Safety of transforaminal lumbar interbody fusion and intervertebral recombinant human bone morphogenetic protein–2

ALAN T. VILLAVICENCIO, M.D., SIGITA BURNEIKIENE, M.D., E. LEE NELSON, M.D., KETAN R. BULSARA, M.D., MARK FAVORS, R.N., AND JEFFREY THRAMANN, M.D.

Boulder Neurosurgical Associates and Boulder Community Hospital, Boulder, Colorado; and University of Missouri, Columbia, Missouri

Object. Recombinant human bone morphogenetic protein–2 (rhBMP-2) is being increasingly used for spinal fusion. There are few data regarding its clinical safety, effectiveness, and clinical outcome when applied on an absorbable collagen sponge (ACS) in conjunction with allograft for transforaminal lumbar interbody fusion (TLIF).

Methods. Seventy-four consecutive patients undergoing TLIF for degenerative disc disease were divided into five groups depending on whether the patient underwent a minimally invasive or open approach, as well as the number of spinal levels surgically treated. Surgery-related data, fusion results, complications, and clinical outcome were evaluated. The mean follow-up duration was 20.6 months (range 14–28 months). The radiographic fusion rate was 100% at 12 and 24 months after the surgery. No bone overgrowth or other complications related to BMP use were demonstrated.

Conclusions. Analysis of the results demonstrated that TLIF combined with a BMP-2–soaked ACS is a feasible, effective, and safe method to promote lumbar fusion. There were no significant intergroup differences in clinical outcome between patients who underwent open compared with minimally invasive procedures. Patient satisfaction rates, however, were higher in the minimally invasive procedure group. The efficacy of BMP-2 was not dependent on which approach was used or the number of spinal levels that were treated.

KEY WORDS • **bone morphogenetic protein** • **transforaminal lumbar interbody fusion** • **spinal surgery** • **minimally invasive surgery**

THE availability of rhBMP-2 for use in clinical practice could theoretically resolve numerous problems related to spinal fusion. Although preclinical experimental results seem promising, initial clinical applications are still in the early phases of study. Several different materials and techniques have been explored in an effort to improve spinal fusion rates. Allograft bone used alone in lumbar fusion has yielded inconsistent results, with arthrodesis rates ranging from approximately 50 to 95%.[10,15,31,42,43] Demineralized bone matrices are known to contain osteoinductive proteins; however, 100 kg of Grafton DBM Putty (Osteotech, Inc., Eatontown, NJ) would be required to yield 6-mg dose of rhBMP-2.[5] In the past AICB was considered the gold standard in spinal fusion applications. Unfortunately, it potentially results in significant additional morbidity because the graft harvesting procedure can be associated with increased EBL and operative time, additional complications such as chronic pain, and prolonged hospital LOS and recovery time.[13,19,25,44]

Several recently developed BMPs have been shown to possess osteoinductive potential capable of stimulating the formation of new bone.[17] This growth factor is thought to promote increased fusion rates more reliably and faster.[9,34] Analysis of recent experimental data has demonstrated increased stiffness in flexion, improved strength of the fusion mass, and superior histologically confirmed fusion rates for rhBMP-2 when it is compared with fusions produced by AICB.[22,23,34–36,38]

In a prospective randomized trial of rhBMP-2 placed in tapered threaded interbody cages compared with cortical allograft dowels for ALIF, investigators found that arthrodesis occurred more consistently in rhBMP-2–treated patients (94.5 and 100% fusion rate with rhBMP-2 compared with 66, 88.7, and 89.5% in the autograft control groups).[9,12,14]

There were no unanticipated adverse events recorded, and in the rhBMP-2 investigational subgroup the authors noted greater improvement rates in clinical outcome, general health status, and functional recovery. In a different study, investigators reported a 100% fusion rate when ALIF was undertaken laparoscopically.[24] Fusion rates have been retrospectively compared after rhBMP-2–cage TLIF and AICB TLIF; although preliminary results were promising (100 and 95%, respectively), the follow-up duration was insufficient (< 3 months) in many cases.[30]

The purpose of the present study was to evaluate the safety and efficacy of rhBMP-2–soaked ACSs in conjunction with allograft for TLIF; we assessed fusion, complications, and clinical outcome (patient's perceived overall effect and satisfaction). A secondary objective was to determine whether the incidence of fusion is dependent on the approach and the number of surgically treated spinal levels.

Clinical Material and Methods

Patient Population

Although all data were collected prospectively, this is a retrospective clinical study in which we evaluate data obtained between October 2002 and December 2003 on patients in whom rhBMP-2 (Infuse Bone Graft; Medtronic Sofamor Danek, Memphis, TN) was used in conjunction with TLIF. Seventy-four patients fulfilled the study criteria (46 women [62%] and 28 men [38%] whose mean age was 56.9 years [range 20–82 years]). Twenty-five patients (33.8%) had previously undergone lumbar surgeries (discectomy, fusion, and decompression). The criteria for determining to undertake an open approach or a minimally invasive approach depended on whether the patient had previously undergone lumbar surgery, the presence of bilateral disease (for example, central canal or lateral recess stenosis) or spondylolisthesis. In determining these factors open surgery was performed in preference to the minimally invasive procedure. Depending on the surgical approach and the number of surgically treated spinal levels, patients were divided into one of five groups: one-level minimally invasive procedure; two-level minimally invasive procedure; one-level open procedure; two-level open procedure; or multilevel (≥ three-level) open procedure. The latter group comprised only three patients and was not included in the statistical analysis of significance or clinical outcome, nor were patient satisfaction rates analyzed.

