinese]. *Zhong Nan Da Xue Xue Bao Yi Xue Ban*. 2006 Oct; 31(5):714-716.
2. Mehta AE, Reyes FL, Faihnern C. Primary radiotherapy of prolactinomas. *Am J Med*. 1989;83:59-68.
3. Nomikos P, Buchfelder M, Fahlbusch R. Current management of prolactinomas. *J Neurooncol*. 2001;54(2):139-150.
4. Pollock B, Brown P, Nippoldt T, Young W Jr. Pituitary tumor type affects the chance of biochemical remission after radiosurgery of hormone-secreting pituitary adenomas. *Neurosurgery*. 2008;62(6),1271-1278.
5. Rush SC, Newell J. Pituitary adenoma; the efficacy of radiotherapy as the sole treatment. *Int J Radiat Oncol Biol Phys*. 1989;17:165-169.

10.1227/NEU.0B013E3181D8CCBC

In Reply:

We thank Sakellaridis and Vasilakis for their interest in our recent paper[1] that concluded "there appears to be a differential sensitivity after radiosurgery for hormone secreting pituitary adenomas." Remission rates are greater for patients with Cushing's disease and acromegaly, whereas radiosurgery is less effective at achieving biochemical remission for patients with prolactinomas."

Clearly the patients having radiosurgery were highly selected from the overall experience at our center for patients with prolactin (PRL) secreting pituitary adenomas. As discussed, the major-

ity of patients respond well to medical therapy and never need to be evaluated for surgical resection, fractionated radiation therapy, or stereotactic radiosurgery. However, all of these patients had failed medical therapy and more than half had persistent PRL elevation despite surgical resection. We noted a significant decrease in the serum PRL for this group, although only 2 of 11 patients (18%) achieved biochemical remission off dopamine agonist therapy. The patients' average prolactin level was reduced from 212 ± 252 ng/mL to 37 ± 29 ng/mL (P =.03).

Moreover, 9 of 11 patients (82%) had improved symptoms and were able to discontinue their dopamine agonist therapy. We discussed the possibility that with longer follow-up after radiosurgery a greater percentage of these patients may onto biochemical remission. Of note, the references provided comparing conventional radiation therapy to our results had median follow-up intervals of 8 and 9 years, respectively,[2,3] compared to 4 years in our series. Also, in those papers as well as the study of Ma et al,[4] a clear definition of biochemical remission was not provided so a fair and honest comparison is not possible. Therefore, in spite of our findings we believe that radiosurgery should still be considered an option for patients with prolactinomas refractory to other treatments.

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1. Pollock B, Brown P, Nippoldt T, Young W Jr. Pituitary tumor type affects the chance of biochemical remission after radiosurgery of hormone-secreting pituitary adenomas. *Neurosurgery*. 2008;62(6),1271-1278.
2. Mehta AE, Reyes FL, Faihnern C. Primary radiotherapy of prolactinomas. *Am J Med*. 1989;83:59-68.
3. Rush SC, Newell J. Pituitary adenoma: the efficacy of radiotherapy as the sole treatment. *Int J Radiat Oncol Biol Phys*. 1989;17:165-169.
4. Ma ZM, Qui B, Hou YH, Liu YS. Gamma knife treatment for pituitary prolactinomas. *Zhong Nan Da Xue Xue Bao Yi Xue Ban*. 2006;31:714-716.

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Posterior Fossa Duraplasty and Hydrodynamic Complications

To the Editor:

We read with great interest the recent article by Moskowitz et al.[1] The authors describe their experience with posterior fossa duraplasty in different pathology using various materials to achieve closure and raises significant issues with the use of collagen matrix.

