Complications Associated WithBoneMorphogenetic Protein in the Lumbar Spine

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abstract

Complications associated with the use of recombinant human bone morphogenetic protein in the lumbar spine include retrograde ejaculation, ectopic bone formation, vertebral osteolysis and subsidence, postoperative radiculitis, and hematoma and seroma. These complications are controversial and remain widely debated. This article discusses the reported complications and possible implications for the practicing spine surgeon. Understanding the complications associated with the use of recombinant human bone morphogenetic protein and the associated controversies allows for informed decision making by both the patient and the surgeon. [Orthopedics. 2017;40(2):e229-e237.]

BACKGROUND AND HISTORY

The use of recombinant human bone morphogenetic protein (rhBMP) for spinal fusion increased dramatically in 2002 after US Food and Drug Administration (FDA) approval was obtained. This approval was based on sponsored human clinical trials that reported excellent fusion rates and outcomes compared with autologous iliac crest bone graft in anterior or lumbar spinal fusion, with limited complications and adverse events.1,4 Of nearly 20 characterized BMP structures,5,6 only 2 rhBMP products have been approved by the FDA for use in humans.7 The first was rhBMP-7 (OP-1; Stryker, Hopkinton, Massachusetts), which was approved in 2001 for the treatment of long bone non-union, and then as part of a humanitarian device exemption, expanded indications were obtained for use in revision postero-lateral lumbar arthrodesis and pseudarthrosis of the lumbar spine.1,3,7 In 2002, rhBMP-2 (inFUSE; Medtronic, Memphis, Tennessee) was approved for use in conjunction with the Lumbar Tapered Fusion Device (LT-Cage; Medtronic) and absorbable collagen sponge carrier for anterior lumbar interbody fusion at a single level between L4 and S1.3,4,7 Cahill et al8 queried the Nationwide Inpatient Sample database and found that the use of rhBMP increased from 0.69% of all spinal fusion procedures in 2002 to 24.89% by 2006.

However, dichotomous opinions on optimal use and safety have surfaced, particularly as a result of potential discrepancies in the types and rates of complications initially reported in sponsored clinical trials compared with publicly accessible FDA

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reports and subsequently published nonsponsored studies.9

During the past decade, the most controversial topics in the spine care community have included complications and adverse events after the use of rhBMP. There are anticipated and unanticipated risks with the adoption and increased use of any new drug or technology. However, some in the spine care community have been alarmed by the various reports of complications associated with the burgeoning use of rhBMP, especially for expanded indications and physician-directed (ie, off-label) use. In 2010, Ong et al10 reported that, among 340,251 operative cases, rhBMP was used in a physician-directed manner in approximately 30% (>100,000) of cases. The most common procedures were posterior lumbar interbody fusion and transforaminal lumbar interbody fusion.7 The reasons for widespread early adoption and increased physician-directed use after postmarket approval of rhBMP are unclear, although potential factors may be perceived issues with iliac crest harvesting, including donor site morbidity, and additional need for operative exposure, with increased operative time and blood loss.11,12 In addition, the high reported fusion rates seemed to justify the associated costs of rhBMP by potentially avoiding the costs and resource use associated with reoperation as a result of pseudarthrosis.13 However, Martin et al14 analyzed the Nationwide Inpatient Sample after reports of additional safety concerns and revelations of financial conflicts of interest for investigators in the pivotal FDA investigational device exemption clinical trials and found that the use of rhBMP for lumbar fusion decreased an average of 11.7% per year after 2008, whereas there was a 7.9% increase per year from 2002 to 2008. Given the continued controversies surrounding the use of BMP in the lumbar spine, this review provides an update on various reported complications and possible implications for spine surgeons.

