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SURGERY

Effectiveness and Safety of Recombinant Human Bone Morphogenetic Protein-2 *Versus* Local Bone Graft in Primary Lumbar Interbody Fusions

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Study Design. Retrospective cohort study.

Objective. To compare clinical outcomes, fusion rates, and rates of complications in posterior lumbar interbody fusions (PLIFs) and transforaminal lumbar interbody fusion procedures with either recombinant human bone morphogenetic protein-2 (rhBMP-2) and local bone graft (LBG) or LBG alone used as graft material.

Summary of Background Data. rhBMP-2 is often used in PLIF and transforaminal lumbar interbody fusion procedures, but is associated with complications. Furthermore, recent evidence suggests that using LBG may be sufficient to induce fusion.

Methods. All patients who underwent primary interbody fusions under a single surgeon were identified from the surgeon's records. In November 2008, the surgeon changed from routinely using LBG to using LBG and rhBMP-2 routinely, limiting selection bias. A retrospective review of prospectively collected data preoperatively and up to 12 months postoperatively was performed. Data collected included visual analogue scale, pain scores for back and leg, Oswestry Disability Index scores, Short-Form 36 (SF-36), standing lumbar radiographs, and clinical notes.

Results. Seventy-seven patients met the study criteria and 70 consented to be part of the study. Fifty-one were treated with rhBMP-2 and 19 with LBG. At 12-month follow-up, no significant differences were seen in visual analogue scale score, Oswestry Disability Index score, or SF-36 scores. A total of 89.5% of the LBG group and 94.1% of the rhBMP-2 group went on to show radiographical evidence of fusion by 12-month follow-up ($P = 0.61$). The rhMBP-2 group had a higher complication rate (41.2% *vs*. 10.5%, incidence rate ratio = 3.91, $P = 0.05$).

Conclusion. In comparison we found no difference in clinical outcomes, comparable rates of fusion and a significant increase in complication rates with rhBMP-2. Using rhBMP-2 may unnecessarily increase the risk of complication in routine PLIF and transforaminal lumbar interbody fusion procedures.

Key words: bone morphogenetic protein, local bone graft, lumbar fusion.

Level of Evidence: 3

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The device(s)/drug(s) is/are FDA approved or approved by corresponding national agency for this indication.

The manuscript includes unlabeled/investigational uses of the products/devices listed below and the status of these is disclosed in the manuscript: Use of rhBMP-2 as bone graft for lumbar spinal surgery using posterior approach.

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Posterior lumbar interbody fusion (PLIF) and transforaminal lumbar interbody fusion (TLIF) techniques have traditionally used autologous iliac crest bone graft (ICBG) as the "gold standard" for achieving fusion. However, due to complications associated with ICBG harvesting, off-label use of recombinant human bone morphogenetic protein-2 (rhBMP-2) has become popular.[1] Since its commercial release, independent studies have associated rhBMP-2 use in these procedures with complications including radiculitis, osteolysis, and ectopic bone formation.[2–9] In addition, authors have more recently reported successful fusion in PLIF and TLIF procedures using local bone graft (LBG) from laminectomies and the posterior elements removed during these procedures, with fusion rates comparable to using ICBG.[10–12] No studies have been identified directly comparing rhBMP-2 to LBG in PLIF and TLIF procedures.

The purpose of this study was to compare clinical and radiographical outcomes, and complication rates, in PLIF and TLIF procedures using LBG alone or rhBMP-2 and LBG as graft material.

MATERIALS AND METHODS

Study Design

The study uses a retrospective cohort methodology. We identified all patients who underwent primary 1- or 2-level

PLIF or TLIF procedures, under the care of a single surgeon, between August 2007 and August 2010. This period was chosen because from November 2008 the surgeon routinely used rhBMP-2 in addition to LBG in all procedures, having used LBG alone prior to this, therefore limiting selection bias. Potential participants were invited by mail to allow their data to be included. Those who consented were classified according to the graft received.

We retrospectively analyzed the medical records of participants, who had been followed up for 12 months by the surgeon with regular prospective assessments of pain, quality of life, disability, and radiological outcomes. Height, weight, body mass index, and smoking status were documented. Participants were excluded if they had a previous history of spinal fusion, their fusions extended more than 2 levels, or if ICBG was used. Ethical approval for this study was granted by the Tasmanian Human Research Ethics Committee (reference number H11704).

