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Clinical Study

Clinical sequelae after rhBMP-2 use in a minimally invasive transforaminal lumbar interbody fusion

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Abstract

BACKGROUND CONTEXT: Recent reports of postoperative radiculitis, bone osteolysis, and symptomatic ectopic bone formation after recombinant human bone morphogenetic protein-2 (rhBMP-2) use in transforaminal lumbar interbody fusions (TLIFs) are a cause for concern.
PURPOSE: To determine the clinical and radiographic complications associated with BMP utilization in a minimally invasive transforaminal lumbar interbody fusion (MIS-TLIF) environment.
STUDY DESIGN/SETTING: Retrospective clinical case series at a single institution.
PATIENT SAMPLE: Five hundred seventy-three consecutive patients undergoing an MIS-TLIF.
OUTCOME MEASURES: Reoperation rates and total costs associated with complications of rhBMP-2 use and pseudarthrosis.
METHODS: A retrospective review of 610 consecutive patients undergoing an MIS-TLIF (2007–2010) by a single surgeon at our institution was performed (mean age 48.7 years, range 26–82 years). All patients underwent an MIS laminectomy with bilateral facetectomy, single TLIF cage, unilateral pedicle screw fixation, and 12 mg (large kit) or 4.2 mg (small kit) of rhBMP-2. The BMP-2 collagen-soaked sponge was placed anteriorly in the disc space, followed by local bone graft, and then the cage was filled only with local bone and no BMP-2. Patients were evaluated at 6 months and 1 year with computed tomography (CT) scan. Those demonstrating neuroforaminal bone growth, osteolysis/cage migration, or pseudarthrosis were reviewed, and cost data including direct cost/procedure for both index and revision surgeries were collected.
RESULTS: Of the 573 patients, 10 (1.7%) underwent 15 additional procedures based on recalcitrant radiculopathy and CT evidence of neuroforaminal bone growth, vertebral body osteolysis, and/or cage migration. Thirty-nine patients (6.8%) underwent reoperation for clinically symptomatic pseudarthrosis. Bone overgrowth was associated with nerve impingement and radiculopathy in all 10 patients (small kit, n=9; large kit, n=1). Osteolysis and cage migration occurred in 2 (20%) of these same 10 patients. Average total costs were calculated per procedure ($19,224), and the costs for reoperation equaled $14,785 per encounter for neuroforaminal bone growth and $20,267 for pseudarthrosis.
CONCLUSIONS: Symptomatic ectopic bone formation, vertebral osteolysis, and pseudarthrosis are recognized complications with the use of rhBMP-2 in MIS-TLIFs. Potential causes include improper dosage and a closed space that prevents the egress of the postoperative BMP-2 fluid collection.

FDA device/drug status: Not approved for this indication (Infuse).

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Management of these complications has a substantial cost for the patient and the surgeon and needs to be considered with the off-label use of rhBMP-2.

Keywords: rhBMP-2; Neuroforaminal; Bone growth; MIS-TLIF; Pseudarthrosis

Introduction

The clinical use of purified recombinant osteoinductive proteins to enhance spinal fusion has now entered its second decade. Recombinant human bone morphogenetic protein-2 (rhBMP-2, Infuse; Medtronic Sofamor Danek, Memphis, TN, USA) received US Food and Drug Administration (FDA) approval for the indication of anterior lumbar interbody fusion (LIF) in conjunction with a lumbar-tapered cage (Medtronic Sofamor Danek). In this application, rhBMP-2 is applied to a collagen sponge that serves as a biologic carrier [1–3]. In the anterior fusion clinical trials, no adverse events were reported, and it was noted that clinical outcomes improved in the rhBMP-2–treated group. Once approved by the FDA, the off-label use began in clinical practice in the anterior/posterior cervical and posterolateral lumbar spine in an effort to improve fusion rates. Subsequent reports have demonstrated that application of Infuse in the anterior lumbar spine is not without risk [4,5]. The recently published Yale University Open Access Data (YODA) project meta-analyses have demonstrated that the original studies (RCTs and cohort projects) investigating the complications associated with BMP-2 utilization have underreported or even missed some adverse events because of nontransparent data sharing, selective reporting, duplicate publications, and conflicts of interest [4,5]. Therefore, this article will emphasize the limitations of the published BMP-2 complication literature as reported in the YODA project meta-analyses.