Demographic data, stratified by treatment group, are presented in Table 1. Demographic data were similar in all patient groups with respect to sex and age, but the incidence of previous surgeries was higher (p < 0.001, chi-square test, Table 1) in groups in which open surgery was performed.

All patients underwent extensive preoperative evaluation to isolate the cause of their pain. Indications for surgery included painful degenerative disc disease (with or without radiculopathy), spinal instability, spinal stenosis, facet joint arthropathy, or degenerative spondylolisthesis. Clinical findings were consistent with mechanical back pain with or without radiculopathy, which limited the patient's ability to function. Clinically relevant levels were determined based on their history, physical examination

TABLE 1
Summary of demographic data stratified by procedure

Op	No. of Cases	Mean Age (yrs)	% Male	% Previous Ops
min invasive				
1 level	29	52.8	37.9	20.7
2 levels	14	45.8	50.0	14.3
open				
1 level	18	64.8	38.8	61.0
2 levels	10	66.9	40.0	50.0
≥3 levels	3	55.3	33.3	33.3

status, and diagnostic studies. Although infrequently performed, provocative discography was used to identify a specific intervertebral disc space as a source of pain. A diagnosis of degenerative disc disease was considered if one or more of the following imaging findings were present: decreased disc height and hydration, osteophyte formation, ligamentous thickening, Modic changes, disc herniation, instability, or facet joint degeneration. Lumbar instability was demonstrated on functional flexion–extension radiographs and the diagnosis was established when dynamic anteroposterior translation was greater than or equal to 3 mm and/or angulation was greater than or equal to 10°. All patients underwent conservative therapy for a minimum of 6 months before the surgery unless their symptoms were progressive or existed in conjunction with radiographically documented gross spinal instability. Patients with a history of hypersensitivity to protein pharmaceutical medications, collagen, or anaphylaxis were excluded from the study.

Structural bone allografts (Synthes, Oberdorf, Switzerland, or Lanx, Boulder, CO) and locally harvested autograft bone were used in all patients in addition to rhBMP-2. If insufficient autograft was available during the TLIF approach, then some morselized allograft was used only in patients requiring additional PLF. In 23 (74.2%) of 31 patients who underwent an open procedure, posterolateral application of BMP was used as well. The decision to perform additional PLF was based on the surgeon's preference and the extent of the exposure required to perform the necessary decompression/interbody fusion.

Standard postoperative instructions limited the patient's bending, lifting, and twisting. Patients were cautioned against and restrained from using nonsteroidal antiinflammatory steroid drugs for 3 to 6 months following surgery. Patients were mobilized on postoperative Day 1 and no external orthosis was required in any patient.

Outcome Measures

Plain radiography was conducted to evaluate fusion status and possible ectopic bone formation at 3, 6, 12, and 24 months and thin-cut 1-mm CT scanning was performed at 12 and 24 months. Complications related to the surgical procedure, additional surgical interventions, and allergic reactions were documented.

Fusion was defined as an evidence of trabecular bone bridging documented on CT scans; furthermore, it was defined on plain radiographs as less than a 5° difference in angular motion between flexion and extension and the absence of radiolucency lines greater than 2 mm in thickness

covering more than 50% of the superior or inferior surface of the grafts.[7,21] All x-ray films were evaluated by an independent radiologist.

Overall clinical success was evaluated using postoperative questionnaires. MacNab criteria[2,27] were used to assess clinical outcome as a patient's perceived global effect of the surgical treatment. Results were classified as excellent (free from all pain); good (minor intermittent discomfort not interfering with normal activities); fair (improvement in symptoms but persistent low-back pain or sciatica interfering with capacity to engage in full normal activities); and poor (no change or worsening in symptoms). Excellent/good and fair/poor perceptions were combined.

Satisfaction with results was evaluated postoperatively using the Patient Satisfaction with Results survey (PhDx Systems, Albuquerque, NM; Table 2). Scores for each question were evaluated separately and compared among the groups.

An independent reviewer (M.F.) who did not participate in direct patient care explained and administered questionnaires at the 12-month follow-up visits.

