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SPINE: BMP (K SINGH, SECTION EDITOR)

A consensus statement regarding the utilization of BMP in spine surgery

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Abstract Recombinant human bone morphogenetic protein - 2 (rh-BMP-2) was first approved by the United States Food and Drug Administration (FDA) in 2002 for use in anterior lumbar interbody fusions. Since that time, it has been estimated that "off label" use accounts for 85 % of applications. Original, industry sponsored studies demonstrated superior fusion rates with decreased incidence of complications when compared with traditional iliac crest bone graft. These studies have been criticized for potential bias and newer research has detailed potential complications as well as alternative applications. Potential off label uses of rhBMP-2 include: anterior lumbar fusions, single level posterior lumbar fusions, multiple level posterior lumbar fusions, posterior cervical fusions, long deformity fusions, in the presence of vertebral osteomyelitis, and in patients with history of malignancy. A review of the literature related to rhBMP-2 was conducted to evaluate its use for the above-mentioned applications with a special focus on fusion rates, observed complications, and clinical or radiographic outcomes.

Keywords Spine · Fusion · Lumbar · Cervica · Deformity · Malignancy · Osteomyelitis · rhBMP-2 · Bone morphogenetic protein · Arthrodesis · Complications · Infuse · Bone graft · Nonunion · Pseudarthrosis

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Introduction

Recombinant human bone morphogenetic protein - 2 (rhBMP-2, Infuse (Medtronic Minneapolis, Minnesota)) is a widely used adjuvant for spinal fusion surgery worldwide. Although originally approved by the United States Food and Drug Administration (FDA) in 2002 for use in anterior lumbar interbody fusions with a proprietary titanium interbody cage [1], it is estimated that 85 % of rhBMP-2 utilization is beyond the limits in which it was originally studied [2]. Several studies have demonstrated superior fusion rates and low levels of complications when compared with traditional iliac crest autograft (ICBG) [3–5]. However, subsequent reports, beyond the FDA trials, have criticized the methodology of the original rhBMP-2 studies due to potential investigator financial conflicts of interest and possible underreporting of complications [6•].

Recently, the Yale University Open Data Access (YODA) Project conducted 2 meta-analyses, which included data from the Medtronic (Minneapolis, Minnesota) sponsored trials to evaluate the safety and effectiveness of rhBMP-2 in spinal fusion [7••, 8••]. One meta-analysis indicated that at 24-month follow-up, patients who received rhBMP-2 demonstrated higher radiographic fusion rates (12 %) than those with ICBG (CI 1.02–1.23) [8••]. However, since both the rhBMP-2 and ICGB cohorts were associated with marked improvements in the baseline pain scores, the authors concluded that the benefits of rhBMP-2 over ICBG may not be clinically meaningful. Both meta-analyses also reported that while cancer was more common with the use of rhBMP-2, definite conclusions could not be made based on the available evidence.

Although the YODA studies provided an overview of risks and effectiveness of rhBMP-2, there may be specific patients or types of procedures that may benefit more from rhBMP-2 than others. It is our hypothesis that BMP-2 is advantageous in cases that involve a challenging fusion environment. The purpose of this article is to review the literature and develop consensus guidelines for the utilization of rhBMP-2 in common and challenging clinical scenarios including: anterior lumbar fusion, single level posterior lumbar fusion, multilevel posterior lumbar fusion, posterior cervical fusion, long deformity fusion, in the presence of vertebral osteomyelitis, and for patients with a history of malignancy.

Anterior lumbar fusions

Literature review

Much of the original literature demonstrated equivalence or superiority of rhBMP-2 over iliac crest autograft in anterior lumbar interbody fusion (ALIF). A prospective study of 131 patients undergoing single level ALIF with allograft dowels with either rhBMP-2 or autograft demonstrated 100 % fusion vs 89 % fusion, respectively, at 12 months ($P<0.05$) [9]. This rate declined to 81.5 % in the autograft group at 2 years. In another randomized study of 279 patients undergoing ALIF with tapered interbody cages, the radiographic fusion rates were 94.5 % for patients receiving rhBMP-2 compared with 88.7 % for autograft patients. This study also demonstrated that the mean operative time and blood loss were less in the rhBMP-2 group (1.6 h vs 2.0 h and 109.8 mL vs 153.1 mL, respectively) [3]. At 6-year follow-up, 98 % (128 of 130) of the patients treated with rhBMP-2 demonstrated a solid fusion [10]. The secondary surgery rate was 6.7 % at less than 2 years postoperatively and 3.7 % at between 2 and 6 years postoperatively. Pain and functional scores improved throughout the course of the study.