Complications in the cervical spine (wound complications, dysphagia, dysphonia) have surfaced over the last several years prompting the FDA to issue a public health warning in 2008 for the off-label use of BMP-2 in this application [5]. Ectopic bone formation has been reported in both the epidural space and the insertional track when rhBMP-2 was used in posterior LIFs, but the harm data were too inadequate to achieve statistical significance in the YODA project [5–7]. Clinically significant neural compromise was noted by Chen et al. [8] in a case series of four patients after the off-label use of rhBMP-2 after minimally invasive transforaminal lumbar interbody fusions (MIS-TLIFs), but the YODA project noted that this outcome measure was poorly classified in the literature with variable reporting of neurologic events [5].

This institutional review board–approved study reviews a single surgeon/single institution experience of more than 500 patients who underwent MIS-TLIFs with rhBMP-2 over a 4-year period including clinical sequelae and direct cost per procedure for both index and revision surgeries. None of the contributing authors have conflicts of interest with Medtronic Sofamor Danek.

Materials and methods

Patient data

After institutional review board approval, a retrospective review of all consecutive patients undergoing an MIS-TLIF by a single surgeon was performed. Patients receiving rhBMP-2 along with an interbody graft were identified. Patients were evaluated based on routine CT evaluation (at 6 months) and with additional diagnostic imaging if neurologic or radiculopathic findings were present (CT myelography).

Data were collected with regard to patient age, diagnosis at index procedure, operative time, interbody graft preparation and materials, time to onset of initial symptoms, and the subsequent revision surgery (hospital direct costs and physician charges). Diagnoses for the primary procedure included recurrent herniated nucleus pulposus, spinal stenosis associated with a degenerative spondylolisthesis, and degenerative disc disease. Demographic data are presented in Tables 1 and 2. Statistical testing was performed to compare age, gender, smoking status, rhBMP-2 doses, and surgical levels between patients who underwent revisions to those who did not. p Values less than .05 were considered statistically significant.

Surgical technique

A unilateral approach was undertaken through a paramedian skin incision using the Wiltse technique under fluoroscopy. Unilateral pedicle screws were placed percutaneously over a guide wire. The laminectomy, bilateral facetectomy, and TLIF were performed through a unilateral 21-mm nonexpandable tube retractor. No posterolateral fusion was performed. Midline muscular and ligamentous structures were all preserved during the procedure. Local bone graft that had been harvested from the laminectomy and facetectomy was collected in a bone trap and mixed with either a small (4.2 mg) or a large (12 mg) kit of rhBMP-2. The large kit was routinely used for earlier cases because of its hospital formulary availability. At the time of the earlier cases in this series, there were limited data on complications related to BMP. However, once complications started to be case reported, the senior surgeon switched from using a large kit to a small kit of rhBMP-2.

Follow-up

Standard postoperative follow-up included visits at 6 weeks, 3 months, 6 months, and 1 year. Patients were evaluated with routine postoperative CT scans at 6 months

EVIDENCE & METHODS

Context
Complications related to the use of BMP in TLIF have been previously recognized. In this paper, the authors present their experience regarding patients undergoing reoperation.

Contribution
In this clinical case series, the authors found about 2% of patients who had undergone a TLIF with BMP went on to reoperation for bony overgrowth and foraminal stenosis, osteolysis, or cage migration. About 7% underwent reoperation for pseudarthrosis. The average total cost for each revision procedure was approximately $19,000.

Implications
This study provides some good baseline information that might be used for cost comparison to cases in which BMP is not used. Importantly, care must be taken to consider technical differences between surgeons, recognizing that the current data reflect a single-surgeon's experience. It may well be that technical differences might significantly increase or decrease the risks of complications with the use of BMP.

—*The Editors*

and 1 year (as part of normal clinical practice), or if they were clinically symptomatic with radiculopathy, then CT myelography was ordered. Pseudarthrosis was diagnosed by a lack of osseous union on CT at 1 year or evidence of loosening of the instrumentation.

Costs

Cost data were collected in terms of cost per procedure for both primary and revision surgeries. The costs reported include the hospital direct costs for surgical services, implants, room and board, blood transfusion, imaging, laboratory tests, pharmacy, physical/occupational therapy, and physician charges.

Results

A total of 610 patients were identified who underwent an MIS-TLIF with rhBMP-2 (2007–2010). There were 573 (93.9%) patients with a minimum of 12-month follow-up who included CT scans at both 6 months and 1 year (Fig. 1). The primary diagnosis was degenerative spondylolisthesis with spinal stenosis in 447 (78%) patients, degenerative disc disease in 63 (11%), and recurrent herniated disc refractory to nonoperative care in 63 (11%). There was no difference in the characteristics of patients that dropped out compared with those with complete follow-up (Table 1). The mean age of patients at the time of the primary surgery was 48.7 years (range 26–82 years). Patients who underwent a revision for either neuroforaminal bone growth or pseudarthrosis were significantly younger than those who did not have a revision ($p<.05$ and $<.001$, respectively) (Table 2). The pseudarthrosis group trended toward a significant increase in the prevalence of smokers compared with patients who did not have any revision (41.3% vs. 26.7%, $p<.054$). A large kit of rhBMP-2 was used in 40% of the primary surgeries. However, only one (10%) patient with neuroforaminal bone growth had the large kit ($p<.06$), whereas a significantly greater percentage (56.4%) of patients with clinically symptomatic pseudarthrosis received the large kit ($p<.04$) (Table 2).