Complications

In 2002, Poynton and Lane15 astutely described theoretical complications associated with the use of potent osteobiologics that enhance spinal fusion, such as rhBMP. These complications included “the possibility of bony overgrowth, interaction with exposed dura, cancer risk, systemic toxicity, reproductive toxicity, immunogenicity, local toxicity, osteoclastic activation, and effects on distal organs.”15 With increasing clinical experience outside of controlled clinical trials, surgeons began to highlight complications associated with rhBMP from a more heterogeneous population of patients and with expanded indications. However, controversy remains, and various studies have differed in reported rates of complications associated with rhBMP compared with iliac crest bone graft, with some of the largest database studies reporting no difference in complication rates. In 2011, Williams et al16 queried the Scoliosis Research Society database of 55,862 spinal fusion surgeries. These authors found that 79% of patients received rhBMP and 21% did not. The authors compared complication rates between the groups (with rhBMP vs without rhBMP), excluding anterior cervical fusion, and found no difference in overall complication rates; in addition, multivariate analysis controlling for various confounding variables between groups (age, revision surgery, case complexity) showed no difference in complication rates.16,17 Similarly, in the largest sample size to date, Cahill et al8 queried the Nationwide Inpatient Sample database and identified 70,649 spinal fusion procedures performed in 2006, with rhBMP used in 24.89%. The authors found no difference in overall complication rates between patients with and without rhBMP use, and for those undergoing lumbar fusion, the complication rate was 6.97% for those who were treated with rhBMP vs 7.18% for those who were not treated with rhBMP.8 Conflicting reports have also emerged on long-term safety with exposure to rhBMP, including the potential for stimulation or progression of neoplasms.18-21 The Yale University Open Data Access Project found a slightly increased relative risk of cancer with the use of rhBMP-2, although the absolute risk was very small and likely was clinically insignificant.22-24 However, other studies did not find an association between rhBMP-2 and a detectable increase in the risk of cancer,18 even with high-dose rhBMP-2 in adult patients with spinal deformity.25 Overall, the various nonsponsored clinical trials, specifically, those reporting physician-directed use (ie, posterior lumbar interbody fusion, transforaminal lumbar interbody fusion) of rhBMP in the lumbar spine, are limited in quality. Combined pooled data are difficult to interpret because of methodologic differences in inclusion criteria, retrospective vs prospective design, sample size (mostly small heterogeneous case series), availability of a control group, surgical techniques and instrumentation, rhBMP dosage and carriers, and use of adjuncts to prevent complications (ie, fibrin glue).17,26 Therefore, it is difficult to draw definitive conclusions on the frequency of complications and risk ratios compared with iliac crest bone graft, guidelines for off-label use, and cost-effectiveness of rhBMP from these studies.17,26 However, recent reports have emphasized several specific complications associated with the use of rhBMP to augment lumbar spine fusion, and these are reviewed later in more detail.

Retrograde Ejaculation

Retrograde ejaculation in men is a known, but uncommon complication after anterior lumbar interbody fusion. It is believed to be caused by damage to the superior hypogastric autonomic plexus during surgical exposure around the aortic bifurcation and lower lumbar levels. Greater risk has been associated with exposure of the L5-S1 disk space, greater number of exposed levels, laparoscopic approach, transperitoneal approach, and revision
In 2004, Haid reviewed the rate of retrograde ejaculation after anterior lumbar interbody fusion with rhBMP-2 compared with 0.6% among those treated without rhBMP-2. Several studies reported similar findings, including the work of Smoljanovic et al., who found a higher rate of retrograde ejaculation associated with rhBMP-2 (7.9% with rhBMP-2 vs 1.4% without rhBMP-2, \( P = .05 \)). Comer et al. also found higher rates of retrograde ejaculation with the use of rhBMP-2 (6.3% vs 0.9% control) in addition to urinary retention (9.7% vs 4.6% control). Food and Drug Administration clinical trial data from the randomized controlled phase also showed a higher rate of retrograde ejaculation in men who underwent open anterior lumbar interbody fusion with rhBMP (6.4% with rhBMP-2 vs 1.5% without rhBMP-2, \( P = .14 \)), although the findings were not statistically significant. In contrast, Lindley et al. compared anterior lumbar interbody fusion with the use of rhBMP-2 with lumbar disk replacement and found no difference in the rate of retrograde ejaculation between groups (7.5% vs 9.8%, respectively). Similarly, Tepper et al. evaluated the rate of retrograde ejaculation after anterior lumbar interbody fusion with quantitative semen analysis, urine analysis, and qualitative standardized questionnaires and found similar rates of retrograde ejaculation with or without the use of rhBMP-2 (9.5% vs 10.0%, respectively).