Although these studies highlight the increased fusion rate with rhBMP-2 vs autograft, there are concerns with regards to a higher rate of retrograde ejaculation with the use of rhBMP-2 in ALIF procedures. However, the methodology for assessing retrograde ejaculation has not been standardized, which may lead to over- or underreporting of this complication [11]. In addition, the YODA reviews demonstrated an increased but not statistically significant rate of retrograde ejaculation in rhBMP-2 groups [7••, 8••]. Bone morphogenetic protein may also be associated with abdominal calcification and ectopic bone formation [12]. When encountered, this complication appears to be unique to anterior lumbar surgery and its clinical significance is uncertain.

Lateral transpsoas lumbar interbody fusion is a type of ALIF that is performed by many surgeons through a retroperitoneal approach. Injury to the lumbar plexus is concerning with this procedure and the addition of rhBMP-2 may potentiate injury. In a retrospective review of patients undergoing lateral lumbar interbody fusion (LLIF), there was a significantly higher percentage of patients with early anterior thigh or groin pain (OR 1.987; 90 % CI 1.113–3.488; $P=0.045$), which continued to final follow-up [13]. There was also a significantly higher rate of persistent motor deficit in the rhBMP-2 group at final follow-up (OR 3.060; 90 % CI 1.681–5.571; $P=0.002$). Symptomatic abdominal and retroperitoneal fluid collections and seromas, even on the contralateral side, resulted in neurologic deficits and have been reported [14–16].

Consensus statement

Based upon the published literature, we conclude that rhBMP-2 is likely associated with an increased rate of radiographic arthrodesis when compared with ICBG. However, this does not necessarily translate to an improvement in clinical outcomes. Although rhBMP-2 limits the morbidity associated with harvesting ICBG, which may explain the shorter operative times and less blood loss, patients should be counseled regarding the potential complications that are specific to rhBMP-2 utilization including osteolysis and retrograde ejaculation. rhBMP-2 may also be associated with lumbar plexopathy when utilized in the transpsoas lumbar fusion cases.

Single level posterior lumbar fusions

Literature review

rhBMP-2 has been utilized in an off label manner to supplement posterior spinal fusions [17]. Several studies have examined the benefits and complications associated with its use in posterior lumbar fusions. A 2-year outcomes study of 98 patients demonstrated that the fusion rate for cohorts receiving rhBMP-2 was superior to that of ICBG when rhBMP-2 is administered in single level posterolateral instrumented fusions (88 % vs 73 %, $P=0.051$) [18]. In the same study, blood loss and operative time were decreased with rhBMP-2 utilization. A larger case series of 463 patients further demonstrated that rhBMP-2 is superior to ICBG for achieving fusion (96 % vs 89 %, $P=0.014$) [19]. The authors reported that 60 % of the ICBG group experienced donor site pain at 24 months and incurred a significantly higher reoperation rate when compared with the rhBMP-2 group ($P=0.015$). However, in the YODA Project analysis of 4 Medtronic-sponsored studies with Individual-Patient Data (IPD), the authors found no difference in the rates of arthrodesis or adverse events between the rhBMP-2 and ICBG groups [7••].

Few studies have examined the use of rhBMP-2 in patients at high risk for pseudarthrosis. Glassman et al. noted that in smokers, rhBMP-2 was associated with a 95.2 % fusion rate following a posterolateral fusion, whereas ICBG patients demonstrated a rate of 76.2 % [20]. The authors reported that smokers were not associated with a greater risk of complications with rhBMP-2 utilization.

There are several unique complications of rhBMP-2 that are associated with posterior applications. Postoperative radiculitis and ectopic bone formation have been reported as potential complications of rhBMP-2 in interbody settings. In a review of 119 patients who underwent a TLIF, a 14 % rate of postoperative radiculitis in the rhBMP-2 group was reported compared with 3 % in the autograft group. The authors noted that ectopic bone formation occurred in 2.3 % of patients in the rhBMP-2 group [21]. Neither complication appeared to carry any negative clinical implications. In addition, other studies have demonstrated comparable outcomes associated with rhBMP-2 and autologous bone graft utilization in single level posterior lumbar interbody fusions [22]. As highlighted in the YODA review, more evidence is necessary to identify the unique complications and advantages of rhBMP-2 administration in posterior lumbar fusion.

Consensus statement

Based on the available literature, we conclude that rhBMP-2 may improve the rates of radiographic arthrodesis in posterior lumbar fusion procedures, particularly in patients at high-risk for pseudarthrosis such as smokers. Patients should be counseled about complications specific to rhBMP-2 including increased early back and leg pain. Special precautions should be taken to prevent ectopic bone formation and radiculitis.