Complications

Of the 573 patients who followed up, perioperative complications included transient postoperative radiculitis in 327 (57.0%) patients, dural tears in 23 (4.0%), and wound infections in 3 (0.49%). Postoperative radiculitis was independent of the rhBMP-2 dose ($p>.05$) and typically presented with symptoms of pain radiating to the knee at 10 to 14 days after surgery. All instances of radiculitis resolved spontaneously or after treatment with a Medrol dose pack by 1 month, except for those cases who underwent revision surgery before that time. Two wound infections after primary surgeries were diagnosed on postoperative Day 2 and were identified because of spiking temperatures, wound erythema, and gross purulence. One infection occurred in the postoperative setting of a dural

Table 1
Demographic characteristics of patients undergoing primary MIS-TLIF (N=610)

Factors	Primary cases with 1-year follow-up (n=573)	Primary cases with incomplete follow-up (n=37)	p Value
Male, n (%)	399 (69.6)	24 (64.9)	.542
Female, n (%)	174 (30.4)	13 (35.1)	
Age, y (range)	48.7 (26–82)	49.9 (30–77)	.583
Smoker, n (%)	157 (27.4)	13 (35.1)	.309
Small kit of rhBMP-2, n (%)	344 (60.0)	25 (67.6)	.364
Large kit of rhBMP-2, n (%)	229 (40.0)	12 (32.4)	
L4–L5 (n)	373	20	.174
L5–S1 (n)	200	17	

MIS-TLIF, minimally invasive transforaminal lumbar interbody fusion; rhBMP-2, recombinant human bone morphogenetic protein-2.

Table 2
Demographics of patients undergoing revision (n=49/573)

Factors	No revision (n=524)	Revision patients (n=49)			
		Revisions for neuroforaminal bone growth (n=10)	p Value	Revisions for pseudarthrosis (n=39)	p Value
Male, n (%)	367 (70.0)	7 (70)	.998	25 (64.1)	.437
Female, n (%)	157 (30.0)	3 (30)		14 (35.9)	
Age, y (range)	49.3 (27–82)	41.6 (27–66)	.048	42.1 (26–67)	<.001
Smoker, n (%)	140 (26.7)	1 (10)	.235	16 (41.3)	.054
Small kit of rhBMP-2, n (%)	318 (60.7)	9 (90)	.059	17 (43.6)	.036
Large kit of rhBMP-2, n (%)	206 (39.3)	1 (10)		22 (56.4)	
L4–L5 (n)	340	4	.103	29	.230
L5–S1 (n)	184	6		10	

rhBMP-2, recombinant human bone morphogenetic protein-2.

tear revision for the treatment of neuroforaminal bone growth.

Overall, there were 49 (8.6%) patients who underwent a revision surgery. Ten patients (1.7%) underwent revision surgery for symptomatic neuroforaminal bone growth and/or vertebral body osteolysis with cage migration demonstrated on CT scan. All patients with evidence of neuroforaminal bone growth or osteolysis were symptomatic and underwent a revision surgery. Seven of these patients (70%) were men and three patients (30%) were women, with an average age of 40.3 years (range 26–65 years). All 10 of the initial surgeries were single-level fusions. A small kit of rhBMP-2 (4.2 mg) was used in nine cases, and a large kit (12 mg) was used in one case. Bone overgrowth was associated with nerve impingement and radiculopathy in all 10 patients (Fig. 2). Additionally, cage migration and osteolysis were observed in two (0.35%) of these same patients (Fig. 3), and one (0.17%) patient was observed to have a large calcified fluid collection. Three of the patients had significant medical comorbidities (history of deep vein thrombosis with pulmonary embolism, hypertension), and one patient was a tobacco smoker. In addition, a 6.8% (39/573) of patients

