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Analysis of prevertebral soft-tissue swelling and dysphagia in multilevel anterior cervical discectomy and fusion with recombinant human bone morphogenetic protein–2 in patients at risk for pseudarthrosis

Clinical article

Joseph B. Stachniak, M.D.,[1] Jeffrey D. Diebner, M.D.,[2] Estee S. Brunk, B.S.N., R.N.,[1] and Shelley M. Speed, M.S.N., R.N., A.C.N.P.[1]

[1]Brain and Spine Center of Texas, and [2]Plano Radiology Associates, Plano, Texas

Object. The goal of this study was to demonstrate the incidence of fusion and soft-tissue swelling in multilevel anterior cervical discectomies and fusions (ACDFs) using polyetheretherketone (PEEK) spacers with recombinant human bone morphogenetic protein–2 (rhBMP-2) impregnated in a Type I collagen sponge and titanium plates.

Methods. A single surgeon performed 30 multilevel ACDFs using PEEK spacers with an rhBMP-2 impregnated collagen sponge (0.4 ml, or the equivalent of 0.6 mg rhBMP-2). Soft-tissue swelling was assessed using cervical spine radiographs on postoperative Day 1 and at 2, 6, and 10 weeks and 6 months after surgery. Incidence of dysphagia was assessed with the Cervical Spine Research Society Swallowing–Quality of Life tool. Clinical success was evaluated with the Neck Disability Index, neck pain scores, and arm pain scores. Final fusion was assessed with CT by an independent neuroradiologist.

Results. Patients were followed for 6 months unless they had an incomplete fusion; those patients were reassessed at 9 months. Twenty-four patients underwent 2-level ACDFs and 6 underwent 3-level ACDFs were performed on patients with the following risk factors for pseudarthrosis: smoking (33%), diabetes (13%), and obesity (body mass index ≥ 30 [43%]). Seventeen percent of the patients had multiple risk factors. Soft-tissue swelling peaked at 2 weeks regardless of level of surgery or number of levels treated surgically and decreased to near preoperative levels by 6 months. At 2 weeks, Swallowing–Quality of Life evaluation showed 19% of patients frequently choking on food, 4.8% frequently choking when drinking, and 47.6% with frequent food sticking in the throat. Scores continued to improve, and at 6 months, 0% had frequent choking on food, 6.7% had frequent difficulty drinking, and 6.7% had frequent food sticking in the throat. The Neck Disability Index, neck pain, and arm pain scores all improved progressively over 6 months. Incidence of fusion was 95% at 6 months and 100% at 9 months. There were no rehospitalizations or reoperations for soft-tissue swelling or dysphagia.

Conclusions. Multilevel ACDF procedures using PEEK grafts and rhBMP-2 can be performed safely in patients with multiple risk factors for pseudarthrosis with excellent fusion outcomes. *(DOI: 10.3171/2010.9.SPINE09828)*

Key Words • cervical spine • dysphagia • anterior cervical discectomy and fusion • polyetheretherketone spacer • recombinant human bone morphogenetic protein

The use of rhBMP-2 (INFUSE, Medtronic Spinal and Biologics) has a history of improving fusion rates in the thoracolumbar spine with a low incidence of complications.[3–9] More recently, rhBMP-2 has been used in the cervical spine with a reported increased incidence of soft-tissue swelling or complications as high as 27.5%, prompting an FDA warning.[13,15] However, controversy has risen over the appropriate dose of rhBMP-2 to be placed in grafts. The amounts studied range from 0.6 mg (or the equivalent of 0.4 ml of rhBMP-2) to 1.05 mg (0.7 ml) to 2.1 mg (1.4 ml) on the absorbable collagen sponge per cervical level.

Despite the large numbers of ACDF procedures performed, little has been done to systematically and quantitatively study the incidence of radiographically demonstrated soft-tissue swelling, and the incidence of dysphagia is poorly described. We report our experience in 30 patients with multiple risk factors for pseudarthrosis who underwent ACDF using PEEK spacers filled with a collagen sponge soaked with rhBMP-2. We examined the incidence of soft-tissue swelling and fusion using lateral cervical spine radiographs and CT scans, the incidence of dysphagia using the SWAL-QOL questionnaire, and the relationship between cervical edema and dysphagia in these patients.