Multiple level posterior lumbar fusions

Literature review

Multilevel posterior spinal fusions for degenerative indications carry unique considerations pertaining to the use of rhBMP-2. Autograft techniques have become increasingly difficult, as there is a finite amount of bone graft available from either iliac crest or local autograft. Iliac crest donor site morbidity has been reported to be as high as 60 % [23], which leaves many surgeons seeking alternatives substitutes. A 2013 study of 509 patients (872 levels fused) with an average of 59-month follow-up demonstrated a 98.4 % rate of solid fusion when utilizing rhBMP-2 in multilevel TLIF and instrumented posterior lumbar fusions (average TLIF levels 1.7, pedicle screw levels, 3.6) [24]. At 5-year follow-up, there was a low rate of ectopic bone growth (0.6 %) [25]. Furthermore, a retrospective study of 1158 patients undergoing single and multiple level posterior lumbar fusions with rhBMP-2 demonstrated low rates of complications [26]. Ectopic bone formation was noted in 0.3 % of patients and seroma formation in 2.8 % of patients. This data supports low levels of complications when rhBMP-2 is used in posterior surgery. rhBMP-2 has even been shown to be efficacious in non-instrumented single and multiple level fusions in elderly patients [27, 28] and to reduce the rate of nursing home discharge in elderly patients, perhaps due to the decreased morbidity as compared with ICBG harvest [29]. rhBMP-2 was not associated with greater complication or reoperation rates in the elderly population [30].

Consensus statement

Although there are limited studies which examine only multilevel posterior degenerative lumbar fusions, the data provides evidence that rhBMP-2 is a promising adjunct to provide higher rates of fusion without increasing rates of complications.

Posterior cervical fusions

Literature review

Risks associated with rhBMP-2 utilization in anterior cervical fusions are well documented. Several authors have reported cases of wound infections and retropharyngeal edema which required reoperation [31–33]. Recently, studies have evaluated the risks and benefits of rhBMP-2 use in posterior cervical fusions. A retrospective analysis of 29 patients who underwent posterior cervical fusion reported 3 cases of pseudarthrosis [34]. No patient required reoperation and there were no adverse events or cases of heterotopic bone formation. A 2013 study examined rhBMP-2 for complex and revision posterior cervical fusions [35]. Of the 57 patients, 84 % had previous cervical surgery and 42 % had existing nonunions. Overall, the authors reported an 89.5 % fusion rate. There were 14 complications of which 7 required reoperation. There was 1 patient with respiratory complications after surgery, which was treated with delayed ventilator weaning. These results demonstrate that rhBMP-2 may be of benefit in high-risk patients, although larger studies are warranted. Another study of patients who underwent instrumented posterior cervical fusion reported a higher incidence of wound complications with rhBMP-2 vs iliac graft [36]. (14.6 % vs 2.8 %), but the difference was not statistically significant (P=0.113). Iliac graft donor site morbidity was common and the authors suggested that surgeons must weigh the risk of adverse events at the donor sites against those of the

posterior cervical wound complications. Cahill et al. reported that 2.1 % of patients who received rhBMP-2 in posterior cervical fusions experienced dysphagia [37]. This was the same rate as the allograft group. In addition, Hiremath et al. reported 1 case of neck swelling in their review of 16 posterior cervical fusions with rhBMP-2, which resolved with steroid treatment [38]. There were no controlled trials for the YODA studies to analyze for posterior cervical fusion cases.

Consensus statement

Based on the current literature, rhBMP-2 appears to be an alternative to ICBG in posterior cervical fusions. The use of rhBMP-2 in posterior cervical fusions is likely safer than in anterior approaches. In addition, rhBMP-2 utilization may lower the rate of reoperation and pseudarthrosis, particularly among high-risk patients. Surgeons should consider the possibility of adverse events including wound complications and seromas. Furthermore, subfascial drain usage should also an option.

Lumbar deformity fusions

Deformity fusions pose an especially challenging fusion environment due to iatrogenic instability from osteotomies and mechanical demands on instrumentation. Deformity fusion may involve a large number of levels of fusion and, therefore, there may be inadequate autograft bone. In addition, larger incisions increase the risk of wound complications while multilevel fusions potentiate pseudarthrosis. rhBMP-2 carries promise for promoting solid fusion in these complex cases [39]. A review of 63 patients undergoing long fusion to the sacrum with a minimum 4-year follow-up demonstrated that 93.5 % of patients receiving rhBMP-2 had solid fusion, compared with 71.9 % of patients with ICBG [40]. Another radiographic study of 55 patients demonstrated that 9 patients who received ICBG developed pseudarthrosis while only 1 patient rhBMP-2 developed a nonunion [41].