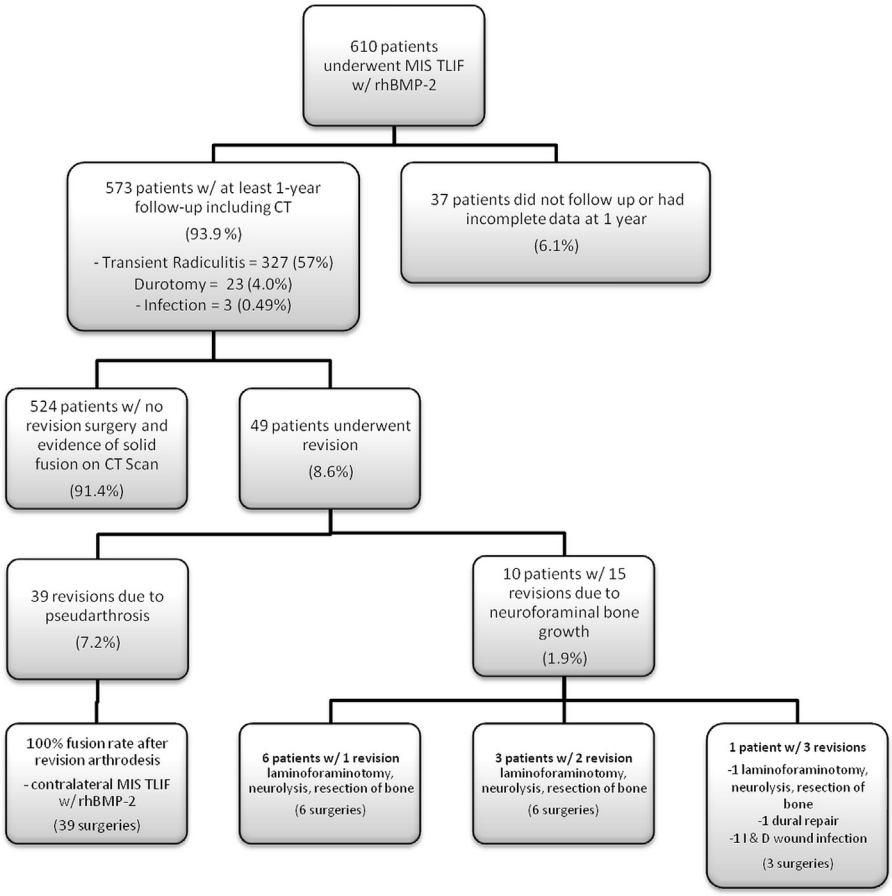

Fig. 1. Schematic demonstrating the breakdown of revision surgeries and additional procedures from the initial patient cohort.