SURGICAL METHOD

Procedures were performed using the same technique by a single surgeon. PLIF was performed using a bilateral approach to the disc space and use of 2 R90 ramps (Medtronic, Minneapolis, MN). PLIF was largely used for correction of significant spondylolisthesis, marked reduction in disc height, or bilateral stenosis. TLIF was performed in all other cases, with a unilateral approach with a single Capstone cage (Medtronic) or Concord cage (Depuy, Raynham, MA). Polyaxial pedicle screws for fixation were used in all cases. LBG was morselized by bone milling, and 6 to 9 cm^3 placed in the interbody space with or without rhBMP-2. When rhBMP-2 was used, collagen sheets soaked with rhBMP-2, as per manufacturer's instructions, were cut into pieces and layered "lasagna" style, with the LBG in the interbody space, with a layer of LBG forming the most posterior layer. Milled LBG or rhBMP-2 sheets rolled and filled with milled LBG, forming a "sushi roll," were then placed bilaterally in the paravertebral gutters for posterolateral fusion. On the basis of the manufacturer's kit sizes, approximately 1.5 to 2.1 mg of rhBMP-2 was used per level of interbody fusion, and 5.2 to 6.0 mg for each side of posterolateral fusion.

Outcome Measures

Clinical outcomes were assessed using back and leg pain visual analogue scales (VAS), Oswestry Disability Index (ODI) for low back pain and Short-Form 36 (SF-36), which were routinely collected preoperatively, and at 6 weeks, 3 months, 6 months, and 12 months postoperatively.[13–16]

Radiographical assessment was based on standing lumbar radiographs, obtained routinely preoperatively, within days after surgery and at 6 weeks, 3 months, 6 months, and 12 months postoperatively. If patients had not achieved adequate levels of pain reduction in their back or legs, computed tomographic (CT) scans were requested. Fusions were graded with deidentified images by 2 independent radiologists, and the treating surgeon, blinded to the use of rhBMP-2, using the Bridwell *et al*[17] fusion grading system. Successful fusion was defined as Bridwell grade I or II, where there was disagreement between the graders, the consensus view was obtained.

Complications postsurgery were defined as any adverse event that occurred in the 12-month follow-up period, which had a negative effect on patient recovery and/or outcomes. Complications, including radiculitis, osteolysis, ectopic bone formation, adjacent segment disease (ASD), and other postoperative complications considered relevant, were determined through the assessment of clinical notes, imaging, and clinical outcome measures, for the 12-month follow-up period.

To assess radiculitis we first looked for radiculopathy; defined as persistent or worsening leg pain of a radicular pattern compared with preoperative levels, as determined from VAS scores and clinical notes. A diagnosis of radiculitis was made only in those whose pain was radicular in nature and not attributable to an alternative diagnosis, as documented in clinical notes and imaging findings.

Statistical Techniques

Descriptive statistics were calculated including frequencies for categorical variables, and the mean and standard deviations (SD) for continuous variables. Univariate analyses were performed using independent *t* tests for continuous data, and the χ^2 or Fisher exact test, for categorical measures. Outcomes of pain (VAS), disability (ODI), and quality of life (SF-36) are rank-order scales. Means, SDs, and differences between means (odds ratios; 95% confidence intervals [CIs]; *P* values) were estimated by repeated-measures mixed methods linear regression, and adjusted for age, sex, interbody levels fused, operation type (TLIF or PLIF), smoking status, and diabetes. During this mixed methods analysis significant violations of the assumptions of linear regression (heteroskedasticity, skewness and kurtosis of residuals, and nonlinearity of association in various combinations) were identified. However, the results of these "parametric" analyses did not differ from equivalent rank-order "nonparametric" analyses using repeated measures ordered logistic regression. Therefore, the mixed methods linear regression results are presented to aid clinical understanding by the readership. *P* values were corrected for multiple comparisons where appropriate by the Holm method. The effects of missing outcome measurements was corrected by multiple imputation, based on age, sex, interbody levels fused, operation type (TLIF or PLIF), smoking status, and diabetes in each separate time period of measurement. The proportion of patients that did not achieve fusion was compared using Cox proportional hazard regression (hazard ratio; 95% CI; *P* value). Poisson regression was used to estimate the (incidence rate ratio; 95% CIs; *P* values) for complications adjusted for age, sex, interbody levels fused, operation type (TLIF or PLIF), smoking status, and diabetes. All analyses were performed using STATA MP/12.1 (College Station, TX).