Abbreviations used in this paper: ACDF = anterior cervical discectomy and fusion; BMI = body mass index; NDI = Neck Disability Index; PEEK = polyetheretherketone; rhBMP-2 = recombinant human bone morphogenetic protein–2; SWAL-QOL = Swallowing–Quality of Life.

Methods

Patient Population

We retrospectively reviewed the cases of 30 patients who underwent ACDF with PEEK spacers filled with an rhBMP-2 impregnated Type I collagen sponge and titanium plates between August 2006 and June 2008. Six men and 24 women with an average age of 53 years (range 28–66 years) participated in the study (Table 1). Average BMI was 28.8 (range 20–45). Patients were found to have the following risk factors for pseudarthrosis (Table 2): smoking (33%), diabetes (13%), and obesity (BMI ≥ 30 [43%]). Seventeen percent of the patients had multiple risk factors. One patient had a previous ACDF procedure at C5–6. The sites of the ACDF procedures were C3–4/C4–5 in 1 patient, C4–5/C5–6 in 7 patients, C5–6/C6–7 in 16 patients, C3–4/C4–5/C5–6 in 2 patients, C3–4/C5–6/C6–7 in 1 patient, and C4–5/C5–6/C6–7 in 3 patients (Table 3).

Each patient underwent a lateral cervical spine radiograph on postoperative Day 1 and at 2, 6, and 10 weeks after surgery. The amount of soft-tissue swelling from C-3 through C-7 was assessed and measured in millimeters by an independent neuroradiologist. Final evidence of fusion was assessed with cervical CT scans at 6 months after surgery. If fusion was not achieved at that time, a repeat CT scan was performed at 9 months. Incidence of dysphagia was evaluated at the same time intervals using the SWAL-QOL questionnaire, which is a 5-point scale assessing difficulty with eating, drinking, and having food stick in the throat.[11] Clinical status was assessed using the NDI as well as neck pain and arm pain scores (10 points maximum for intensity and 10 points maximum for frequency).[6]

Surgical Technique

All of the patients underwent an ACDF procedure by a single surgeon using the Smith-Robinson technique. Total operative time and retractor time were recorded for each patient. All of the patients had 0.4 ml (or 0.6 mg) of rhBMP-2 per level. Each of the sponges was soaked in rhBMP-2 for a minimum of 15 minutes and placed into a PEEK spacer. No additional sponge was placed anywhere other than inside the PEEK graft. There were no attempts to segregate the disc space with fibrin glue or other sealants. No irrigation was performed after graft placement, and very few patients had placement of a surgical drain. Patients were rarely given intraoperative dexamethasone, but most patients had a dexamethasone taper of 2 mg 4 times/day for 4 days, then 1 mg 4 times/day for 4 days, and then 0.5 mg 4 times/day for 4 days. Seven of 30 patients did not take steroids because of noncompliance with medical orders or because of diabetes. No patient wore a cervical collar postoperatively.

Statistical Analysis

For assessing the statistical significance of the relationship between cervical swelling and the amount of dysphagia, an ANCOVA was conducted. The relationship between age and BMI and cervical swelling at baseline was assessed using the Spearman rank order correlation coefficient (Spearman rho). Independent t-tests were conducted for each time point and number of levels operated on. At each time point, Fisher exact tests were conducted to examine differences in dysphagia by number of levels operated on. To assess the relationship between operative time and swelling, a Pearson correlation was used.

TABLE 1: Demographic data in 24 women and 6 men who underwent ACDF using PEEK spacers and an rhBMP-2 impregnated collagen sponge

Variable	Mean ± SD	Range
age (yrs)	52.5 ± 9.13	28–66
weight (lbs)	177.7 ± 45.5	104–288
height (in)*	65.2 ± 4.0	57–73
BMI	28.8 ± 6.6	20–45

* Data missing in 1 patient.

Results

Surgical Data and Hospital Stay

Twenty-four patients had a 2-level ACDF, and 6 patients had a 3-level ACDF (Table 3). Average operative time for these patients was 107 minutes (range 60–159 minutes; Table 4). Average static retraction time was 76 minutes (range 50–144 minutes). Average hospital stay was 1.5 days (range 1–4 days). Average blood loss was 47 ml, and average intravenous fluids received were 1138 ml. Blood loss had insignificant effects on soft-tissue swelling. The average length of incision was 3.68 cm.