A prospective, multicenter study of 279 patients was conducted to evaluate the incidence of complications of rhBMP-2 vs ICBG use in long deformity fusions [42]. The number of levels fused, estimated blood loss, and duration of hospital stay were similar between the 2 groups. Operative time, number of osteotomies, and combined anterior/posterior fusions were higher in the rhBMP-2 group. The rhBMP-2 group incurred more overall complications per patient than the ICBG group, however, when linear regression and multivariable models were applied, there was no evidence of association between the use of rhBMP-2 and complications. A separate review of high dose rhBMP-2 in deformity surgery found no association between increasing doses of rhBMP-2 and radiculopathy or seroma [43].

Many patients with deformity fusions develop pseudarthrosis at L5-S1. A recent study demonstrated that a posterolateral dose of rhBMP-2 at L5-S1 resulted in comparable outcomes compared with TLIF at L5-S1. The operative time, perioperative morbidity, and cost were greater in the TLIF group [44]. Therefore, posterolateral rhBMP-2 may be a viable alternative to increase the fusion rate at L5-S1 in deformity operations.

Consensus statement

Based on the current literature, rhBMP-2 appears to an acceptable alternative to ICBG in deformity fusions. The available literature suggests that rhBMP-2 may increase the fusion rate and may lower the rate of reoperation and pseudarthrosis. Surgeons should consider subfascial drain usage in deformity fusions to reduce the risk of symptomatic seromas, hematomas, and wound complications.

Vertebral osteomyelitis

FDA device labeling, based on the initial studies, lists “active infection at the operative site” as a contraindication to the use of Infuse [1]. However, pyogenic vertebral osteomyelitis is an especially challenging fusion environment due to the ability of the bacteria to impair fusion, the colonization of instrumentation, and impaired vascularity in fusion beds. Because of these factors, the efficacy of ICBG, the gold standard of spinal fusion, is limited in vertebral osteomyelitis. There are limited case series describing the usage of rhBMP-2 in established vertebral osteomyelitis. In an infected rabbit model, the use of rhBMP-2 did not increase the morbidity or mortality rate, and improved fusion rates compared with autograft [45]. A report of 20 patients with vertebral osteomyelitis treated with rhBMP-2 demonstrated a 100 % rate of clinical and radiographic fusion at 2-year follow-up, with few minor complications [46]. All patients were treated with anterior column debridement and instrumented reconstruction followed by intravenous (IV) antibiotics. A similar study published in 2007 followed 14 patients with vertebral osteomyelitis who underwent circumferential fusion with rhBMP-2 [47]. All patients had clinical resolution of infections, normalized laboratory values, and achieved fusion at 2-year follow-up without BMP related complications. Another retrospective study of 15 patients with vertebral osteomyelitis demonstrated 100 % fusion and no recurrent infections during the twenty-month follow-up [48]. All patients were treated with a 1-level corpectomy followed by an instrumented fusion and at least 6 weeks of IV antibiotics. No cases of recurrent hardware infection were reported. Although no unique complications

have been reported with the use of rhBMP-2 for vertebral osteomyelitis, there is very limited data on this subject.

Consensus statement

Based on the current literature, there is some evidence that rhBMP-2 is a safe and efficacious alternative to ICBG in vertebral osteomyelitis/discitis fusion cases. The available literature suggests that rhBMP-2 may result in an acceptable fusion rate, at least no worse than that of ICBG autograft. There does not appear to be unique complications specific to rhBMP-2 utilization in patients with vertebral osteomyelitis/discitis.

Patients with history of malignancy

Bone morphogenetic proteins function through intracellular signaling pathways [49]. Many of these pathways have been implicated in oncogenesis and tumor suppression. BMPs can potentiate malignancy of several tumor types [50] while suppressing other cancers [51]. The function and effect of bone morphogenetic proteins appear to vary as a function of the tumor cell cycle. According to the FDA, Infuse is contraindicated in patients who have an active malignancy or who are undergoing treatment for malignancy [1]. Carragee et al. raised concern over the incidence of new cancers with the use of high dose rhBMP-2 in spinal fusions (AMPLIFY) [52]. Four hundred, sixty-three patients were followed over a 60-month period. At 2-year follow-up, there were 15 new cancers in 11 patients in the rhBMP-2 group and only 2 new cancers in the control group. At the final follow-up, there were 20 new cancers in the rhBMP-2 group compared with 5 in the control group. Another retrospective cohort study examined Medicare data for patients who underwent spinal fusion with rhBMP-2 [53]. The authors concluded that there was no increased risk for the development of pancreatic cancer in patients who received rhBMP-2. Bone morphogenetic proteins appear to have varying effects on different cancer types. There is some evidence that rhBMP-2 may suppress oncogenesis in vitro in some studies and other evidence that rhBMP-2 potentiates oncogenesis [51, 54–57]. Clinically, there is a case report that rhBMP-2 potentiated multiple myeloma in a patient with a history of a solitary plasmacytoma [15]. The authors suggested that patients with abnormal electrophoresis results, even in the absence of multiple myeloma, might be a relative contraindication for use of rhBMP-2.