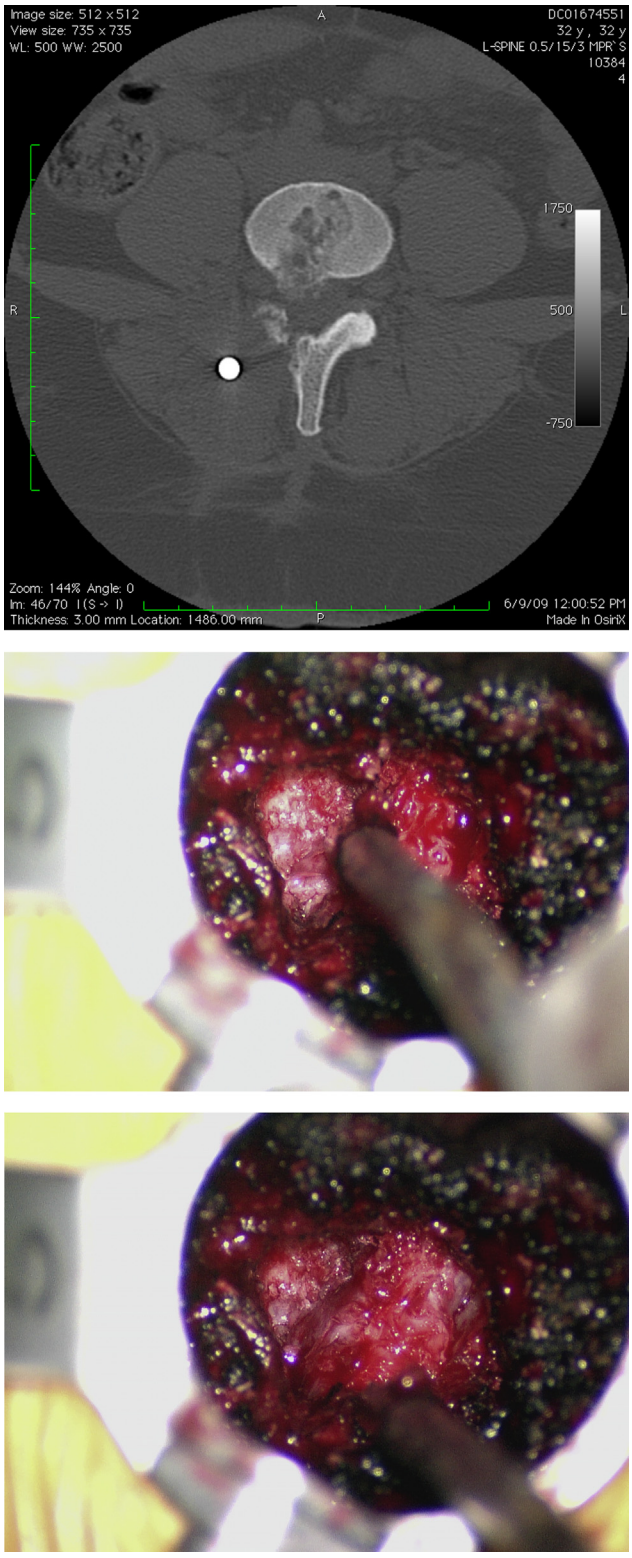

Fig. 2. Axial computed tomography image (Top) demonstrating right neuroforaminal bone growth at L4/L5. (Middle) An intraoperative image with the exiting nerve root retracted superiorly revealing the ventral surface bone growth. (Bottom) Intraoperative imaging revealing the ventral surface bone growth resected and the exiting nerve root neurolysed.

were identified as having pseudarthrosis confirmed by CT scan evaluation. All patients found to have a pseudarthrosis were clinically symptomatic and underwent a revision arthrodesis.

Surgical outcomes

For the 573 primary procedures, average surgical time was 105 minutes (range 68–164 minutes) and average estimated blood loss was 63 mL (range 50–100 mL), whereas length of stay was 2.4 days (range 1–4 days) (Table 3).

For the 15 revision procedures in those patients with neuroforaminal bone growth (10 patients), the average surgical time was 57.1 minutes (range 32–177 minutes), average estimated blood loss was 64.4 mL (range 50–200 mL), and average length of stay was 2.25 days (range 1–8 days) (Table 3).

Description of revision surgeries

Ten patients underwent a total 15 revision surgical procedures for a diagnosis of neuroforaminal bone growth (Fig. 1). Thirteen of these revision surgeries consisted of laminoforaminotomies with neurolysis and excision of the bone growth from the ventral aspect of the canal. Seven patients underwent a single revision, whereas three patients underwent two revisions with laminoforaminotomy, neurolysis, and foraminal bone resection because of continued symptoms after the first revision. Intraoperative inspection in these patients revealed adherence of the neural structures to the surface of the ectopic bone that required microscopic dissection to free the dura and nerve root sheath. In the two patients with osteolysis (Fig. 3), intraoperative exploration revealed absence of trabecular bone within the vertebral body, graft subsidence, and loss of end-plate integrity. One patient also underwent lumbar dural repair and an additional procedure for irrigation and debridement of a subsequent lumbar wound infection.

In patients presenting with clinically symptomatic pseudarthrosis (39/573), revision arthrodesis procedures consisted of contralateral MIS-TLIF, pedicle screw instrumentation, and the use of local bone graft augmented with a small kit of rhBMP-2.

Cost analysis

The average total cost per primary procedure equaled $19,224. Average costs for revision surgery equaled $14,785 per encounter for those patients undergoing intervention for either neuroforaminal bone growth and/or cage migration with vertebral body osteolysis. The primary decrease in hospital directs costs during the revision procedures was related to the lack of implant utilization. Last, in patients undergoing revision procedures for clinically symptomatic pseudarthrosis, the average total costs for