Surgical Procedures

Open or minimally invasive percutaneous TLIF was performed via an intervertebral approach. The rhBMP-2 solution was applied to a Type I bovine Helistat ACS (Integra Life Sciences, Plainsboro, NJ), which has a 2- to 4-week resorption period. For intervertebral applications, after disc material had been removed and endplates prepared, a collagen sponge was placed anteriorly against the anterior anulus fibrosis, followed by locally harvested autograft bone obtained during the TLIF approach (partial removal of the facet joint). This was then followed by application of one or two structural bone allografts and the addition of cancellous bone. If insufficient autograft was available during TLIF, morselized allograft was utilized (ChronOS granules; Synthes). If PLF was performed in addition to intervertebral fusion, cancellous bone granules (auto- or allograft) were wrapped into a rhBMP-2–soaked ACS and applied posterolaterally in the decorticated intertransverse process area. The rhBMP-2–impregnated ACS volumes of 2.8 to 8 ml with either 4.2 or 12 mg of protein were used for these procedures.

For open TLIF, the interlaminar space and facet joints were exposed via a midline incision at the appropriate level. After PS/rod placement on the contralateral side, the underlying disc space was exposed by removing the lateral margin of the ligamentum flavum. Unilateral facetectomy and distraction of the interlaminar space via the base of the spinous processes was completed. Depending on clinical presentation, a laminectomy may have been performed. Bilateral laminectomy was reserved for patients in whom preoperative imaging revealed clinically significant bilateral neural element compression. The side of the transforaminal approach to the intervertebral disc space was selected based on preoperative symptoms. Using a soft-tissue dissector, the peridural tissues including the nerve root were only very slightly retracted. The anulus fibrosus was incised and disc material removed with pituitary rongeurs. Angled and straight curettes were used to scrape the remaining disc material and cartilage. After sizing the interbody space, rhBMP-2, locally harvested autograft, and/or allograft cancellous bone with one or two structural allografts were positioned anteriorly, against the anterior anulus, as described. Posterior PS instrumentation was positioned on the contralateral side; rods were contoured in lordosis and placed appropriately. The construct was compressed to establish an optimal graft–bone interface and to reestablish lumbar lordosis at the surgically treated segments. The wound was closed in layers by using interrupted VICRYL Plus Antibacterial Suture (Ethicon, Irvine, CA) and Steri-Strip (3M Health Care Professionals, St. Paul, MN) on the skin.

For the percutaneous TLIF procedure, an incision of approximately 1.5 cm was made over the spinous processes, and the frame (Stealth NeuroStation; Sofamor Danek) was secured appropriately with the assistance of a scope navigation system (MKM Zeiss, Oberkochen, Germany). The Iso-C 3D fluoroscopy (Siemens Medical Solutions, Erlangen, Germany) was then used to obtain images, and the data were transferred over to Stealth NeuroStation. Using the Jamshidi image-guidance trocar, the pedicles were identified in the 3D view and the trocar insertion was followed by guide wire placement. The PSs were placed over the guide wires as previously described.[37] The rod was then placed and a slight distraction was created at the intervertebral space. If using the Sextant system, the METRx tube (Medtronic Sofamor Danek) was inserted. If a herniated disc or foraminal stenosis was present and predominantly unilateral, that side was chosen and microscopic visualization was used to undertake a complete facetectomy and foraminotomy. Laminectomy was performed depending on clinical presentation. After the disc space was identi-

TABLE 2
*Summary of responses to the Patient Satisfaction with Results survey**

Question	Minimally Invasive Op (%)		Open Op (%)	
	1 Level	2 Levels	1 Level	2 Levels
I can do the things I thought I would be able to do after surgery	54.5	71.9	59.4	55.6
I was helped as much as I thought I would be by my surgery	84.1	71.9	65.6	63.9
My pain was reduced as much as I expected it to be after the surgery	81.8	75.0	62.5	61.1
The benefits of my care outweighed the setbacks it caused me	86.4	71.9	70.3	69.4
Overall I am happy with the care I am receiving for lower back &/or legs	88.6	87.5	75.0	66.7
All things considered, I would have the surgery again for the same condition	84.1	68.8	67.2	69.4

* Answers were scored on a scale from 0 to 100 (100 = definitely true; 75 = mostly true; 50 = don't know; 25 = mostly false; and 0 = definitely false.

fied radiographically and microscopically, a complete discectomy was performed using straight and angled curettes and the pituitary rongeurs. The endplates were prepared and cancellous bone (locally harvested auto- or allograft), along with a structural bone allograft and rhBMP, were placed as described. The construct was compressed to establish an optimal graft–bone interface and to restore lumbar lordosis at the surgically treated segments.

A second 3D Iso-C image was reconstructed to verify the correct positioning of the screws. The wound was closed in layers using interrupted VICRYL Plus Antibacterial Suture and Steri-Strip on the skin.

Statistical Analysis

The results are reported as means ± SDs and percentages when applicable. Statistical significance was set at a probability value of 0.05. The Student t-test was performed for independent continuous quantitative variables. The chi-square or the Fisher exact test was used to analyze categorical values. Analysis of variance was conducted to assess Patient Satisfaction with Results data.

Results

Seventy-one patients (96%) attended follow up for a minimum of 12 months. The mean follow-up duration was 20.6 months (range 14 to 28 months).