Consensus statement

Based on the current literature, we cannot draw a definitive recommendation for the use of rhBMP-2 in patients with a history of cancer. The evidence regarding this association is conflicted and should be presented to patients as such.

Discussion

Since its initial FDA approval in 2002, the use of rhBMP-2 has increased exponentially in spine surgery. Early studies demonstrated a high degree of heterogeneity in the reporting of complications. This is largely due to the wide variations in patient demographics, surgical technique, delivery methods, dosing, and conflicts of interest. Until recently, many studies relied upon small case series, which lacked substantial statistical power (Table 1 summarizes reviewed literature pertaining to fusion rates and clinical outcomes when using rhBMP-2 in spinal fusions). The literature demonstrates that rhBMP-2 utilization is associated with higher rates of radiographic fusion when compared with autograft. Interestingly, higher rates of fusion do not appear to be correlated with better clinical outcomes or patient satisfaction. Both the treatment and control groups regularly demonstrated significant improvements in all scoring categories. Three studies noted that patients who received rhBMP-2 reported faster improvements in outcome scores when compared with autograft. However, statistical differences were not demonstrated at further follow-up intervals [17, 58, 59].

Studies comparing rhBMP-2 to autograft report a higher incidence of certain complications in patients receiving rhBMP-2 (Table 2 summarizes articles reviewed which related to complications from the use of rhBMP-2). Most complications are related to wound issues such as seroma, hematoma, and infection. Postoperative radiculitis, ectopic bone formation, cyst formation, and bone resorption were also reported. Despite the complications, few were considered “major” and did not lead to higher rates of secondary surgeries in most studies.

The YODA analyses presented unique data that had not been previously published [7••, 8••]. Anterior lumbar, posterior lumbar, and anterior cervical approaches were separately analyzed. rhBMP-2 was associated with greater radiographic fusion rates by 12 % at 2-year follow-up. Results indicated that although SF-36 and ODI scores were improved statistically in patients receiving rhBMP-2, both groups experienced such significant improvements that the authors believed the extra benefit associated with rhBMP-2 was minimal. Analgesia use, hospitalization, and return to work or activity were similar for both groups. Operative time was 21 minutes shorter in the rhBMP-2 group and is attributed to the lack of bone graft harvest. The authors noted that there was a high confidence interval when comparing safety profiles of rhBMP-2 and autograft. This is an indication that more high quality research is required to fully evaluate the true incidence of complications.

Table 1 Reviewed literature with reported radiographic and clinical outcomes

Authors	Design	*n* =	Approach	Outcomes	Duration of follow-up	% Fused rhBMP-2	% Fused control	Clinical outcomes
Boden et al. (2000)	Prospective randomized	14	ALIF	Radiographic / clinical	24 mo	100.00 %	66.66 % (autograft)	ODI improved sooner in rhBMP-2 group (3 mo). Both groups showed similar improvements at 6 mo and throughout the duration.
Barkus et al. (2002)	Prospective randomized. (Part 1)	279	ALIF	Radiographic / clinical	24 mo	94.50 %	88.7 % (autograft)	At all intervals, improvements in ODI, back pain, leg pain, and neurologic status observed in both groups.
Burkus et al. (2006)	Prospective randomized	131	ALIF	Radiographic	24 mo	100.00 %	81.5 % (autograft)	NR
Barkus et al. (2009)	(Part 2)	130	ALIF	Radiographic / clinical	72 mo	98.00 %	NR	Beginning at 6 wk. Improvements in ODI, SF-36, back pain and leg pain observed at all intervals.
Slosar et al. (2007)	Prospective randomized	75	ALIF with posterior pedicle screw fixation	Radiographic / clinical	24 mo	100.00 %	89 % (allograft)	RhBMP-2 group had statistically higher ODI and NRS scores at 6 mo postop. At 1 and 2 yr, both groups had statistically significant improvements.
Haid et al. (2004)	Prospective randomized	67	Single level PLIF	Radiographic / clinical	24 mo	92.30 %	77.8 % (autograft)	ODI, SF-36, back pain and leg pain scores improved at all intervals for both groups. Back pain improvements nearly double with rhBMP-2 than control at 24 mo No statistically significant difference in satisfaction.
Michielsen et al. (2013)	Prospective randomized	40	Single level PLIF with pedicle screw fixation	Radiographic / clinical	24 mo	100.00 %	100.00 %	Statistical improvements in all scoring for both groups. No statistical difference between groups.
Dimar et al. (2006)	Prospective randomized	98	Single level PLIF with pedicle screw fixation	Radiographic / clinical	24 mo	90.60 %	73.33 % (autograft)	No significant differences in any outcome measure at any interval.
Glassman et al. (2007)	Retrospective	148	Single level PLIF with pedicle screw fixation	Radiographic / clinical	24 mo	100 % (nonsmokers) 95.2 % (smokers)	94.1 % (nonsmokers) 76.2 % (smokers)	All scores (ODI, SF-36, back pain, leg pain) improved in all groups at all intervals. Improvements were greater for nonsmokers than smokers.
Dimar et al. (2009)	Prospective randomized	410	Single level PLIF with pedicle screw fixation	Radiographic / clinical	24 mo	96.00 %	89 % (autograft)	ODI, SF-36, back pain and leg pain showed similar improvements for both groups at all intervals.
Dawson et al. (2009)	Prospective randomized	46	Single level PLIF with pedicle screw fixation	Radiographic / clinical	24 mo	95.00 %	70 % (autograft)	Significant improvements in both groups. "Trend toward greater improvements" in the investigational group.