Soft-Tissue Swelling

To determine trends in the development of soft-tissue swelling, an independent neuroradiologist measured the amount of soft-tissue swelling on plain radiographs at all levels in the cervical spine on postoperative Day 1 and at 2, 6, and 10 weeks and 6 months after surgery. We clearly saw a relative peak of soft-tissue swelling (in millimeters) at 2 weeks, with a gradual decrease over time toward the 6-month mark. Measurement of soft-tissue swelling in millimeters is recorded in Table 5. All cervical spine levels were measured for the presence of swelling, regardless of level of operation, to determine the presence of variations at the operative level and if the changes affected the entire cervical spine. Although the amount of radiographically demonstrated swelling became very significant at times (Fig. 1), none of the patients on the dexamethasone taper required additional medical intervention, including rehospitalization or reoperation.

Dysphagia

Dysphagia was assessed using the SWAL-QOL questionnaire. A score of 1 or 2 indicates the patient almost always or often had difficulty; a score of 3 indicates the patient sometimes had difficulty; and a score of 4 or 5 indicates the patient rarely or never had difficulty. Patients initially had significant problems with food sticking in the throat (Fig. 2A), eating (Fig. 2B), and drinking (Fig.

TABLE 2: Risk factors for pseudarthrosis

Risk Factor	No. of Patients (%)
smoker	
yes	10 (33)
no	16 (53)
quit	4 (13)
diabetic	
yes	4 (13)
no	26 (87)
BMI	
obese (≥30)	13 (43)
overweight	5 (17)
normal weight	12 (40)
previous cervical surgery	
yes	1 (3)
no	29 (97)

2C); however, this difficulty improved with time, especially after 2 weeks. There were no significant differences in swelling at the 2-week time point related to eating dysphagia ($p = 0.909$), drinking dysphagia ($p = 0.737$), or food-sticking dysphagia ($p = 0.146$). There were no statistical differences in dysphagia between the patients who received the dexamethasone taper and those who did not.

Neck Disability Index and Neck and Arm Pain

Neck and arm pain were assessed using the neck and arm pain questionnaire. As expected, there was a general trend toward progressive improvement in NDI scores and in neck and arm pain scores from surgery over time (Table 6).

Fusion

An independent neuroradiologist assessed fusion on lateral cervical spine radiographs obtained at 2, 6, and 10 weeks after surgery and using cervical CT scans at 6 months after surgery. One patient who did not have evidence of fusion by that time underwent another CT scan at 9 months. Bone formation occurred in some patients as early as 6 weeks after surgery. At 6 months 95% of patients had experienced a successful fusion, and at 9 months 100% of patients had successful fusion. The patient who did not show evidence of final fusion until 9 months had undergone a previous cervical fusion procedure, had a 3-level ACDF, and was a smoker. Bone formation was often very impressive and easily documented, occurring between the radiograph markers within the PEEK graft (Fig. 3). No statistically significant relationships between diabetes and fusion ($p = 0.241$), previous surgery and fusion ($p = 0.501$), or sex and fusion ($p = 0.490$) were identified.

Discussion

Soft-Tissue Swelling and Dysphagia

Literature on the incidence of dysphagia and soft-tissue swelling is tremendously variable and incompletely described.[14] Sanfilippo et al.[12] examined the incidence of

TABLE 3: Site of ACDF procedure

Surgical Site	No. of Patients (%)
C3–4, C4–5	1 (3)
C4–5, C5–6	7 (23)
C5–6, C6–7	16 (53)
C3–4, C4–5, C5–6	2 (7)
C3–4, C5–6, C6–7	1 (3)
C4–5, C5–6, C6–7	3 (10)

soft-tissue swelling after ACDF but only looked at a few specific levels of the cervical spine and did not consider the level of operative treatment and length of retraction time. The incidence of dysphagia and/or soft-tissue swelling tended to increase with the number of operated levels or complexity of the procedure. The study by Baskin and associates[2] involving 33 patients (18 of whom received rhBMP-2) did not report any problems with soft-tissue swelling or dysphagia. However, the study did describe 2 cases of heterotopic bone formation as a complication of rhBMP-2. The series by Shields et al.[13] involving 151 patients examined a diverse patient population that included cervical discectomies at varying levels and numbers of levels, as well as corpectomies. Concentrated doses of rhBMP-2 (up to 2.1 mg/level) were used, which potentially exacerbated soft-tissue swelling or dysphagia, or both, particularly in multilevel procedures. The incidence of complications in this series was 23.2%, which also included hoarseness/vocal cord palsy, lung collapse, Horner syndrome, syndrome of inappropriate diuretic hormone, superficial stitch abscess, and graft dislodgment and resorption. The authors acknowledged that their incidence of soft-tissue swelling was more significant than with the 0.6 mg per level dose used by Baskin et al.[2]