Operative Data

A minimally invasive approach was used in 43 patients (58%) and an open approach in 31 (42%). Thirty-four patients (60%) underwent a one-level TLIF, 27 patients (36%) a two-level, and three patients (4%) a three-level procedure. The five groups are represented in Table 3. There was no statistically significant difference in operating room time when comparing the minimally invasive and open surgery groups; however, the EBL was decreased, and this decrease was statistically significant in one-level minimally invasive surgery compared with one-level open surgery (p = 0.02) and in two-level minimally invasive surgery compared with two-level open surgery (p = 0.001) (Table 3). The hospital LOS was also shorter and statistically significant in patients who underwent one-level minimally invasive surgery compared with those who underwent one-level open surgery (p = 0.02); the same was true for the two-level minimally invasive procedure compared with the two-level open procedure (p = 0.03).

Summary of Complications

There were no complications or allergic reactions directly related to the rhBMP-2 use. An rhBMP-2 antibody evaluation was not conducted in this study. Surgery-related complications are presented in Table 4. The Fisher exact test demonstrated a statistically significant difference (p = 0.003) between the minimally invasive and open approaches.

The criteria for determining neural injury complications were strict; any new or increased neurological deficit was included in the analysis, even if it was transient and lasted fewer than 3 months. Complications in five patients in the one-level and one in the two-level minimally invasive groups were successfully treated conservatively (physical

TABLE 3
Summary of perioperative data stratified by procedure*

Op	OR Time (min)	EBL (ml)	LOS (days)
min invasive			
1 level	192.5 ± 51.0	143.5 ± 90.5	2.8 ± 1.8
2 levels	297.7 ± 43.4	353.6 ± 366.6	3.8 ± 2.2
open			
1 level	219.2 ± 74.0	379.2 ± 172.0	4.4 ± 2.1
2 levels	360.6 ± 101.4	800.0 ± 248.6	6.2 ± 2.9
≥3 levels	429.0 ± 166.9	600.0 ± 424.3	3.0 ± 2.0

* Data are presented as the means ± SDs. Abbreviation: OR = operating room.

therapy and/or steroid agent injections); one patient in each group continued to suffer radiculopathy symptoms at the last follow up despite conservative treatment. The increased number of neural injury complications (20.7 and 14.3%, respectively, in the one- and two-level minimally invasive groups) all occurred in the first 15 cases treated percutaneously, and thus seemed to be related to the learning curve.

A PS was considered malpositioned if a cortical breach was more than 2 mm, even if it was lateral and/or asymptomatic. The accuracy of screw placement was verified on thin-slice (1–1.5 mm) postoperative helical CT scans in cases involving the open TLIF procedures, and/or it was confirmed using the intraoperative isocentric fluoroscopy in cases involving the minimally invasive TLIF procedures. One patient in the two-level percutaneous group required reoperation for the screw repositioning; a 6-mm medial wall perforation was identified on the postoperative CT scan. In this case postoperative isocentric fluoroscopy was not performed. In two patients in the one-level and four in the two-level open TLIF groups, PSs were malpositioned between 2 and 4 mm; these were lateral perforations. We elected to leave these in place because they caused no symptoms. One patient each in the one-level open and two-level percutaneous groups and two patients in the two-level open group had asymptomatic perforations of fewer than 2 mm. These screw perforations were also left untreated because of the size of the pedicles.

The higher rate of screw malposition associated with the open TLIF procedure was thought to be due to the fact that intraoperative isocentric fluoroscopy was performed in patients undergoing minimally invasive PS placement, which may increase the accuracy of screw placement.[40] Additionally Iso-C allows for intraoperative verification of screw placement and repositioning.

In some cases the complications required further surgical intervention. In one patient allograft was removed 15 months postoperatively because it migrated posteriorly into the epidural space and caused nerve root impingement and radiculopathy. Five patients underwent a second surgery to extend the fusion to an adjacent level during the follow-up period. There were two minimally invasive and three open procedures performed in these patients initially. Additional PLF was undertaken in one of three open surgery–treated patients. There were four one-level procedures and one two-level procedure. The mean interval before reoperation was 9.7 months (range 1.5–14 months).

TABLE 4
Surgery-related complications stratified by procedure

Complication	Min Invasive Op (%)		Open Op (%)		
	1 Level	2 Levels	1 Level	2 Levels	≥ 3 Levels
CSF leak	1 (3.4)	0	2 (11.1)	0	0
screw malposition	0	2 (14.3)	3 (16.7)	6 (60.0)	1 (33.3)
graft malposition	0	0	1 (5.5)	0	0
hematoma	1 (3.4)	0	1 (5.5)	0	0
infection	0	1 (7.1)	0	0	1 (33.3)
neural injury	6 (20.7)	2 (14.3)	1 (5.5)	0	0
total	8 (27.6)	5 (35.7)	8 (44.4)	6 (60.0)	2 (66.3)

* CSF = cerebrospinal fluid.

Radiographic Outcomes

Radiography demonstrated successful fusion in all patients by 10 months. The mean time to fusion was 4.1 months (range 2–10 months) (Fig. 1). Solid fusion at the surgically treated level(s) at 12 and 24 months was confirmed on thin-cut CT scans. No ectopic bone formation was identified.