RESULTS

Participants

Seventy of a possible 77 participants (91%) consented and were classified to either the LBG group (27%) or rhBMP-2

group (73%). The 2 groups were compared at baseline with respect to important clinical and demographic features; no significant differences were found (Table 1). There was no significant difference in procedure (PLIF or TLIF), preoperative back pain levels or ODI scores (Table 1). However, the rates of 2-level compared with 1-level fusions differed with 1/19 (5.3%) of patients in the LBG having 2-level interbody fusion compared with 17/51 (33.3%) in the rhBMP-2 group ($P = 0.016$).

CLINICAL OUTCOMES

The mean back pain scores at all postoperative periods were improved from the preoperative mean values for both treatment groups (Table 2); no significant differences in reductions in pain between groups were seen. The LBG group was limited in the number of patients with complete data for leg pain VAS, with only 1 patient having completed the score preoperatively. Of the data adequate for analysis, mean leg pain scores improved after surgery in each group (Table 2). The mean differences showed greater reductions in pain in the rhBMP-2 group. At all postoperative visits, both treatment groups showed improved ODI compared with the preoperative scores, with no differences between groups (Table 2).

Postoperatively, increases in all SF-36 measures were seen in both groups (Table 3). In general, quality of life as measured by SF-36 did not seem to differ in a clinically important manner between the 2 groups.

Seventeen of 19 (89.5%) patients in the LBG group and 48/51 (94.1%) of rhBMP-2 group achieved fusion by 12-month follow-up ($P = 0.37$). One patient from the LBG group had no radiographs for analysis.

Complications

Overall, 23 (32.9%) participants had a total of 34 postoperative complications. Eight patients experienced more than one complication. The complication rate for individuals in the LBG group was 2/19 (10.5%), and 21/51 (41.2%) in the rhBMP-2 group ($P = 0.05$); complications experienced by patients are detailed (Table 4).

One patient (5.3%) in the LBG group and 14 (27.5%) in the rhBMP-2 group experienced postoperative radiculopathy ($P = 0.09$). The cause in the participant from the LBG group was thought to be ASD. Of the 14 in the rhBMP-2 group, a potential cause was identified in 8. These included the development of ectopic bone (n = 3); a malpositioned pedicle screw (n = 1); the development of ASD (n = 3) in whom the symptoms reduced with further surgery; and osteolysis (n = 1). Six patients (11.8%), 4 of whom had CT scans and 2 had radiographs only, had no adequate explanation, and were regarded as having radiculitis.

There were 7 cases of ectopic bone; all in the rhBMP-2 group. Of these, 3 cases developed radicular pain and 4 experienced an otherwise unremarkable postoperative period. Three patients, all from the rhBMP-2 group, developed

TABLE 1. Patient Characteristics in LBG and rhBMP-2 Groups

Characteristic	Group		*P*
	LBG (N = 19)	rhBMP-2 (N = 51)	
Male, n (%)	7 (36.8)	28 (54.9)	0.18
Mean age at surgery, yr (SD)	56.49 (13.41)	54.99 (10.71)	0.63
Mean height cm (SD)	168.79 (9.75)	169.16 (10.31)	>0.90
Mean weight kg (SD)	85.50 (21.57)	81.12 (13.57)	0.42
Mean BMI (SD)	30.20 (5.07)	28.60 (4.25)	0.33
Current smoker, N (%)	1 (5.3)	11 (21.6)	0.28*
Diabetes, n (%)	2 (10.5)	3 (5.9)	0.61*
Workers compensation claim, n (%)	0	4 (7.8%)	0.57
Spondylolisthesis†	14 (73.7)	27 (52.9)	0.12
Spinal stenosis†	9 (47.4)	28 (54.9)	0.57
Disc disease†	1 (5.3)	8 (15.7)	0.43*
1-level interbody fusion	18 (94.7)	34 (66.7)	
2-level interbody fusion	1 (5.3)	17 (33.3)	0.016
TLIF	9 (47.4)	30 (58.8)	
PLIF	10 (52.6)	21 (41.2)	0.39

**Using the Fisher exact adjustment for small numbers.*

†Fifty-two patients had more than 1 diagnosis.