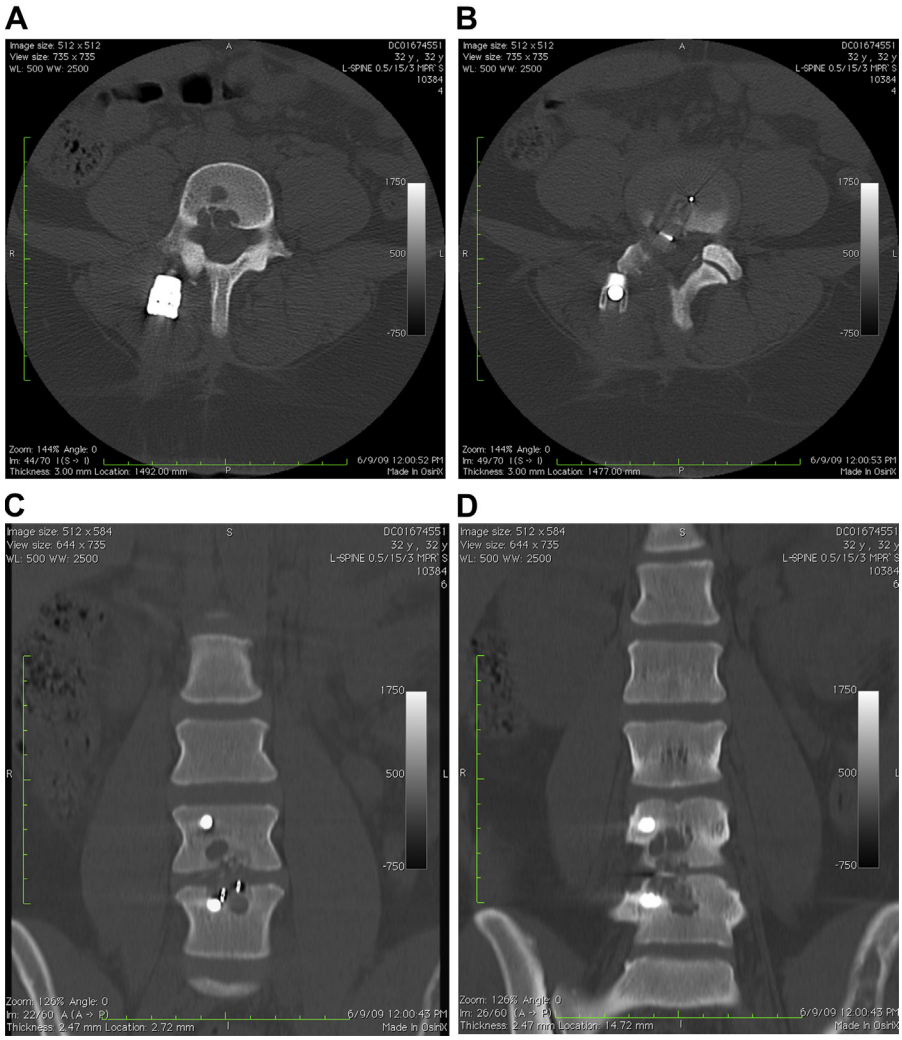

Fig. 3. Axial (A, B) and coronal (C, D) computed tomography images demonstrating vertebral osteolysis at L4/L5. Case migration (B) and subsidence (C) are also observed in conjunction with osteolysis.

revision surgery equaled $20,267. The overall cost per case when incorporating the additional costs from all revision procedures is $20,990 per patient.

Discussion

The YODA project meta-analyses emphasized the need for more transparent and definitive evidence regarding the rhBMP-2–associated complications [5]. Our large, nonconflicted study aims to add to the surgical literature regarding the utilization of rhBMP-2 in an off-label manner. This is the largest study to date that specifically addresses the complications of rhBMP-2 use in the setting of an MIS-TLIF. In addition, this is the only study to our knowledge that addresses the additional hospital costs of treating neuroforaminal bone growth.

Other studies have explored this topic of heterotopic bone formation in differing types of spine surgeries [9]. Specifically, one retrospective review of 119 patients compared 33 patients undergoing a single-level TLIF receiving iliac crest with 86 patients receiving rhBMP-2 [10]. The most common complications found in the rhBMP-2 group consisted of postoperative radiculitis (14.0%), vertebral body osteolysis (5.8%), ectopic bone formation (2.3%), and lumbar wound infection (3.5%) [10]. The YODA project assessed these studies and their findings and concluded that the limited data and the poor quality of ascertainment precluded any definitive conclusion.

Table 3
Clinical parameters of primary and revision procedures for patients with neuroforaminal bone growth

Factors	Primary (n=10 cases)	Revision—ectopic bone (n=15)
Average surgical time (min) (range)	105.0 (68–164)	57.1 (32–177)
Average estimated blood loss (mL) (range)	63.0 (50–100)	64.4 (50–200)
Average length of stay (d) (range)	2.40 (1–4)	2.25 (1–8)
Average duration from previous surgery (mo) (range)	—	8.3 (0.9–24.7)

Several techniques, similar to our method, have been proposed to prevent the formation of heterotopic bone formation in the neuroforamen. Some authors have proposed packing morselized bone as the initial barrier, posterior to the cage, and then subsequently adding allograft as the secondary barrier to prevent leakage into the canal [8]. Furthermore, the addition of fibrin glue as a tertiary barrier has shown to be effective in both human and animal studies to prevent escape of rhBMP-2 into the spinal canal [11]. Rihn et al. [10] found that the use of a hydrogel sealant (Duraseal; Confluent Surgical, Inc., Waltham, MA, USA) in a series of rhBMP-2–treated patients reduced the rate of postoperative radiculitis from 20.4% to 5.4% (p=.047). The YODA project demonstrated that none of these trials have sufficiently defined ''radiculitis,'' and therefore, the reported incidences should be taken with some level of caution [5]. In addition, the YODA project did not assess the effectiveness of these techniques to prevent the development of heterotopic bone growth. It should be noted that we did not observe any patients to have asymptomatic neuroforaminal bone growth. The simple technique currently used by the senior surgeon (KS) is to apply bone wax to the annulotomy defect sealing the intervertebral space from the spinal canal.