Clinical Outcome

Clinical outcome, defined by patients' perceived overall treatment effect, was excellent/good in 81.3 and 75% in the one- and two-level minimally invasive groups, respectively, compared with 72.7 and 60% in the one- and two-level open surgery groups (Table 5). This difference was not statistically significant (p = 0.1). Patient satisfaction rates were higher in the one- and two-level minimally invasive groups. The analysis of variance was performed to analyze intergroup differences, and the difference was statistically significant (p = 0.01). Results are presented in Table 2.

Discussion

The use of BMP theoretically results in a more reliable and rapid fusion and potentially eliminates the need for AICB harvesting. In a cost analysis in which the price of rhBMP-2 was compared with AICB in cases of single-level ALIF, the investigators found the cost of BMP to be offset over 2 years, when pain and complications associated with AICB graft along with fusion failures were taken into account.[1] The purpose of the present study was to evaluate the safety and efficacy of rhBMP-2 in conjunction with TLIF and to assess fusion, complications, and clinical outcome as patients' perceived overall treatment effect and satisfaction. A secondary objective was to determine whether efficacy of fusion is dependent on the approach and number of spinal levels surgically treated.

Efficacy of Fusion

The efficacy of BMPs was initially thought to be dose dependent.[41] Sandhu, et al.,[34] subsequently reported a linear relationship when minimal effective concentrations were reached. Site and carrier specificity[3,28] in the existing clinical and experimental studies has also been evaluated. It appears that BMP-2 is the most effective osteogenic factor in in vitro studies of osteoblastic progenitor cells.[32]

Different types of cells may predominate at interbody and PLF sites, which could help to explain why a 20-mg dose of rhBMP-2 was required to achieve PLF[7] compared with 4.2 to 12–mg doses that the Food and Drug Administration approved effective for anterior intervertebral applications. When added to biphasic calcium phosphate (Medtronic Sofamor Danek, Memphis, TN) granules, higher doses of rhBMP-2 have been advocated to achieve PLF.[7] In one study fusion rates were 100% in the BMP-2 group in patients treated with or without PSF and 40% in patients who underwent autograft-augmented instrumentation. Faster and greater clinical improvement was noted in the rhBMP-2 group in which PSF had not been performed.

The smaller dose required for interbody fusion makes the combination of rhBMP-2 and TLIF very attractive. In this treatment strategy interbody graft material was used but without the additional morbidity associated with an anterior approach. In our study we found that a 100% fusion rate was not dependent on the approach (minimally invasive or open) or the number of surgically treated levels when using the same BMP dose approved by the Food and Drug Administration for ALIF.

Burkus and associates[13] performed integrated analyses of data from several clinical trials comparing rhBMP-2 and autograft bone use in open and laparoscopic ALIF approaches. Statistical analysis revealed significant rhBMP-2 superiority. Fusion rates were 94.4% for rhBMP-2 and 89.4% for autograft. Recombinant human BMP-2 was associated with 54-minute shorter operative time, 66 ml less EBL, and almost a day (0.9) shorter hospital LOS; however, operative time and EBL were higher in laparoscopically assisted compared with open procedures. Analysis of the data in our study revealed no statistically significant difference in operative times and a significantly decreased EBL in patients undergoing minimally invasive surgery.

Safety of rhBMP-2

Ectopic bone formation has been reported in the anterior epidural space posterior to the fixation devices and in the track of the insertion when intervertebral fusion was performed via a posterior lumbar interbody fusion approach.[4,21,28] In these series, heterotopic bone growth developed in 24 (69%) of 35 patients.[21] There were no clinical symptoms related to heterotopic bone growth, and the authors were not sure whether this was related to the surgical technique or BMP characteristics per se. Fusion rates

FIG. 1. Preoperative anteroposterior *(upper left)* and lateral *(upper right)* radiographs. Postoperative anteroposterior *(lower left)* and lateral *(lower right)* radiographs obtained at 4 months later, revealing intervertebral and PLF.

TABLE 5
Summary of Macnab criteria for outcome

Outcome Category	Min Invasive Op		Open Op	
	1 Level	2 Levels	1 Level	2 Levels
excellent/good	81.3%	75.0%	72.7%	60.0%
fair/poor	18.7%	25.0%	27.3%	40.0%
total no. of cases	27	14	18	10

were lower in the BMP-2 group than in the autograft group (77.8 and 92.3%, respectively).[21] This finding was not confirmed by the preliminary results reported by investigators evaluating rhBMP-2 efficacy and safety in TLIF.[30] These authors performed a retrospective study in which they compared the efficacy of BMP with AICB grafts. They placed BMP inside cages and anterior to the cage and concluded that BMP is safe when the sponges are placed away from the dura mater. One of the limitations of this preliminary study was that the follow-up period was insufficient: its duration had not even reached 3 months for two patients, although the mean time to fusion was 3 to 4 months. Bone formation associated with rhBMP-2 application has been shown to occur faster[30] and fusion documented at 3[30] or 6 months had not changed at 12- or 24-month follow-up examination.[9] Therefore, if bone overgrowth or rhBMP-2–induced restenosis was going to occur, it should have developed earlier in the postoperative period.[33] In our study no ectopic bone formation was observed when rhBMP-2 was placed on an ACS, in addition to allograft bone, cancellous bone, and locally harvested autograft.