Estimates of the rate of retrograde ejaculation after anterior lumbar interbody fusion, with or without rhBMP-2, have varied widely. Based on the available literature, it is difficult to draw a definitive conclusion on the association of rhBMP-2 with retrograde ejaculation. In addition to the use of rhBMP-2, numerous potential confounding variables during anterior lumbar interbody fusion could cause retrograde ejaculation. In any study, the following factors would be particularly difficult to control and analyze: technical skill and expertise of the exposure surgeon, extent of dissection, and amount of electrocautery used. Also, validated methods for qualitative screening and quantitative verification of retrograde ejaculation remain unclear. Despite the shortcomings in the literature, retrograde ejaculation is a significant complication, especially for young, healthy men and their families. Therefore, if anterior lumbar interbody fusion is recommended, the spine surgeon must thoroughly counsel and educate men on the risk of retrograde ejaculation, and decision making on the use of rhBMP-2 should be shared and based on the specific clinical situation (ie, osteoporosis, tobacco use, pseudoarthrosis) and the current available literature.

**Ectopic Bone Formation**

The role of the potent osteogenic molecules rhBMP-2 and rhBMP-7 led to various reports of ectopic ossification, which is defined as bone formation outside the intended fusion area. In early animal studies of BMP (extracted from long bones of rabbits), investigators were keenly aware of the potential for uncontrolled bone growth, and many experimental models were tested, with inconclusive findings. Miyamoto et al. tested a rodent model with BMP (prepared from murine osteosarcoma and partially purified) that was implanted in the lumbar extradural space. At 8 weeks, they found ossification and hypotrophy of the ligamentum flavum, with secondary spinal cord compression and areas of degeneration and demyelination. Mimatsu et al. tested a rabbit L5 laminectomy model with rhBMP-2 implanted over the ligamentum flavum and found new bone formation on the dorsal side of the spinal canal that resulted in anterior-posterior flattening of the spinal cord; however, the cord compression caused no myelopathy or neurologic sequelae. Meyer et al. reported similar findings in a canine L5 laminectomy model, with rhBMP-2 applied on a collagen sponge over exposed dura. This resulted in ectopic bone along the laminectomy defect, with no deleterious neurologic effects. These studies were performed with nearly 10 times higher concentrations of rhBMP-2 than required for posterior lumbar fusion in animal models. However, in other studies, investigators did not show ectopic bone formation, even with a laminectomy defect, and some suggested that the collagen carrier is a potential risk factor.

In a rat and rabbit model, Hsu et al. found no ectopic bone formation in animals implanted with rhBMP-2 without a carrier, even at high concentrations, compared with typical ossicle formation when rhBMP-2 was implanted on an absorbable collagen sponge carrier.

As in various animal experiments, reported rates and clinical consequences of ectopic bone formation with the use of rhBMP-2 in humans have been inconclusive. In particular, the rate of clinical symptoms and sequelae from ectopic bone growth after rhBMP-2 application is unclear, with some studies describing no deleterious consequences and others reporting significant neural compression and radiculopathy as a result of ectopic bone within the spinal canal or neuroforamina after posterior or transforaminal lumbar interbody fusion. In 2004, Haid et al. reported the results of an FDA clinical trial of the use of rhBMP-2 for posterior lumbar interbody fusion that was stopped after only 9 months and enrollment of 67 subjects. The trial was stopped because 75% (24 of 32) of patients in the rhBMP-2 group (dosage, 4.0-8.0 mg on absorbable collagen sponge) had ectopic bone formation in the epidural space or...
neuroforamina on 6-month postoperative computed tomography (CT) imaging (thin-cut, 1-mm) and plain radiographs compared with only 13% (4 of 31 patients) in the iliac crest bone graft group ($P<.0001$). However, no patients had adverse clinical outcomes or symptoms as a result of ectopic bone. In 2007, Joseph and Rampersaud reported a prospective observational study of 33 patients with posterior or transforaminal lumbar interbody fusion. In their study, 20.8% (5 of 24 levels) in the rhBMP-2 group (4.2 mg/level on absorbable collagen sponge) showed ectopic bone in the epidural or foraminal area compared with 8.3% (1 of 12 levels) in the group that was not treated with rhBMP-2. Similarly, these authors reported no clinical consequences in either group as a result of ectopic bone.