LBG indicates local bone graft; rhBMP, recombinant human bone morphogenetic protein-2; PLIF, posterior lumbar interbody fusion; TLIF, transforaminal lumbar interbody fusion; BMI, body mass index; SD, standard deviation.

TABLE 2. Back and Leg Pain, and Oswestry Disability Index in LBG and rhBMP-2 Groups

	LBG			LBG			Difference		
	n	Mean*	SD	n	Mean*	SD	Mean*	95% CI	*P*†
Back pain VAS‡§									
Preop	14	7.33	1.55	47	6.89	1.74	−0.46	(−1.91 to 0.99)	0.53
6 wk¶	1	2.20		33	2.82	2.67			
3 mo	6	1.24	1.17	39	2.33	2.56			
6 mo	2	0.11	1.41	42	3.00	2.81			
12 mo	13	2.32	3.23	31	2.70	2.94	0.85	(−0.97 to 2.68)	>0.90
Leg pain VAS§									
Preop	1	2.82	0.00	33	6.01	1.89	3.19	(−1.53 to 7.91)	0.74
6 wk¶				33	1.15	2.56			
3 mo	1	0.81	0.00	37	1.50	2.71			
6 mo	3	2.39	4.77	40	1.73	3.10			
12 mo	12	1.81	3.08	31	1.78	3.19	−3.23	(−7.96 to 1.50)	0.73
ODI*									
Preop	17	38.9	13.3	51	40.9	15.0	1.9	(−7.1 to 11.0)	0.68
6 wk¶	2	22.4	37.7	38	30.8	17.2			
3 mo	10	19.3	16.7	43	23.5	19.0			
6 mo	8	12.5	18.8	40	20.6	17.3			
12 mo	16	18.7	19.1	31	17.9	19.4	−2.6	(−11.4 to 6.0)	>0.90

**Mean and SD pain or disability in patient groups without or with rhBMP-2, and mean difference (with 95% CIs and P values) between groups at each time period; estimated by repeated-measures mixed methods linear regression, adjusted for age, sex, operation type (PLIF or TLIF), number of vertebral levels fused, smoking history and diabetes mellitus status.*

†P values were corrected for multiple comparisons using the Holm method.

‡Back and leg pain measured by VAS (0 [no pain]–10 [greatest pain]); ODI (0 [no disability]–100 [greatest disability]).

§The mean postop pain/disability scores were estimated as the average score during the 12-month period, weighted for the length of time since the previous score measurement.

¶During the earlier period when the patient group was receiving LBG, functional scores (especially leg pain VAS) were not recorded routinely at 6 wk.

LBG indicates local bone graft; rhBMP, recombinant human bone morphogenetic protein-2; PLIF, posterior lumbar interbody fusion; TLIF, transforaminal lumbar interbody fusion; VAS, visual analogue scale; preop, preoperative; postop, postoperative; ODI, Oswestry Disability Index; SD, standard deviation; CI, confidence interval.

vertebral osteolysis. All 3 cases had resolved at 12 months. Two cases presented with worsening low back pain, whereas 1 had no other problems during the postoperative phase.

Four patients out of 70 (5.7%) developed ASD by 12-month follow-up; 1 from the LBG group (5.3%) and 3 patients from the rhBMP-2 (5.9%) group. All were reoperated on within 12 months post primary fusion. Overall, 5 patients out of 70 (7.1%) had been reoperated on by their 12-month follow-up visit, 1 (5.3%) in the LBG group, and 4 (7.8%) in the rhBMP-2 group. This was not a significant difference ($P = 0.18$).

DISCUSSION

Copay *et al*[18] designate the minimum clinically important differences at 1 year after lumbar surgery as an improvement in ODI of 12.8 points, in SF-36 (PCS) of 4.9, and in VAS of 1.2 points for back pain, and 1.6 points for leg pain. Both groups in this study cohort achieved these scores comfortably. Carragee and Cheng[19] reported that in patients undergoing lumbar fusion for spondylolisthesis and degenerative disc disease, the patient-reported minimum acceptable outcomes were a reduction in pain to 3/10 or less, and improvement in ODI of 20 points or more. In this study, both groups had achieved all of these outcomes at the 12-month follow-up.