McClellan et al. [12] report on another complication of vertebral bone resorption after the use rhBMP-2 in a traditional TLIF procedure. They assessed 26 patients and 32 levels with follow-up CT scans and noted bone resorption defects in 22 of these 32 levels (69%). Additionally, the bone resorption defects were further broken down into mild and moderate defects based on the degree of absence of bridging bone between facet articulations or vertebral end plates. The most severe form that was associated with osteolysis demonstrated graft subsidence and loss of endplate integrity. The reason stated by the authors for this relatively high osteolysis was the robust bone remodeling ability of rhBMP-2. The YODA project determined that osteolysis was a seldom reported complication, and this lack of data prevented any definitive conclusion [5]. In our study, two (0.35%) of the patients had severe osteolysis that demonstrated graft subsidence and cage migration. Interestingly, the amount (small kit, 4.2 mg) of rhBMP-2 used in these two patients seems to be substantiated by similar amounts in other TLIF studies [12,13]. We did not observe any patient who underwent operative intervention alone for osteolysis. Furthermore, we also did not observe any clinically asymptomatic vertebral osteolysis.

Some clinical studies have speculated that the complications associated with rhBMP-2 use relate mainly to the dosage [14], whereas others have found that BMP-2–related complications are dose independent (36–320 mg) [15]. The evidence provided by the YODA project meta-analyses must be taken into consideration when interpreting the accuracy and significance of these published findings [4,5]. Doses in many studies, where no instances of heterotopic bone formation have occurred, are usually around 1.5 mg/mL [2,16,17]. Our study found no connection between increased dosages and increased ectopic bone formation and/or osteolysis (nine patients 4.2-mg BMP-2, one patient 12-mg BMP-2). Interestingly, a significantly greater number of patients who underwent revisions for pseudarthrosis received the large kit of rhBMP-2 in the primary procedures (p<.04). However, this may represent a surgical learning curve as the large kit of rhBMP-2 was mostly used during the earlier cases in this series.

This present study represents the largest nonconflicted reported series of patients treated with an MIS-TLIF and rhBMP-2. Recombinant human bone morphogenetic protein-2 appears to be a powerful bone graft enhancer that allows for increased rates of arthrodesis in a challenging unilateral MIS-TLIF model (6.8% pseudarthrosis rate [n=39/573]). However, with rhBMP-2's off-label usage, there is a low but clinically significant rate of neuroforaminal bone growth that does occur (1.7%, n=10/573). These data attempt to address the apparent lack of sufficient evidence regarding this complication as cited by the YODA project. It should be noted that the costs of revision surgical intervention for neuroforaminal bone growth should be taken into serious consideration ($14,785). These data are novel and have not been assessed by the recent YODA project analyses. In this series, the average cost per revision for pseudarthrosis was greater than the revision costs for neuroforaminal bone growth ($20,267). When we calculate the overall cost per TLIF including both primary and revision cases, the average cost of treatment is $20,990 for these 573 patients. Furthermore, 37 patients did not have complete follow-up. If we assume the worst-case scenario that all 37 of these patients underwent revision for pseudarthrosis (the more expensive of the two revision procedures), the overall cost per patient may be as high as $22,113. The increase in cost because of neuroforaminal bone growth should be evaluated in the context of a potential decreased need for reoperation secondary to pseudarthrosis. Our analysis supports the view that osteolysis and cage migration, although less frequent (0.35%, n=2), are potential complications that can occur because of bone remodeling properties of rhBMP-2.

Of course limitations exist in the present study in that it is the experience of only a single surgeon at a single academic institution. Furthermore, only unilateral fixation was used in this setting. We theorize that the lack of postoperative dead space may lead to a concentration of the postoperative seroma high in BMP-2 concentration. Theoretically, this seroma may increase the likelihood of BMP-2–induced radiculitis, vertebral osteolysis, and neuroforaminal bone growth. Although radiographic fusion in our review was blinded, inter- and intraobserver reliabilities of fusion assessment were not performed. Additionally, a control group (local bone only) was not compared. A historical control by the senior surgeon does exist, but the sample size is small with high pseudarthrosis rates being present in this challenging fusion environment using only

unilateral fixation [18]. Nevertheless, this study emphasizes the importance of discussing with patients the risks (osteolysis, radiculitis, and neuroforaminal bone growth) and benefits (increased fusion rates) of BMP-2 so that an informed decision can be made together with patient and physician preferences. Finally, it is important to point out that the costs reported in this study are hospital direct costs and physician charges and do not capture the costs of rehabilitation, outpatient medications, other physician interventions, and indirect costs such as societal costs, lost wages, and lost productivity. Hospital costs and physician reimbursement will vary between different hospitals and geographic locations as these data are sensitive and vary according to geographic region and environment.