In the aforementioned PLIF and rhBMP-2 studies,[4,21,28] cylindrical threaded cages were used as the carrier, and the authors reported posterior ectopic bone formation, perhaps related to surgical technique or the rhBMP-2 carrier itself. Poynton and Lane[33] reviewed the available literature for safety issues including bone overgrowth and uncontrolled bone formation, interaction with exposed dura mater, and osteoclastic activation. They concluded that bone overgrowth might have been related to incorrect place-

ment, inadequate retention by some carriers, excessively bleeding bone surfaces, and inadvertent exposure of the adjacent levels. The TLIF approach differs from that of PLF (in theory) by requiring a more lateral-to-medial trajectory, thus necessitating less retraction of the exiting (superior) nerve root and thecal sac. This slight change in trajectory could potentially eliminate the ectopic bone formation that has been reported in the anterior epidural space posterior to the fixation devices. Moreover, we placed the rhBMP-2 and locally harvested autograft anteriorly in the disc space and then inserted one or two structural allografts posteriorly. Although we found no evidence of ectopic bone formation in the anterior epidural space posterior to the structural allografts, one allograft migrated posteriorly into the epidural space and caused postoperative nerve root impingement and radiculopathy, thus requiring surgical intervention and removal of the graft.

The ACS has a capacity for retention and slow release of the matrix.[18] It binds up to 97% of rhBMP-2 in "normal operating conditions" or up to 72% in centrifugation.[29] Because bone graft and cancellous bone granules are load bearing, ACS is not subjected to significant loads and forces. Even if BMP escapes from the sponge during insertion or when pressure is applied to the intervertebral space, it results in minimal systematic exposure. In in vivo studies it has been demonstrated that 100% rhBMP-2 has rapid clearance (half-life 6.7 minutes in nonhuman primates) if injected intravenously, or the concentration decreases up to 20% in approximately 12 days when applied locally to the ACS carrier.[29] The authors of experimental studies have demonstrated that intramuscular applications of rhBMP-2 alone did not induce osteogenesis in vivo.[26,39] Additionally, based on experimental[8] and clinical radiographic studies,[11] it has been observed that the bone formation process develops from outside the implant in toward the center until the entire component is replaced by the trabecular bone. In summary, the safety and osteogenicity of rhBMP-2–soaked ACS is based on the material's slow release from the carrier, adequate exposure to the target cells, and rapid systematic clearance. Then again, restenosis of the decompressed site may be enhanced by bone growth stimulators; however, it should be mentioned that even when stimulators were not used, bone regrowth was observed in 20% of patients for more than 20%[20] or even 44% of patients for more than 41 to 100%[16] of the original laminectomy site. Baskin, et al.,[6] reported the results of a pilot study in which they evaluated the safety and efficacy of rhBMP-2–soaked collagen carrier placed inside an allograft ring in patients undergoing anterior cervical fusion. In two patients in this group and one patient

in the control (autograft) group, ectopic bone formation was demonstrated anterior to the segments adjacent to the treated level. The authors thought that this was related to the surgical technique rather than rhBMP-2 because it occurred in both groups and the same surgeon performed all surgeries. Additionally, they hypothesized that the overgrowth of bone or ligament could be an expected pathophysiological response due to disc degeneration and segmental instability.

Despite the increased interest and increasing potential of minimally invasive approaches in spinal surgery, clinical data supporting improved outcome are lacking. Minimally invasive TLIF can in theory involve only minimal iatrogenic tissue injuries and still accomplish the traditional goals of surgery. Statistical analysis of our clinical results (MacNab criteria) revealed no significant intergroup difference between the open and minimally invasive cases; however, patient satisfaction rates were significantly higher in the latter group. This could be partially attributed to the surgical technique itself or to the higher incidence of previous surgeries in the open surgery groups (two-level open surgery 50 and one-level open surgery 61%) and the significantly higher complication rate. The radiographically documented efficacy of BMP-2–induced fusion was not dependent on whether open or minimally invasive surgery was used or the number of treated spinal levels.

The major limitation of this study was that it was essentially a retrospective review even though data were accumulated prospectively. Patients were not randomized, and standardized pre- and postoperative outcome assessment tools were not used. The only significant demographic difference identified between the groups, however, was the incidence of previous surgeries, which was higher in the open surgery group than the minimally invasive groups. Although the primary objective of this study was to evaluate the safety of rhBMP-2 when used in the TLIF approach, the secondary objective was to determine whether the efficacy of fusion is dependent on the approach and number of surgically treated spinal levels. This does not seem to be the case for one- and two-level procedures.

Conclusions

Although further prospective clinical studies are needed to validate the safety of rhBMP-2 used in conjunction with TLIF, our results indicate that the rhBMP-2–augmented TLIF appears to be a feasible, effective, and safe method of spinal lumbar fusion.