There was no evidence that one treatment was clinically superior at reducing pain and disability, or improving quality of life. Michielson *et al*[20] similarly, found no clinical difference in terms of VAS, ODI, or SF-36 scores, when comparing rhBMP-2 to ICBG in instrumented single-level posterior lumbar interbody fusions, in a prospective, randomized trial, and their 12-month scores were similar to the scores seen in our study. Therefore, the use of rhBMP-2 in primary TLIF or PLIF procedures may be unnecessary and cost inefficient in achieving clinical improvement, in posterior interbody fusions.

TABLE 3. SF-36 Physical Scales in LBG and rhBMP-2 Groups

	LBG			rhBMP-2			Difference		
	N	Mean*	SD	N	Mean*	SD	Mean*	95%CI	*P*†
Physical functioning‡									
Preop	17	34.5	21.7	51	36.7	20.5	2.2	(−11.8 to 16.1)	0.76
6 wk¶	2	50.7	58.7	38	55.8	26.5			
3 mo	10	69.9	20.9	42	60.6	26.8			
6 mo	8	71.2	28.5	42	66.5	26.7			
12 mo	16	69.2	30.6	31	68.5	32.5	−2.9	(−18.1 to 12.2)	>0.90
Bodily pain‡									
Preop	17	12.9	8.5	51	14.1	5.7	1.2	(−10.1 to 12.5)	0.83
6 wk¶	2	31.7	24.7	37	22.6	18.0			
3 mo	10	29.9	27.2	41	34.1	24.9			
6 mo	8	59.1	33.7	42	37.5	22.2			
12 mo	16	40.5	32.4	31	45.2	31.5	3.4	(−10.5 to 17.3)	0.62
Physical Component Scales‡§									
Preop	17	39.4	16.4	51	33.2	12.9	−6.2	(−16.7 to 4.2)	0.48
6 wk¶	2	43.1	36.8	39	45.0	14.8			
3 mo	10	60.2	18.2	42	52.7	20.4			
6 mo	8	76.2	22.6	42	58.0	21.7			
12 mo	16	61.1	27.6	31	60.9	26.8	5.4	(−5.7 to 16.5)	>0.90
Mental Component Scales‡§									
Preop	17	67.1	21.7	51	55.6	19.3	−11.5	(−22.4 to −0.6)	0.08
6 wk¶	2	66.2	57.3	39	65.7	19.6			
3 mo	10	83.2	12.2	42	72.8	21.3			
6 mo	8	93.8	9.2	42	76.2	20.7			
12 mo	16	80.1	23.4	31	71.4	23.7	2.8	(−8.2 to 13.8)	0.62
Overall SF-36‡									
Preop	17	51.3	18.7	51	42.9	15.6	−8.3	(−18.9 to 2.2)	0.24
6 wk¶	2	54.5	46.7	39	53.5	16.5			
3 mo	10	70.0	15.3	42	62.3	21.1			
6 mo	8	84.7	16.9	42	67.1	21.9			
12 mo	16	70.2	24.8	31	66.6	25.8	4.7	(−6.0 to 15.6)	>0.90

**Mean and SD pain or disability in patient groups without or with rhBMP-2, and mean difference (with 95% CIs and P values) between groups at each time period; estimated by repeated-measures mixed methods linear regression, adjusted for age, sex, operation type (PLIF or TLIF), number of vertebral levels fused, smoking history and diabetes mellitus status.*

†P values were corrected for multiple comparisons using the Holm method.

‡All SF-36 scales (0 [worst quality of life]–100 [best quality of life]).

§The mean postop pain/disability scores were estimated as the average score during the 12-month period, weighted for the length of time since the previous score measurement.

¶During the earlier period when the patient group was receiving LBG, functional scores were not recorded routinely at 6 wk.

LBG indicates local bone graft; rhBMP, recombinant human bone morphogenetic protein-2; PLIF, posterior lumbar interbody fusion; TLIF, transforaminal lumbar interbody fusion; preop, preoperative; postop, postoperative; SF-36, Short Form 36; SD, standard deviation; CI, confidence interval.