Although the method and type of duraplasty, the role of multilayer closure and method of exposure of posterior fossa contents (craniectomy vs craniotomy; midline vs lateral approach) have been implicated in complications following posterior fossa surgery, the principal factor responsible for hydrodynamic complications is associated hydrocephalus, which may be unrecognized prior to surgery or underappreciated in the postoperative period. The role of hydrocephalus as a major contributor to failure of cerebrospinal fluid (CSF) containment (pseudomeningocele, CSF leak) has been shown to be independent of the methods of duraplasty. We,[2-4] as well as others,[5,6] have reported that water-tight dural closure in posterior fossa surgery is not mandatory. Table 1 documents all previous reports of the clinical use of bovine collagen duraplasty (DuraGen®) (supratentorial and posterior fossa) in various conditions, inclusive of Chiari malformations.[5] Analysis of these studies revealed the rate of CSF leakage ranges from 0% to 4.5%, the formation of pseudomeningoceles ranges between 3.8% to 15.4% and the development of wound infections ranges from 1.9% to 6.1%. Hydrodynamic complications following cranial surgery reported by studies using subfascial drains[2-4] vs those with no drains[5,6] were: CSF leakage 4.5% vs 1.8%; and pseudomeningocele formation 6.5% vs 15.4%. Aseptic meningitis using bovine collagen duraplasty was reported at 0% for all studies. Furthermore, even in spinal surgery where the risk of CSF leak may be higher due to the hydrostatic pressure when standing, the reported risk of hydrodynamic complications with[7] and without[6] drains is significantly lower than that reported by the authors for posterior fossa surgery. However, the largest study published to date on posterior fossa duraplasty (n=454) using var-

TABLE 1. Incidence of complications following posterior fossa duraplasty using bovine collagen (Duragen®) based grafts.[a]

Author	Total Cases, N	Posterior Fossa Cases, N	Collagen Implant	CSF Leakage		Pseudomeningocele		Wound Infection
				Non-Posterior Fossa Cases, %	Posterior Fossa Cases, %	Non-Posterior Fossa Cases, %	Posterior Fossa Cases, %	
Narotam[3]	459	67	Sponge	0	4.5	0	ND	6.1
Narotam[5]	79	11	Matrix	0	0	3.2[b]	9.1	3.8
Stendel[8]	191	26	Matrix	2.6	ND	2.6	15.4	2.6
Posterior Fossa Surgery, %								
Danish[1]		56	Matrix	1.8			8.9	3.6
Narotam[6]		52	Matrix	0			3.8	1.9

[a] CSF, cerebrospinal fluid; ND, no data available.
[b] Occult, clinically asymptomatic, detected on 3-month follow-up magnetic resonance imaging.

ious materials,[8] reported a useful metric: pseudomeningocele rate of 12.3% and CSF leak rate of 4.6%. In our experiences with on lay DuraGen® (sponge and matrix), we have reported on comparable posterior fossa CSF leak rates of consistently below 5%.[2-4] In our most recent experience with posterior fossa collagen matrix duraplasty, we reported that early and timeous use of CSF diversion with ventriculostomy drainage during the primary surgery (31% of patients), multi-layered wound closure, and closed suction wound drainage to obliterate the dead space protected the suture line resulting in no CSF leaks.[4]

Moskowitz et al[1] report significantly higher "failure of CSF containment" or hydrodynamic complications in all groups using the bovine collagen with the highest being in the suturable type collagen (25%). Even the 22 patients who had primary closure of the dura had a higher than normal complication rate (18.2%) with 2 patients (9.1%) having a CSF leak despite no reported hydrocephalus in this group. The authors mention that 18 patients had CSF diversion during the perioperative period, (17 ventriculostomies for hydrocephalus and 1 prophylactic lumbar subarachnoid drain), however in Table 2 of the original manuscript, 14 patients and 9 patients in the results section are reported to have hydrocephalus. The authors do not document the presence of hydrocephalus prior to surgery and whether CSF diversion was practiced a priori in these patients. Furthermore, how many patients with pre-operative hydrocephalus who did not have temporary or permanent CSF diversionary procedures went on to have hydrodynamic complications? What is the author's definition of delayed hydrocephalus and how many patients developed this complication?