References

1. Ackerman SJ, Mafilios MS, Polly DW Jr: Economic evaluation of bone morphogenetic protein versus autogenous iliac crest bone graft in single-level anterior lumbar fusion: an evidence-based modeling approach. **Spine 27:**S94–S99, 2002
2. Ahn Y, Lee SH, Park WM, Lee HY, Shin SW, Kang HY: Percutaneous endoscopic lumbar discectomy for recurrent disc herniation: surgical technique, outcome, and prognostic factors of 43 consecutive cases. **Spine 29:**E326–E332, 2004
3. Akamaru T, Suh D, Boden SD, Kim HS, Minamide A, Louis-Ugbo J: Simple carrier matrix modifications can enhance delivery of recombinant human bone morphogenetic protein-2 for posterolateral spine fusion. **Spine 28:**429–434, 2003
4. Alexander JT, Branch CL, Haid RW, Rodts GE, Subach BR, Shaffrey CI: An analysis of the use of rhBMP-2 in PLIF constructs: Clinical and radiographic outcomes. International Society for the Study of the Lumbar Spine Meeting. Vancouver, Canada, 2003
5. Bae HW, Zhao L, Kanim L, Wong P, Dawson EG, Delamarter R: Inter- and intravariability of BMP's in commercially available demineralized bone matrices, **International Society for the Study of Lumbar Spine Meeting.** Vancouver, Canada, 2003
6. Baskin DS, Ryan P, Sonntag V, Westmark R, Widmayer MA: A prospective, randomized, controlled cervical fusion study using recombinant human bone morphogenetic protein-2 with the CORNERSTONE-SR allograft ring and the ATLANTIS anterior cervical plate. **Spine 28:**1219–1225, 2003
7. Boden SD, Kang J, Sandhu H, Heller JG: Use of recombinant human bone morphogenetic protein-2 to achieve posterolateral lumbar spine fusion in humans: a prospective, randomized clinical pilot trial: 2002 Volvo Award in clinical studies. **Spine 27:**2662–2673, 2002
8. Boden SD, Martin GJ Jr, Horton WC, Truss TL, Sandhu HS: Laparoscopic anterior spinal arthrodesis with rhBMP-2 in a titanium interbody threaded cage. **J Spinal Disord 11:**95–101, 1998
9. 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 25:**376–381, 2000
10. Brantigan JW: Pseudarthrosis rate after allograft posterior lumbar interbody fusion with pedicle screw and plate fixation. **Spine 19:**1271–1280, 1994
11. Burkus JK, Dorchak JD, Sanders DL: Radiographic assessment of interbody fusion using recombinant human bone morphogenetic protein type 2. **Spine 28:**372–377, 2003
12. Burkus JK, Gornet MF, Dickman CA, Zdeblick TA: Anterior lumbar interbody fusion using rhBMP-2 with tapered interbody cages. **J Spinal Disord Tech 15:**337–349, 2002
13. Burkus JK, Heim SE, Gornet MF, Zdeblick TA: Is INFUSE bone graft superior to autograft bone? An integrated analysis of clinical trials using the LT-CAGE lumbar tapered fusion device. **J Spinal Disord Tech 16:**113–122, 2003
14. Burkus JK, Transfeldt EE, Kitchel SH, Watkins RG, Balderston RA: Clinical and radiographic outcomes of anterior lumbar interbody fusion using recombinant human bone morphogenetic protein-2. **Spine 27:**2396–2408, 2002
15. Buttermann GR, Glazer PA, Hu SS, Bradford DS: Revision of failed lumbar fusions. A comparison of anterior autograft and allograft. **Spine 22:**2748–2755, 1997
16. Chen Q, Baba H, Kamitani K, Furusawa N, Imura S: Postoperative bone re-growth in lumbar spinal stenosis. A multivariate analysis of 48 patients. **Spine 19:**2144–2149, 1994
17. Cheng H, Jiang W, Phillips FM, Haydon RC, Peng Y, Zhou L, et al: Osteogenic activity of the fourteen types of human bone morphogenetic proteins (BMPs). **J Bone Joint Surg Am 85:**1544–1552, 2003 (erratum in **J Bone Joint Surg Am 86:**141, 2004)
18. Geiger M, Li RH, Friess W: Collagen sponges for bone regeneration with rhBMP-2. **Adv Drug Deliv Rev 55:**1613–1629, 2003
19. Gibson S, McLeod I, Wardlaw D, Urbaniak S: Allograft versus autograft in instrumented posterolateral lumbar spinal fusion: a randomized control trial. **Spine 27:**1599–1603, 2002
20. Guigui P, Barre E, Benoist M, Deburge A: Radiologic and computed tomography image evaluation of bone regrowth after wide surgical decompression for lumbar stenosis. **Spine 24:**281–289, 1999
21. Haid RW, 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 4:**527–539, 2004
22. Holliger EH, Trawick RH, Boden SD, Hutton WC: Morphology of the lumbar intertransverse process fusion mass in the rabbit

model: a comparison between two bone graft materials—rhBMP-2 and autograft. **J Spinal Disord 9:**125–128, 1996