In conclusion, in this prospective nonconflicted nonrandomized study, rhBMP-2 was shown to be effective for arthrodesis in the setting of a unilateral MIS-TLIF. However, complications of neuroforaminal bone growth, osteolysis, and pseudarthrosis can arise with this off-label usage. This study offers critical data to address the lack of definitive evidence regarding these complications in the current published literature, as mentioned in the recent YODA project publications. These complications, although infrequent, lead to increases in total hospital direct costs, significant resource utilization, and the need for additional operative intervention. Most importantly, the risks and benefits of rhBMP-2 in an MIS-TLIF should be thoroughly discussed with the patient such that an informed decision should be made regarding its usage.

References

[1] Boden SD, Zdeblick TA, Sandhu HS, Heim SE. The use of rhBMP-2 in interbody fusion cages: definitive evidence of osteoinduction in humans: a preliminary report. Spine 2000;25:376–81.

[2] Burkus JK, Gornet MF, Dickman CA, Zdeblick TA. Anterior lumbar interbody fusion using rhBMP-2 with tapered interbody cages. J Spinal Disord Tech 2002;15:337–49.

[3] 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.

[4] Simmonds MC, Brown JV, Heirs MK, et al. Safety and effectiveness of recombinant human bone morphogenetic protein-2 for spinal fusion: a meta-analysis of individual-participant data. Ann Intern Med 2013;158:877–89.

[5] Fu R, Selph S, McDonagh M, et al. Effectiveness and harms of recombinant human bone morphogenetic protein-2 in spine fusion: a systematic review and meta-analysis. Ann Intern Med 2013;158:890–902.

[6] Haid RW, Branch CL, Alexander JT, Burkus JK. Posterior lumbar interbody fusion using recombinant human bone morphogenetic protein type 2 with cylindrical interbody cages. Spine J 2004;4:527–38.

[7] McKay B, Sandhu HS. Use of recombinant human bone morphogenetic protein-2 in spinal fusion applications. Spine 2002;27(1 Suppl): S66–85.

[8] Chen N-F, Smith ZA, Stiner E, et al. Symptomatic ectopic bone formation after off-label use of recombinant human bone morphogenetic protein-2 in transforaminal lumbar interbody fusion. J Neurosurg Spine 2010;12:40–6.

[9] Muchow RD, Hsu WK, Anderson PA. Histopathologic inflammatory response induced by recombinant bone morphogenetic protein-2 causing radiculopathy after transforaminal lumbar interbody fusion. Spine J 2010;10:e1–6.

[10] Rihn JA, Patel R, Makda J, et al. Complications associated with single-level transforaminal lumbar interbody fusion. Spine J 2009;9:623–9.

[11] Patel VV, Zhao L, Wong P, et al. An in vitro and in vivo analysis of fibrin glue use to control bone morphogenetic protein diffusion and bone morphogenetic protein-stimulated bone growth. Spine J 2006;6:397–403.

[12] 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: 483–6.

[13] Lewandrowski K-U, 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: 609–14.

[14] Boden SD, Martin GJJ, Horton WC, et al. Laparoscopic anterior spinal arthrodesis with rhBMP-2 in a titanium interbody threaded cage. J Spinal Disord Tech 1998;11:95–101.

[15] Maeda T, Buchowski JM, Kim YJ, et al. Long adult spinal deformity fusion to the sacrum using rhBMP-2 versus autogenous iliac crest bone graft. Spine 2009;34:2205–12.

[16] Brower RS, Vickroy NM. A case of psoas ossification from the use of BMP-2 for posterolateral fusion at L4–L5. Spine 2008;33: E653–5.

[17] Villavicencio AT, Burneikiene S, Nelson EL, et al. Safety of transforaminal lumbar interbody fusion and intervertebral recombinant human bone morphogenetic protein-2. J Neurosurg Spine 2005;3: 436–43.

[18] Singh KMD, Smucker JDMD, Boden SDMD. Use of recombinant human bone morphogenetic protein-2 as an adjunct in posterolateral lumbar spine fusion: a prospective CT-scan analysis at one and two years. [Article]. J Spinal Disord Tech 2006;19:416–23.