TABLE 4. Complications in LBG and rhBMP-2 Groups

	LBG (N = 19)		rhBMP-2 (N = 51)		Comparison		
Complication	**N**	**%**	**N**	**%**	**IRR**	**95% CI**	***P***
Overall postoperative complications	2	10.5	21	41.2	4.66	(1.57–13.82)	0.05
Radiculopathy	1	5.3	14	27.5	5.18	(0.76–35.54)	0.09
Radiculitis	0	0.0	6	11.8			
Osteolysis	0	0.0	3	5.9			
Ectopic bone	0	0.0	7	13.7			
Malposition of instruments	0	0.0	1	2.0			
Hematoma	0	0.0	1	2.0			
UTI	0	0.0	1	2.0			
Pneumonia	0	0.0	1	2.0			
PE	1	5.3	0	0.0			
ASD within 12 mo	1	5.3	3	5.9	2.09	(0.38–11.38)	0.40
Reoperation within 12 mo	1	5.3	4	7.8	3.37	(0.57–19.96)	0.18

LBG indicates local bone graft; rhBMP, recombinant human bone morphogenetic protein-2; IRR, incidence rate ratio; ASD, adjacent segment disease; UTI, urinary tract infection; PE, pulmonary embolus.

To date, we are unable to identify other studies directly comparing interbody fusion rates using rhBMP-2 and LBG, although there are studies on each graft's ability to induce fusion in PLIF and TLIF procedures,[2,7,10–12,21,22] with LBG shown to be capable of inducing interbody fusion in up to 3 levels with rates ranging from 95.8% to 100%.[10–12] Our study found 89.5% of participants treated with LBG alone, achieved fusion by their 12-month follow-up, albeit that our study had only one 2-level interbody fusion in the LBG group, reducing generalizability to single-level fusions. Reported rates of fusion with the use of rhBMP-2 range from 95.8% to 100% in patients who underwent PLIF and TLIF.[2,7,20,21] In our study, 94.1% treated with rhBMP-2 achieved fusion by 12 months, with no significant difference in fusion rates between our LBG and rhBMP-2 groups.

Complications associated with rhBMP-2 use in PLIF/TLIF procedures have previously been documented.[2–9,20,22–25] This study found a significant difference in the complication rate between the LBG and rhBMP-2 groups (10.5% *vs*. 41.2%), with an incidence rate ratio of 4.66 (95% CI, 1.57–13.82; $P = 0.05$).

Rihn *et al*[3] found complication rates of 45.5% in their ICBG group and 33.6% in rhBMP-2 groups. The difference was not statistically significant, with the most common complications in the ICBG group being related to iliac crest graft harvesting, such as donor site pain and infection, complications avoided in our cohort by the use of LBG. The complication rate not related to ICBG harvesting was close to 10%, similar to that seen in the LBG group of our study. Miura *et al*[10] recorded similar complication rates to us after PLIF procedures using LBG. Michielson *et al*[20] found higher rates of osteolysis and ectopic bone formation when using rhBMP-2 in posterior interbody fusions when compared with using ICBG. The clinically significant higher rate of complications seen in the rhBMP-2 group of our study included complications previously demonstrated in other studies, such as radiculitis, osteolysis, and ectopic bone.[2–9,20,22–24]

Radiculopathy was demonstrated in 14 of 51 (27.5%) patients in the rhBMP-2 group. Explanations were found in 8 patients; the 6 cases for which no explanation was found were classified as radiculitis. Other studies, defining radiculitis as worsening leg pain after surgery in a dermatomal distribution, have found lower rates than us in the rhBMP-2 groups,[2,3,8,9] with Mindea *et al*[8] demonstrating a rate of 11% and Rihn *et al*[3] a rate of 14%. These are comparable to our rate of radiculitis (11.8%). Mindea *et al*[8] looked only at radiculitis that developed in the first few days postsurgery and resolved by 6 weeks, whereas Rihn *et al*[3] looked beyond that time, similar to our study. Both Mindea *et al*[8] and Rihn *et al*[3] studied TLIF procedures, and found the radicular symptoms ipsilateral to the side of TLIF approach. This pattern was seen in 5 of the 6 cases of radiculitis in our study; the other patient underwent PLIF and subsequently developed a unilateral radicular pain. It is unclear as to whether rhBMP-2 or the transforaminal approach is responsible for postoperative radiculitis. In our study, there were comparable numbers of TLIF procedures in each group, with no cases of radiculitis documented in the LBG group, which suggests rhBMP-2 may have been a contributing factor. Small numbers have precluded confidence in the results; however, based on our findings and other studies, it is possible that the increased rates of radiculopathy and radiculitis seen in this study are associated with rhBMP-2.