23. Itoh H, Ebara S, Kamimura M, Tateiwa Y, Kinoshita T, Yuzawa Y, et al: Experimental spinal fusion with use of recombinant human bone morphogenetic protein 2. **Spine 24:**1402–1405, 1999

24. Kleeman TJ, Ahn UM, Talbot-Kleeman A: Laparoscopic anterior lumbar interbody fusion with rhBMP-2: a prospective study of clinical and radiographic outcomes. **Spine 26:**2751–2756, 2001

25. Kleeman TJ, Hiscoe AC: Laparoscopic ALIF: rhBMP-2 with titanium cages vs. autograft with bone dowels. **15th Annual North American Spine Society Meeting.** New Orleans, Louisiana, 2000

26. Lucas PA, Syftestad GT, Goldberg VM, Caplan AI: Ectopic induction of cartilage and bone by water-soluble proteins from bovine bone using a collagenous delivery vehicle. **J Biomed Mater Res 23:**23–39, 1989

27. Macnab I: Negative disc exploration. An analysis of the causes of nerve-root involvement in sixty-eight patients. **J Bone Joint Surg (Am) 53:**891–903, 1971

28. McKay B, Sandhu HS: Use of recombinant human bone morphogenetic protein-2 in spinal fusion applications. **Spine 27:**S66–S85, 2002

29. Medtronic Sofamor Danek, Inc: **Summary of Safety and Effectiveness Data, 2002** (http://www.fda.gov/cdrh/pdf/P000028b.pdf)

30. Mummaneni PV, Pan J, Haid RW, Rodts GE: Contribution of recombinant human bone morphogenetic protein-2 to the rapid creation of interbody fusion when used in transforaminal lumbar interbody fusion: a preliminary report. Invited submission from the Joint Section Meeting on Disorders of the Spine and Peripheral Nerves, March 2004. **J Neurosurg Spine 1:**19–23, 2004

31. Nugent PJ, Dawson EG: Intertransverse process lumbar arthrodesis with allogeneic fresh-frozen bone graft. **Clin Orthop Relat Res 287:**107–111, 1993

32. Phillips F, Cheng H, Jiang W, Breyer B, Zhou L, Feng T, et al: The osteogenic activity of BMP's: Implications in spine fusion, International Society for the Study of Lumbar Spine. Vancouver, Canada, 2003

33. Poynton AR, Lane JM: Safety profile for the clinical use of bone morphogenetic proteins in the spine. **Spine 27:**S40–S48, 2002

34. Sandhu HS, Kanim LE, Kabo JM, Toth JM, Zeegen EN, Liu D, et al: Effective doses of recombinant human bone morphogenetic protein-2 in experimental spinal fusion. **Spine 21:**2115–2122, 1996

35. Sandhu HS, Toth JM, Diwan AD, Seim HB III, Kanim LE, Kabo JM, et al: Histologic evaluation of the efficacy of rhBMP-2 compared with autograft bone in sheep spinal anterior interbody fusion. **Spine 27:**567–575, 2002

36. Schimandle JH, Boden SD, Hutton WC: Experimental spinal fusion with recombinant human bone morphogenetic protein-2. **Spine 20:**1326–1337, 1995

37. Schwender JD, Holly LT, Rouben DP, Foley KT: Minimally invasive transforaminal lumbar interbody fusion (TLIF): technical feasibility and initial results. **J Spinal Disord Tech 18:**S1–S6, 2005

38. Sheehan JP, Kallmes DF, Sheehan JM, Jane JA Jr, Fergus AH, diPierro CG, et al: Molecular methods of enhancing lumbar spine fusion. **Neurosurgery 39:**548–554, 1996

39. Takaoka K, Nakahara H, Yoshikawa H, Masuhara K, Tsuda T, Ono K: Ectopic bone induction on and in porous hydroxyapatite combined with collagen and bone morphogenetic protein. **Clin Orthop Relat Res 234:**250–254, 1988

40. Villavicencio AT, Burneikiene S, Bulsara KR, Thramann JJ: Utility of computerized isocentric fluoroscopy for minimally invasive spinal surgical techniques. **J Spinal Disord Tech 18:**369–375, 2005

41. Wang EA, Rosen V, D'Alessandro JS, Bauduy M, Cordes P, Harada T, et al: Recombinant human bone morphogenetic protein induces bone formation. **Proc Natl Acad Sci U S A 87:**2220–2224, 1990

42. Wetzel FT, Hoffman MA, Arcieri RR: Freeze-dried fibular allograft in anterior spinal surgery: cervical and lumbar applications. **Yale J Biol Med 66:**263–275, 1993

43. Wimmer C, Krismer M, Gluch H, Ogon M, Stockl B: Autogenic versus allogenic bone grafts in anterior lumbar interbody fusion. **Clin Orthop Relat Res 360:**122–126, 1999

44. Younger EM, Chapman MW: Morbidity at bone graft donor sites. **J Orthop Trauma 3:**192–195, 1989