Although the FDA clinical trials were stopped early because of ectopic bone formation with the use of rhBMP-2 for posterior lumbar interbody fusion, several subsequent clinical studies reported no cases of ectopic bone formation with the use of rhBMP. In particular, in 2004, Mummaneni et al. in a study of 24 patients, and in 2005, Villavicencio et al. in a study of 74 patients, reported no cases of ectopic bone formation after transforaminal lumbar interbody fusion augmented with rhBMP-2. However, these authors described advancements in techniques for back-filling the interbody space and using a sealant over the annulotomy site, theoretically creating a barrier and maintaining the rhBMP within the anterior disk space and interbody cage. In addition, Patel et al. used a rat model to show that fibrin glue can limit rhBMP-2 diffusion and provide a protective barrier to elution; however, it also inhibited the osteogenic effects of rhBMP-2, with decreased bone formation at the site of intended fusion.

In contrast to studies reporting no clinical sequelae, in 2008, Wong et al. reported 5 patients who were referred to them after posterior or transforaminal lumbar interbody fusion augmented with rhBMP-2. These patients had symptomatic ectopic bone that caused neural compression. Average time from index surgery to identification of the ectopic bone was 8.4 months, and the authors noted that the revision surgeries were very difficult because the ectopic bone adhered to neural structures, requiring meticulous microscopic dissection of the dura and nerve root sheath. Three patients had moderate improvement of radicular symptoms after revision surgery. The authors identified possible risk factors as postoperative hemotoma or sterile fluid collections (3 of 5 patients), irritation of the wound after rhBMP-2 placement, and placement of deep subfascial drains (3 of 5 patients).

In a 2010 series by Chen et al., 4 of 37 patients (11%) who were treated with rhBMP-2 to augment minimally invasive transforaminal lumbar interbody fusion had ectopic bone and clinical symptoms of neural compression. Of these patients, 3 had revision surgery, with removal of the “encasing bone mass” within the spinal canal or neuroforamina, with complete resolution of symptoms. In 2009, Rihn et al. reported 1 case of symptomatic ectopic bone formation among 48 patients after treatment with rhBMP-2 during transforaminal lumbar interbody fusion. Radicular pain resolved after revision surgery, with excision of the ectopic bone within the L5-S1 neuroforamen. Other reports have described ectopic bone formation after the use of rhBMP-2, such as within the retroperitoneal space after the use of rhBMP-2 for anterior and lateral lumbar fusion procedures, as well as bilateral epidural cyst formation that caused progressive postoperative neural compression. Surgical excision of bilateral epidural cysts provided complete relief of pain, and histopathologic findings showed osteoid and woven bone surrounded by an inflammatory fibrovascular stroma.

Overall, the evidence suggests that formation of ectopic bone can occur after posterior or transforaminal lumbar interbody fusion procedures with or without rhBMP-2, with some studies implicating higher rates with the use of rhBMP-2. In most cases, ectopic bone does not appear to cause clinical sequelae, but symptomatic neural compression has been described, with some patients requiring revision surgery and painstaking decompression of neural structures encased within bone.

The effectiveness of techniques to prevent the formation of ectopic bone has been incompletely evaluated, and these include placing the BMP product in the most anterior portion of the disk space, using a layering technique with back-filling the disk space with additional bone graft posterior to the interbody cage, and using a barrier such as fibrin glue or dural sealant over the annulotomy site.

Although the risks and consequences of ectopic bone formation with rhBMP-2 are debatable, surgeons should counsel patients on the potential increased risk of this complication, particularly with off-label use of rhBMP-2 for augmentation within the interbody space during posterior or transforaminal lumbar interbody fusion.

### Vertebral Osteolysis and Subsidence

Along with the ability of rhBMP-2 and rhBMP-7 to promote bone formation, some reports have described excessive bone resorption as well as graft-cage subsidence and migration at interbody fusion sites augmented with rhBMP. Osteolysis is the normal initial phase of the bone remodeling cycle, and a small amount of graft subsidence is part of fusion biology. However, when intensified by rhBMP-2 or rhBMP-7, in some cases, severe end-plate erosion with severe cage subsidence occurs as a result of loss of mechanical end-plate stability, cage migration, or allograft fracture.

Several studies showed that vertebral osteolysis is caused by osteoclast activation associated with the use of rhBMP, and this effect is postulated to be dose dependent. At the molecular level, BMP interacts with specific
receptors on the surface of cells, inciting a cascade of gene transcription and signaling that can activate or suppress various extra- and intracellular events. Therefore, in addition to signaling osteogenic activation, BMP also acts in various other pathways linked to limb and nervous system development, renal repair and development, and importantly, osteoclastic remodeling. In 1995, Kanatani et al found osteoclastic induction in vitro with BMP-2. Other investigators reported synergism of BMP-2 with interleukins in osteoclastic development.