Table 1 (continued)

Authors	Design	*n* =	Approach	Outcomes	Duration of follow-up	% Fused rhBMP-2	% Fused control	Clinical outcomes
Boden et al. (2002)	Prospective randomized	25	PLIF with or without pedicle screw fixation	Radiographic / clinical	24 mo	100 % (with or without pedicle screws)	40 % (autograft/ pedicle screw)	Statistically significant improvements in ODI score with rhBMP-2 alone seen at 6 wk. RhBMP-2/pedicle screw at 3 mo and control group at 6 mo Improvements in all groups maintained through follow-up.
Glassman et al. (2008)	Prospective randomized	106	PLIF with pedicle screw fixation	Radiographic / clinical	24 mo	86.30 %	70.8 % (autograft)	Improvements in ODI, SF-36 back pain and leg pain scores at all intervals. No statistical significance.
Geibel et al. (2009)	Retrospective	48	PLIF	Radiographic / clinical	17 mo (average)	100 %	NR	No rhBMP-2 associated complications. High patient satisfaction scores.
Mulconrey et al. (2008)	Prospective randomized noncontrolled	98	ALIF, PLIF with pedicle screw fixation	Radiographic	24 mo	95 % (assuming all applications)	NR	NR
Maeda et al. (2009)	Retrospective	55	ALIF, PLIF with or without pedicle screw fixation	Radiographic / clinical	24 mo	95.70 %	71.9 % (autograft)	NR
Hurlbert et al. (2013)	Prospective randomized	197	Posterior lumbar with pedicle screw fixation	Radiographic / clinical	24–48 mo	96 % (6 mo) 98 % (12 mo) 97 % (24 mo) 94 % (48 mo)	43 % (6 mo) 57 % (12 mo) 70 % (24 mo) 69 % (48 mo)	Excellent improvements in all clinical scoring criteria post operatively. No statistical difference between investigational and control group.
Rihn et al. (2009)	Retrospective	48	TLIF	Radiographic / clinical	19.4 (radiographic) 27.4 (clinical)	95.80 %	NR	Odoms: 71 % good to excellent results. Patient satisfaction: 84 % somewhat to very satisfied. 84 % very likely to undergo procedure again for similar symptoms
Crandall et al. (2013)	Retrospective	509	TLIF	Radiographic / clinical	59 mo (average)	98.40 %	NR	Significant improvements in all scores observed at least 24 mo post operatively.
Kim et al. (2013)	Cohort	63	ALIF, PLIF, (Thoracic to Sacrum)	Radiographic / clinical	4–14 y	93.50 %	71.9 % (autograft)	No statistical difference in ODI scores between the groups. Only the self- image score demonstrated statistically significant differences.
Hamilton et al. (2011)	Retrospective	53	Posterior cervical	Radiographic / clinical	24 mo	100 % 94 % bilateral	NR	NR
Hodges et al. (2012)	Retrospective	29	Posterior cervical	Radiographic / clinical	>12 mo	89.00 %	NR	No adverse events related to BMP reported.