Smucker and associates[15] examined 234 patients over a 2-year period and found a higher incidence of soft-tissue swelling after ACDF in patients receiving rhBMP-2 (27.5%) than in the patients who did not receive rhBMP-2 (3.6%). Unfortunately, there were some statistically significant differences in the characteristics of the 2 patient groups requiring a multivariate logistic regression analysis. There was variability in the number of sponges used per level with no determination of the exact dose of rhBMP-2 applied. The investigators did not believe it was possible to determine the exact dose used. In contrast, we

TABLE 4: Variables measured during surgery

Variable	Mean ± SD	Range	No. of Patients*
op time (min)	107 ± 27.13	60–159	29
retraction time (min)	76 ± 25.32	50–144	30
length of hospitalization (days)	1.5 ± 0.776	1–4	30
blood loss (ml)	47 ± 52.61	0–250	30
intravenous fluids (ml)	1138 ± 394.55	500–1800	28
incision (cm)	3.68 ± 1.01	2.5–6.4	25

* Data not available for all 30 patients in each category.

TABLE 5: Cervical soft-tissue swelling*

Assessment Period	Swelling†	Range	No. of Patients‡
baseline (postop Day 1)	12.4 ± 5.7	5–30	28
2 wks	21.8 ± 5.0	13–32	21
6 wks	20.6 ± 5.6	12–35	24
10 wks	18.4 ± 5.2	10–32	22
6 mos	14.2 ± 3.4	8–21	21

* Measured radiographically at all levels regardless of operative level.
† Values (in mm) given as means ± SDs.
‡ Data not available for all 30 patients in each category.

were able to show consistency of dose from assay analysis with all patients receiving a 0.4-ml sponge soaked with 0.6 mg of rhBMP-2 per level. In the study by Smucker et al., the rhBMP-2 group was more likely to have undergone a multilevel ACDF than the non–rhBMP-2 group. Even after controlling for potential confounding variables, patients receiving rhBMP-2 were 10.1 times more likely to experience soft-tissue swelling than those who did not receive it. Smucker and associates were among the first to accurately describe a time window for the observed soft-tissue swelling that occurred, in a delayed manner, from several days to weeks after surgery. They reported that swelling peaked at 4.2 days. Although the exact timeline for soft-tissue swelling has yet to be described, many investigators believe it starts several days after surgery, with a peak in the 2nd to 4th weeks, with resolution sometime after this.

Vaidya et al.[18] described their experience in 46 patients undergoing ACDF with a combination of allograft and demineralized bone matrix or PEEK spacers and 1 mg of rhBMP-2 per level. The study revealed an increased incidence of soft-tissue swelling and dysphagia in the rhBMP-2 group (85%) compared with the non–rhBMP-2 group (56%). Endplate resorption was first noted at 1.5 months in 100% of patients who received rhBMP-2.

Tumialán and associates[16] observed a correlation between the total dose of rhBMP-2 and the incidence of dysphagia when comparing single-level ACDF procedures with 2-, 3- and 4-level ACDF procedures. The incidence of dysphagia was 1 (1%) in 96 in the single-level group; 2 (3.2%) of 62 in the 2-level group; 7 (19.4%) of 36 in the 3-level group; and 4 (66%) of 6 in the 4-level group. The investigators did qualify this observation with a suggestion to study the problem prospectively because dysphagia is a known of complication of ACDF, even without the use of rhBMP-2. They also suggested that the lower incidence of dysphagia in their study might have been related to placement of the rhBMP-2 sponges exclusively within the grafts. This placement may limit extravasation into surrounding soft tissues. In the studies by Shields et al.[13] and Smucker et al.,[15] rhBMP-2 sponges were placed both in or around the grafts, or both.