In 1999, in an early report of rhBMP-7 osteolysis by Laursen et al, severe bone resorption was seen on CT imaging at 3 and 6 months postoperatively in 1 of 5 patients with thoracolumbar trauma fixation augmented with rhBMP-7. Fusion occurred by 1 year. Similarly, in 2006, McClellan et al provided an early account of osteolysis in transformaminal lumbar interbody fusion augmented with rhBMP-2. Their study found osteolysis in 22 of 32 levels (69%) on CT imaging 3 months postoperatively, with 5 (15%) also showing graft subsidence. The authors characterized the extent of osteolysis and found 50% with mild bone defects (<25% graft area and <3×3 mm), 18% with moderate bone defects (25%-75% graft area and <5×5 mm), and 32% with severe bone defects (>75% and >1×1 cm). Since these reports were published, numerous studies have described osteolysis, subsidence, and cage migration, although the rate, severity, and effect on outcomes have varied widely.

In 2010, in a systematic review, Mroz et al found a mean 44% rate of bone resorption, a mean 25% rate of graft subsidence, and a mean 27% rate of cage migration for lumbar interbody fusion augmented with rhBMP-2. Their review also found that most series reporting rhBMP-related osteolysis showed few reoperations and no long-term adverse effect on clinical outcomes, with the area of bone resorption filling in and fusing by 9 to 12 months. However, in reported cases of reoperation as a result of rhBMP-related osteolysis, some studies found interbody devices to be “grossly loose,” with soft, compromised end plates requiring revision with larger interbody devices for mechanical stability.

Results of different studies are difficult to compare because of differences in rhBMP-2 dosage, placement of rhBMP-2 within or around the cage, and cage material (ie, allograft, titanium, polyether ether ketone) and because few studies controlled for patient factors such as bone mineral density, body mass index, and pre-existing subchondral cysts or voids. Also, studies used different methods to assess the severity of osteolysis, subsidence, and final fusion (eg, plain radiographs, standard CT images, thin-cut, 1-mm CT images). In addition, in the analysis of interbody device subsidence and migration, there are many confounding factors that may be difficult to control and evaluate in any study, such as the technical skill and expertise of the surgeon performing disk space preparation, violation of the end plate during decortication, and placement of an oversized interbody device. Although rhBMP-related osteolysis appears to be a valid phenomenon, with infrequent long-term sequelae and need for reoperation, various factors may increase the risk of this complication. Potential techniques to avoid osteolysis include careful preparation of the end plate, decreasing the dosage of BMP within the interbody space cage-graft, and selection of an appropriate size of interbody cage-graft.

Postoperative Radiculitis

As previously discussed, BMP induces a cascade of intra- and extracellular responses. In particular, BMP is believed to interact with cytokines and interleukins to stimulate a local inflammatory response. However, placement of high doses of rhBMP-2 in proximity to neural elements, particularly during posterior or transformaminal lumbar interbody fusion, may lead to postoperative radiculitis without structural neural compression. However, postoperative leg pain after posterior transformaminal lumbar interbody fusion can be caused by multiple techni- cal aspects of the procedure, including incomplete decompression, instrumentation malpositioning, implant migration, and iatrogenic neural injury as a result of retraction or manipulation. In patients with postoperative leg pain in the acute or subacute setting, a compressive mechanism (ie, pedicle screw breech, hematoma or seroma, bone fragment) should be ruled out with advanced imaging with CT scan, magnetic resonance imaging, or myelography. Consequently, an association between postoperative radiculitis and the use of rhBMP is difficult to determine, and the diagnosis is typically made through exclusion. Even without the use of BMP, reported rates of radiculitis associated with transformaminal lumbar interbody fusion range from 2% to 7%.

In 2009, Mindea et al reported minimally invasive transformaminal lumbar interbody fusion augmented with rhBMP-2 and found that 11% (4 of 35) of patients had postoperative radiculitis, pain, and paresthesias on the same side as the facetectomy and decompression, with no compressive etiology identified on postoperative CT imaging. In addition, most patients had symptoms approximately 2 to 4 days postoperatively and were treated nonoperatively, with symptoms resolving within 6 weeks. Similarly, in 2009, Rihn et al reported that postoperative radiculitis occurred in 14% (12 of 87) of patients after transformaminal lumbar interbody fusion augmented with rhBMP-2 compared with 3% (1 of 33) of patients treated without rhBMP-2. However, in another report, Rihn et al found that the rate of rhBMP-related radiculitis decreased from 20.4% (10 of 54 patients) to 5.4% (2 of 37 patients) when hydrogel dural sealant was used as a barrier over the posterior annulotomy.