Table 2 Reviewed literature with reported rhBMP-2 complications

Authors	Design	*n* =	Approach	Duration of follow-up	Complications rhBMP-2	Complications control	% Complications requiring reoperation	Comments
Carragee et al. (2011)	Retrospective	243	ALIF	NR	7.30 %	0.60 %	0.00 %	Retrograde ejaculation.
Lubelski et al. (2013)	Retrospective	110	ALIF	17.5 mo (rhBMP-2) 30.8 mo (control)	22 % (overall) 8 % (RE)	20 % (overall) 8 % (RE)	0.00 %	Urological complications, Retrograde ejaculation.
Rihn et al. (2009)	Retrospective	119	TLIF	19.1 mo (radiologic) 27.6 mo (clinical)	29.1 % (overall) 14 % (postop radiculitis). 5.8 % (osteolysis) 2.3 % (ectopic bone). 3.5 % (lumbar wound infection)	45.5 % (overall) 30.3 % (persistent donor site pain) 3.1 % (donor site infection). 6.1 % (lumbar wound infection) 3.0 % (postop radiculitis)	12.1 % (autograft). 9.3 % (rhBMP-2) *P*=.65	Postoperative radiculitis, Osteolysis, Ectopic bone formation, infection, donor site pain.
Rihn et al. (2009)	Retrospective	48	TLIF	19.4 (radiographic)	27.1 % overall complications.	NR	10.4 % overall (5 patients)	Wound infection, Hematoma, Seroma, Malpositioned screw.
				27.4 (clinical)	16 % transient radiculitis 6 % vertebral osteolysis 4 % nonunion 2 % ectopic bone formation		1 wound infection 1 Hematoma 1 Seroma 1 malpositioned screw 1 symptomatic ectopic bone	Symptomatic ectopic bone
Owens et al. (2011)	Retrospective	204	TLIF	>3 mo	21.6 % (overall) 6.4 % (major) 16.7 % (minor) 6.4 % (neurologic)	NR	6/13 patient with neurologic complication required reoperation.	Seroma, hematoma, neurologic injury, vascular injury, wound infection.
Knox et al. (2011)	Retrospective	58	TLIF	4.3 mo (avg)	27.6 % osteolysis overall 31.6 % of patients with osteolysis had graft subsidence. 8.8 % cage migration	NR	0	Osteolysis, graft subsidence. Cage migration
Garrett et al. (2010)	Retrospective	130	PLIF	>3 mo	6 (4.6 %) : painful seroma	NR	6 (4.6 %)	Painful seroma
Michielsen et al. (2013)	Prospective randomized	40	1 level PLIF with pedicle screw fixation	24 mo	5 % (postop radiculopathy) 100 % (end plate resorption) 36 % (osteolysis) . 10 % (cyst formation). 36 % (ectopic bone formation)	10 % (donor site pain)	0.00 %	Transient radiculopathy Endplate resorption Osteolysis Cyst formation
Glassmann et al.(2011)	Retrospective	1037	Posterior Lumbar	>3 mo	18.3 % (overall) 7.8 % (major) 10.2 % (minor)	NR	2.12 % (deep wound infection) 0.96 % (wound hematoma) 0.58 % (screw malposition) 0.29 % (epidural hematoma) 0.29 % (excessive blood loss) 0.68 % (radiculopathy)	Major surgical complications listed are those which may require reoperation or leave permanent injury. Few are believed to be related to rhBMP-2.

Table 2 (continued)

Authors	Design	*n* =	Approach	Duration of follow-up	Complications rhBMP-2	Complications control	% Complications requiring reoperation	Comments
Carragee et al. (2013)	Retrospective (AMPLIFY)	397 (24 mo) 292 (54 mo)	PLIF with pedicle screw fixation	24 mo 54 mo	3.37 incidence rate at 24 mo (15 events) 2.15 incidence rate at 54 mo (20 events)	0.50 incidence rate at 24 mo (2 events) 0.60 incidence rate at 54 mo (5 events)	NR	New cancer diagnosis.
Hoffmann et al. (2013)	Retrospective	1158	PLIF with or without pedicle screw fixation	12 mo	3.5 % (nonunion) 2.8 % (seroma) 1.4 % (ectopic bone) 2.2 % (infection)	NR	10.1 % (nonunion, ectopic bone, seroma, infection)	Evaluated for complications requiring reoperation. Nonunion, ectopic bone, infection, seroma, dural tear
Bess et al. (2013)	Prospective	279	PLIF, Posterior lumbar, PLIF+posterior lumbar, Anterior lumbar	>3 mo	1.4: overall complications per patient. 0.9: minor complications per patient . Early complications more common.	0.6 overall complications per patient 0.2 minor complications per patient.	0.2 complications requiring reoperation (rhBMP-2). 0.3 complications requiring reoperation (control)	No statistical difference between complication rates: neurologic, wound, infection
Hurlbert et al. (2013)	Prospective randomized	197	Posterior lumbar with pedicle screw fixation	24–48 mo	6: Noninfectious wound complications: 11: Wound infections: 2: Symptomatic Nonunions	Noninfectious wound complications: 4 Wound infections: 5 Symptomatic Nonunions: 2	Nonunions: 2 patients (control) 2 patients (study Wound Infections: 5 patients (control) 11 patients (study)	Wound infections, noninfective wound complications, nonunions
Hoffmann et al. (2013)	Retrospective	482	Posterior Lumbar with instrumentation (≤3 levels)	15.8 mo	3.7 % nonunion 3.1 % painful seroma 3.1 % excess bone formation. 2.3 % infection. 0.2 % malpositioned implants.	NR	10.4 % overall	No significant difference in complications or outcomes between young and elderly patients.
Hamilton et al. (2011)	Retrospective	53	Posterior cervical	40 mo	3.8 % which includes: 1 superficial wound complication. 1 adjacent level degeneration.	NR	1 revision secondary to adjacent level degeneration.	Adjacent segment degeneration, superficial wound complication.
Mesfin et al. (2013)	Retrospective	502	Thoracic, lumbar interbody fusion	42 mo	16.6 % major perioperative complications 3.4 % cancer prevalence 1 % radiculopathy 0.6 % seroma	NR	2.4 % deep infection 2 % junctional kyphosis 0.8 % instrumentation failure. 0.6 % sterile seromas 0.4 % epidural hematoma. 0.4 % malpositioned screws. 0.4 % coronal decompensation 0.4 % distal segment degeneration.	High dose BMP. Cancer prevalence not associated with BMP-2