Ectopic bone has been documented with rhBMP-2 use in lumbar spine surgery,[2,3,9,20,21] with rates ranging from 2.3%[3]

to 70.6%.[21] Haid *et al*[21] first documented the occurrence of ectopic bone formation associated with rhBMP-2 use in PLIF procedures, but did not associate it with any adverse clinical outcomes. Since then, others have reported on ectopic bone being associated with radiculitis.[2,3,9] Our study found 7 cases of ectopic bone, all in the rhBMP-2 group (13.7%); 3 developed radiculitis. Haid *et al*[21] had CT scans for all patients and found that 75% of those undergoing PLIF developed ectopic bone in the spinal canal, but were asymptomatic. Rihn *et al*[3] found 2 of 86 (2.3%) patients undergoing TLIF and treated with rhBMP-2 developed symptomatic ectopic bone as diagnosed by CT scan. Similar to our study, CT scans were only available in patients with radiculitis warranting further investigation. Therefore, both Rihn *et al*[3] and our study may have underestimated ectopic bone growth by missing asymptomatic cases. Despite this, we have documented cases of ectopic bone formation associated with rhBMP-2 use and have found an association with radiculitis in some cases.

Osteolysis has previously been identified as a concern with the use of rhBMP-2 in PLIF and TLIF procedures[2–7,20,25] with reported rates as high as 100% when CT scanning is routinely performed. Although most cases resolve, osteolysis is often associated with transient increases in back pain,[2,3,25] and can lead to further complications such as graft subsidence and cage migration.[5,6] We documented 3 cases, all in the rhBMP-2 group (5.9%) and none in the LBG group. All resolved and went on to fuse by 12-month follow-up. Two were associated with transient increases in back pain. None were associated with graft subsidence or cage migration.

As with all studies, ours has limitations. First, patient follow-up and data were collected prospectively; however, this was done so with protocols that were not as strict as would be seen in a prospectively designed study. This led to problems with missing data, and some patients did not contribute data for all outcomes, the LBG group leg pain VAS scores were most affected by this. There was also a substantial drop off in patient outcome data from the preoperative measures to the 12-month measures, and from 6 to 12 months in rhBMP-2 group. However, when comparing with clinical notes, the majority of these patients had clinical and radiological follow-up out to 12 months, and had not completed the forms required. Additionally several patients in this group had been discharged at 6 months, with follow-up radiographs at 12 months, but instructed only to return to the treating surgeon if they were experiencing problems. Second, we also compared 2 groups that were treated at different times, with the potential to lead to unknown differences between groups, and our numbers were relatively small. Third, postoperative CT scans were not available for all patients making assessment for fusion, ectopic bone growth and osteolysis less reliable. Fourth, the numbers of cases were small, particularly in the earlier group who did not receive rhBMP-2. As the complication rate in this smaller group was apparently lower than those receiving rhBMP-2, the uncertainty about our estimates of those rates in this group was relatively high, and this has a greater contribution to the uncertainty about the comparative complication rates in the 2 groups.

CONCLUSION

Spinal fusion can be affected by many factors, but despite weaknesses in our study, there was no obvious reason for bias between the groups. The technique used was the same in both groups apart from the use of rhBMP-2 and was performed by the same surgeon. There was a time cut off that determined the group allocation, rhBMP-2 was not used selectively, and groups shared comparable baseline characteristics with regard to factors, which would be the main determinants of bone quality. Although surgery was beneficial for both groups of patients on all clinical outcomes, the overall complication rates were significantly higher in the rhBMP-2 group, with patients treated with rhBMP-2 being 4.66 times more likely to have a postoperative complication. The nature of these complications leads us to hypothesize that, in this unselected population, this may be due to the use of rhBMP-2 and its associated complications of radiculitis, ectopic bone, and osteolysis. Randomized prospective studies would be warranted to further test this hypothesis.

➢ Key Points

- ❑ A single-surgeon retrospective review of prospectively to compare rhBMP-2 with LBG in routine PLIF and TLIF procedures.
- ❑ In comparison we found no difference in clinical outcomes, comparable rates of fusion and a significant increase in complication rates with rhBMP-2 use.
- ❑ Using rhBMP-2 may unnecessarily increase the risk of complications in routine PLIF and TLIF procedures.

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