In the study by Aryan et al.,[1] 4 of the 6 patients who underwent multilevel cervical corpectomies for osteomyelitis experienced either dysphagia or dysphonia immediately after surgery. These symptoms resolved by the 4th postoperative day in all but 1 patient, who required

Fig. 1. Lateral cervical spine radiograph at 6 months in this patient shows marked soft-tissue swelling.

placement of a feeding tube for 6 weeks. Surgical drains were used to minimize hematoma or soft-tissue swelling in several studies.[3,13,16,17]

In our series of 30 patients undergoing ACDF procedures, we documented soft-tissue swelling in all levels of the cervical spine, regardless of operative level. We saw marked soft-tissue swelling occurring with rhBMP-2 that peaked radiographically around the 2nd postoperative week. Most patients were treated with a standardized dexamethasone taper postoperatively, which may have limited both the clinical complications and radiographically demonstrated soft-tissue swelling. Surgical drains were not used routinely.

The incidence of dysphagia in our study is somewhat difficult to compare with that reported in previous studies, because we used the SWAL-QOL questionnaire, which divides the incidence of dysphagia into 3 subcategories. Other studies we reviewed did not use this exhaustive tool. Dysphagia did trend toward improvement over the 6-month clinical course in all of the subcategories and resolved in our patients by 1 year. Some other investigators have used either intraoperative or, occasionally, postoperative oral steroids to treat swelling or dysphagia, but they were not used in a consistent postoperative protocol. Although we do not know whether our postoperative steroid protocol is optimal, no postoperative complications requiring rehospitalization or reoperation occurred in our patients.

Increased surgical and retraction times may cause increased soft-tissue swelling and dysphagia. Average surgical time for 2-level ACDF was 100.2 minutes and was 138.8 minutes for 3-level ACDF. Average retraction time for 2-level ACDF was 68.3 minutes and was 115.1 minutes for 3-level ACDF. No data regarding surgical or retraction times in ACDF involving the use of rhBMP-2 are available in the literature for comparison.

We attempted to look at the effects of retraction on cervical swelling. Statistical analysis using the Pearson correlation suggested there was a trend toward increased swelling with longer retraction, but the relationship was

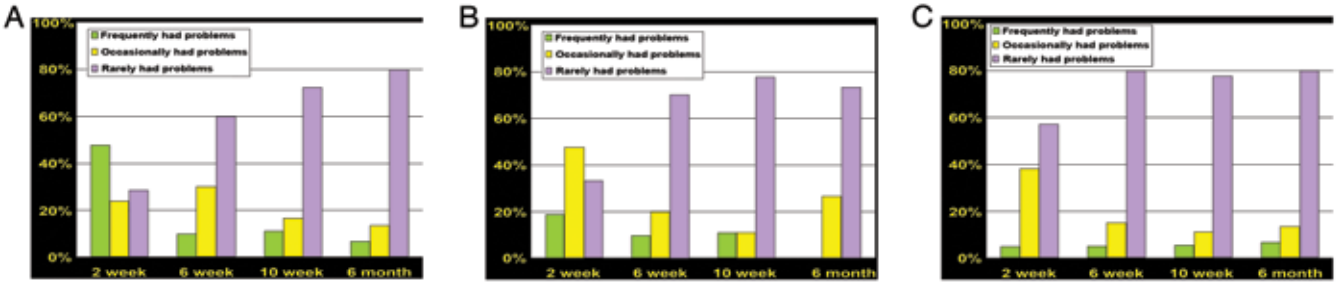

Fig. 2. Bar graphs showing the percentage of patients who experienced difficulty with food sticking in the throat **(A)**, eating **(B)**, and drinking **(C)** as measured by the SWAL-QOL questionnaire at 2, 6, and 10 weeks and 6 months after surgery.

relatively low. Using the Welch ANOVA, we further attempted to analyze the relationship between dysphagia and operative and retraction time. Operative time and retraction time did not differ significantly at any time point with dysphagia except at the 10-week point, which was statistically significant ($p = 0.025$). This unexpected finding may be related to the small number of patients in the study.

Fusion Rates

Baskin et al.[2] reported a 100% fusion rate using allograft and 0.6 mg of rhBMP-2 at 6 months. Lanman and Hopkins[10] reported a 100% incidence of fusion at 3 months using allograft with rhBMP-2 at an unknown dose. Vaidya and associates[17,18] reported a 100% fusion rate at 12 months using 1 mg of rhBMP-2 per cervical level. Tumialán and associates[16] also reported a 100% fusion rate using PEEK grafts and 0.7–2.1 mg of rhBMP-2 per level, but it is not known in what time frame fusion occurred. The study by Aryan et al.[1] reported a 100% fusion rate by 33 months, with 4.2 mg of rhBMP-2 used per level. Several of these patients also underwent posterior cervical stabilization as well.