Although the inflammatory response induced by BMP and its effects on neural
elements are incompletely understood, the current literature suggests that high doses of rhBMP-2 in close proximity to neural elements may cause transient clinical sequelae. However, Dmitriev et al\textsuperscript{84} evaluated the use of rhBMP-2 in a rat spinal cord injury model. Their study found that rhBMP diffuses intrathecally, activates a robust signaling cascade within the spinal cord parenchyma, and may increase glial scarring and affect neurologic recovery. However, in 2011, Glassman et al\textsuperscript{85} evaluated the use of rhBMP-2 in posterolateral lumbar spine fusion, with or without a dural tear, and found no difference in clinical outcomes or postoperative radiculopathy between the groups. The authors concluded that a repairable dural tear does not preclude the use of rhBMP-2 to augment posterolateral lumbar fusion; however, it may be advisable to avoid the use of rhBMP in the setting of an unrepairable dural tear.\textsuperscript{86}

**Hematoma and Seroma**

The robust local inflammatory response to rhBMP-2 also has been associated with increased risk of postoperative seroma or hematoma. In contrast to postoperative radiculitis, which is noncompressive, some surgeons reported neural compression and pain after the use of rhBMP-2 in the lumbar spine among patients with seroma or hematoma. These patients required return to the operating room for drainage. Boden et al\textsuperscript{86} found that 9% (2 of 22) of patients who underwent single-level posterolateral lumbar fusion had hematomas requiring surgical drainage approximately 4 to 5 days postoperatively, and 1 patient had continued paresthesias in both legs. Similarly, in 2011, Owens et al\textsuperscript{86} reported a 6.4% (13 of 204 patients) rate of radiculopathy in the early (3-month) perioperative period after transforaminal lumbar interbody fusion augmented with rhBMP-2. They found that 5 patients (2.5%) required surgical decompression because of a neurocompressive etiology (4 seromas near the neuroforamina, 1 epidural hematoma).\textsuperscript{86}

Despite these reports, large database studies showed no difference in the rate of hematoma or seroma in patients undergoing spinal fusion with or without the use of rhBMP.\textsuperscript{8,16} In a Nationwide Inpatient Sample database review of 13,972 patients, Cahill et al\textsuperscript{8} found that 281 (2%) of patients undergoing lumbar fusion with rhBMP had wound complications as well as hematomas and seromas, and this rate was not different from the 2.1% rate (507 of 22,835 patients) in patients who were not treated with rhBMP. A review of the Scoliosis Research Society morbidity and mortality database by Williams et al\textsuperscript{16} also found no difference in the rate of epidural hematoma or seroma formation between patients undergoing posterior or transforaminal lumbar interbody fusion with and without BMP (posterior lumbar interbody fusion, 0.3% vs 0.3%, respectively; transforaminal lumbar interbody fusion, 0.3% vs 0.2%, respectively). However, these large database reviews were limited in granularity, lacking details on surgical techniques, type of rhBMP, dosage of rhBMP, carrier, and placement. Therefore, given the limitations of the availability and quality of the current evidence, an association between the use of rhBMP to augment lumbar spinal fusion and the risk of postoperative epidural hematoma or seroma remains unresolved.

**CONCLUSION**

Various controversies remain surrounding the complications associated with the use of rhBMP in the lumbar spine, and additional data and studies are needed. There is a potential role for rhBMP in patients with previous autograft harvesting in the setting of a long fusion construct where autologous bone graft harvest may be inadequate. Other potential uses include patients undergoing revision surgery, those with previous pseudarthrosis, and those with poor healing potential (ie, smoking history, diabetes, radiation therapy). However, informed consent must be obtained after the patient is made aware of the reported potential risks. Ultimately, the patient and the surgeon must decide together whether the cost and potential adverse effects are acceptable.

**REFERENCES**


12. Carragee EJ, Bono CM, Scuderi GJ. Pseudo-


75. Knox JB, Dai JM III, Orchowski J. Osteolysis in transformaminal lumbar interbody fusion