Table 2 (continued)

Authors	Design	*n* =	Approach	Duration of follow-up	Complications rhBMP-2	Complications control	% Complications requiring reoperation	Comments
Lykissas et al. (2013)	Retrospective cohort	451	LLIF	15.5 mo	45.8 % immediate postop sensory deficits. 40.3 % persistent sensory deficits. 51.4 % immediate postop motor deficit LE. 48.6 % persistent motor deficit 51.4 % immediate anterior thigh or groin pain.	48.6 % immediate postop sensory deficits. 27.8 % persistent sensory deficits 38.9 % immediate postop motor deficit LE. 23.6 % persistent motor deficit 34.7 % immediate anterior thigh or groin pain.	NR	rhBMP-2 use for LLIF associated with higher rates of postop and persistent sensory and motor deficits as well as anterior thigh and/or groin pain.

Although some studies did report higher levels of complications with rhBMP-2, a 2010 study of osteobiologics noted that although complications occur, few resulted in second surgeries and clinical outcomes were similar when compared with iliac bone graft [23].

Notably, there was a great deal of variation in the dosing of rhBMP-2 in the published studies. An initial industry sponsored study reported using 20 mg of Infuse per side [17], whereas other studies have reported ranges from to 1.8 mg per level in cervical fusions and up to 40 mg in lumbar surgeries [52, 60]. It is reasonable to suspect that there is a dose dependent relationship regarding the fusion and complication rates. However, there is little high quality data on the subject.

Recently, the cost of health care has become increasingly scrutinized with concerns regarding the overall cost associated with rhBMP-2 utilization. Dagostino et al. recently reviewed the Nationwide Inpatient Sample (NIS) of 46,452 patients who underwent thoracolumbar or lumbar arthrodesis from 2002 to 2008 [61•]. The authors demonstrated that the use of BMP increased more than 400 % hospital charges have increased more than $900 million. Supporters have argued that the use of rhBMP-2 carries the potential to decrease revision surgeries, which would offset the higher upfront costs. The Nationwide Inpatient Sample database demonstrated that while surgeries performed for failed fusions did decrease, they did so by a very small margin. Assuming a 20 % representation in the database, the authors believed only 300 revision surgeries were eliminated.

Conclusions

Although the utilization of rhBMP-2 appears to improve radiographic fusions, current evidence demonstrates comparable patient outcomes in spinal surgery when compared with the use of ICBG. With proper patient selection, rhBMP-2 is an effective alternative to ICBG for anterior lumbar, posterior lumbar, or posterior cervical fusions. Evidence also supports that rhBMP-2 is a safe alternative to ICBG in patients with vertebral osteomyelitis or discitis. Patients with active malignancy or a history of malignancy should be counseled on the potential risks associated with rhBMP-2, as the oncogenic association is not fully defined. Further research is necessary to evaluate appropriate dosing as well as to examine specific applications in high-risk populations. As with any surgery, thoughtful conversation with patients should include the risks and benefits associated with any intraoperative product.

Compliance with Ethics Guidelines

Conflict of Interest Brett Walker, John Koerner, and Sriram Sankarayanaryanan declare that they have no conflict of interest. Kris Radcliff has been a consultant for and has received royalties from Globus Medical, has received honoraria from Depuy, and has received travel/accommodations expenses covered or reimbursed from Depuy, Globus, Medtronic, Relievant, and Stryker.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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