The use of craniotomy vs craniectomy to access the posterior fossa contents may also influence the rate of hydrodynamic complications. Midline craniectomy is associated with an increased incidence of post-operative CSF leak, pseudomeningocele, and wound reclosures. CSF leaks are in turn associated with CSF and wound infections. The authors report an unusually high incidence of aseptic meningitis with nearly two-thirds of patients (12 of 19 patients in Table 2) in the bovine collagen group, reporting a higher than normal 12% rate of aseptic meningitis per procedure. How was the diagnosis made, as no details are provided? Surprisingly, given their high hydrodynamic complication rate, the authors do not report on patients that may have had bacterial meningitis, ventriculitis, wound infections or other forms of intracranial suppuration. Similarly, in Table 2, 19 CSF leaks (12%) were reported for all procedures. Given that the authors report total CSF leaks in 15 patients and aseptic meningitis in 13 patients, it implies that even following revision repair, temporary and or permanent CSF diversion, some of their patients continued to have hydrodynamic complications either after repeat surgery and or in a delayed fashion. This may represent on-going under-recognized hydrocephalus. The authors should clarify this further.

Stendel et al[6] recently reported that the multiple fixation of collagen matrix resulted in a higher rate of infections and CSF leaks. No information is provided by the authors as to their method of fixation (on-lay, single, multiple or continuous suture) for the suturable collagen. Majority of the patients had a neoplastic etiology, did the authors look at steroid use as a possible relationship to their complication rate. Did the authors analyze hydrodynamic complications per age as the series includes a pediatric population?

Until the report of Moskowitz et al[1] complications associated with posterior fossa bovine collagen duraplasty had only been reported as an on lay graft technique using collagen sponge (original formulation; Duragen®)[2] and collagen matrix (newer formulation; Duragen Plus™).[4-6,8] Over a 3-year period, the author's (N.N.) personal experience with suturable Duragen (water-tight closure; no drains) in combination with a sealant (Duraseal; Confluent Surgical, Waltham, MA) during 27 posterior fossa craniectomies for resection of tumors resulted in hydrodynamic complications (CSF leak) in a single patient (3.7%). This patient required temporary CSF drainage to control for temporary hydrocephalus and revision surgery. No wound infections or aseptic meningitis were recorded. The recognition and management of hydrocephalus remains a major priority in preventing hydrodynamic complications associated with posterior fossa surgery. We therefore agree with the comments of J.D. Day that the recognition of hydrocephalus is of prime importance, which makes the choice of graft material or closure method irrelevant, with regards the development of hydrodynamic complications.

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1. Moskowitz S, Liu J, Krishnaney AA. Post-operative complications associated with dural substitutes in Suboccipital Craniotomies. *Neurosurgery*. 2009;64(3): 28-34.
2. Narotam PK, van Dellen JR, Bhoola KD. A clinicopathological study of collagen sponge as a dural graft in neurosurgery. *J Neurosurg*. 1995;82(3):406-412.
3. Narotam PK, Reddy K, Fewer D, Qiao F, Nathoo N. Collagen matrix duraplasty for cranial and spinal surgery: a clinical and imaging study. *J Neurosurg*. 2007;106(1):45-51
4. Narotam PK, Qiao F, Nathoo N. Collagen matrix duraplasty for posterior fossa surgery: evaluation of surgical technique in 52 adult patients. *J Neurosurg*. 2009;111(2):380-386.
5. Danish SF, Samdani A, Hanna A, Storm P, Sutton L. Experience with acellular human dura and bovine collagen matrix for duraplasty after posterior fossa decompression for Chiari malformations. *J Neurosurg*. 2006;104(1 Suppl):16-20
6. Stendel R, Danne M, Fiss I, et al. Efficacy and safety of a collagen matrix for cranial and spinal dural reconstruction using different fixation techniques. *J Neurosurg*. 2008;109(2):215-221.
7. Narotam PK, José S, Nathoo N, Taylon C, Vora Y. Collagen matrix (DuraGen) in dural repair: analysis of a new modified technique. *Spine*. 2004;29(24):2861-2867.
8. Parízek J, Mericka P, Nemecek S, et al. Posterior cranial fossa surgery in 454 children. Comparison of results obtained in pre-CT and CT era and after various types of management of dura mater. *Childs Nerv Syst*. 1998;14(9):426-438.

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