Conclusions

Our study showed evidence of bone formation within 2 months, 95% fusion at 6 months, and 100% fusion at 9 months, despite many of our patients having risk factors for pseudarthrosis. We would not advocate the use of rhBMP-2 in the cervical spine for all patients. However, there may be a patient population that warrants the expense or risk of potential side effects, including soft-tissue swelling, to assure fusion. Studies of patients in which rhBMP-2 was used demonstrate fusion rates equal to or better than those using autograft or allograft without

TABLE 6: Neck Disability Index, neck pain, and arm pain scores

Test	Assessment Period	Score*	Range	No. of Patients†
NDI				
	baseline (postop Day 1)	23.9 ± 9.8	7–46	29
	2 wks	21.8 ± 8.3	5–38	28
	6 wks	15.2 ± 7.0	3–35	24
	10 wks	12.7 ± 9.5	0–30	22
	6 mos	11.2 ± 9.5	0–36	21
neck pain‡				
	baseline (postop Day 1)	15.3 ± 4.9	4–20	28
	2 wks	9.6 ± 8.3	2–17	28
	6 wks	8.0 ± 4.6	0–18	28
	10 wks	7.8 ± 5.2	0–15	25
	6 mos	5.8 ± 4.7	0–16	20
arm pain‡				
	baseline (postop Day 1)	12.8 ± 6.1	0–20	28
	2 wks	8.8 ± 6.1	0–18	28
	6 wks	6.3 ± 5.4	0–18	28
	10 wks	5.6 ± 5.8	0–17	25
	6 mos	4.7 ± 4.2	0–14	20

* Values given as means ± SDs.
† Data not available for all 30 patients in each category.
‡ There was a maximum of 10 points for intensity and a maximum of 10 points for frequency.

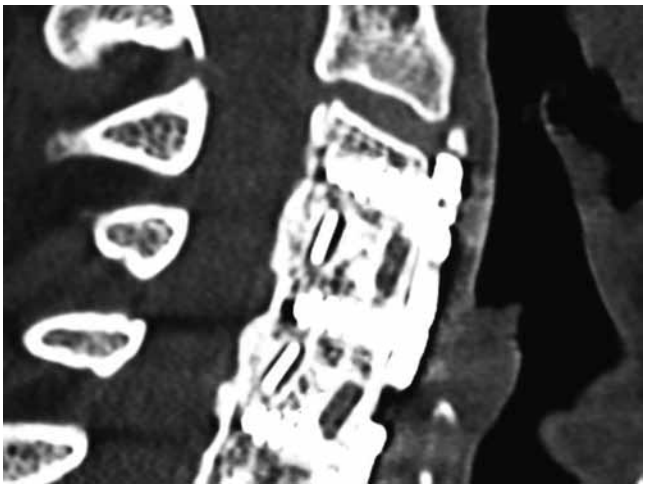

Fig. 3. Fusion is evident on the CT scan obtained in this patient at 6 months after surgery.

rhBMP-2. At this point, it would appear that 0.6 mg of rhBMP-2 is capable of achieving rapid cervical fusion in high-risk patients. As a result, many people believe that a lower dose of rhBMP-2 can still achieve fusion, but with fewer potential side effects.

The current controversy has raised many important questions. What is the appropriate dose of rhBMP-2? Should the rhBMP-2 soaked sponges be contained solely within grafts? Should the grafts be vented or unvented? Should shielding with tissue glue be used in conjunction with rhBMP-2 in ACDF procedures? Some of these questions may be answered with upcoming investigations in the area.

Disclosure

Financial (grant) support for this study was received from Medtronic Spinal and Biologics. Dr. Stachniak was formerly a consultant for Medtronic Spinal and Biologics but received no royalties.

Author contributions to the study and manuscript preparation include the following. Conception and design: Stachniak. Acquisition of data: all authors. Analysis and interpretation of data: Stachniak, Diebner. Drafting the article: Stachniak. Critically revising the article: Stachniak. Reviewed final version of the manuscript and approved it for submission: all authors. Administrative/technical/material support: Brunk, Speed. Study supervision: Stachniak.

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Address correspondence to: Joseph B. Stachniak, M.D., Brain and Spine Center of Texas, 3060 Communications Parkway, Suite 201, Plano, Texas 75093. email: jstachniak@aol.com.