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Does Recombinant Human Bone Morphogenic Protein 2 Affect Perioperative Blood Loss after Lumbar and Thoracic Spinal Fusion?

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Study Design: Retrospective cohort design.

Purpose: This study aimed to determine whether recombinant human bone morphogenic protein 2 (rhBMP-2) reduces total perioperative blood loss during lumbar and thoracic fusion.

Overview of Literature: Previous studies on rhBMP-2 versus iliac crest bone grafting in thoracic and lumbar fusions have yielded mixed results regarding reductions in blood loss and have largely neglected the postoperative period when analyzing total blood loss. Additionally, these studies have been limited by heterogeneity and sample size.

Methods: We analyzed the blood loss patterns of 617 consecutive adult patients undergoing lumbar and/or thoracic fusions requiring subfascial drain placement at a single institution from January 2009 to December 2016. Patients were divided into BMP and non-BMP cohorts, and a propensity score analysis was conducted to account for the differences between cohorts.

Results: At a per-level fused basis, the BMP group exhibited a significant reduction in the intraoperative (66.1 mL per-level fused basis; 95% confidence interval [CI], 127.9 to 4.25 mL; p=0.036) and total perioperative blood loss (100.7 mL per-level fused basis; 95% CI, 200.9 to 0.5 mL; p=0.049). However, no significant differences were observed in an analysis when not controlling for the number of levels or when examining the postoperative drain output.

Conclusion: RhBMP-2 appears to reduce both intraoperative and total blood loss during lumbar and thoracic fusions on a per-level fused basis. This total reduction in blood loss was achieved via intraoperative effects because RhBMP-2 had no significant effect on the postoperative drain output.

Keywords: Lumbar fusion; Recombinant human bone morphogenic protein; Iliac crest bone graft; Perioperative blood loss

Introduction

Recombinant human bone morphogenic protein 2 (rhBMP-2, InFUSE; Medtronic Sofamor Danek, Memphis, TN, USA) has been used as an osteoinductive adjuvant to enhance spinal fusions for more than 15 years [1-3]. Since then, many studies have reported reduction in the operative time and hospital stays, as well as improved fusion rates in patients treated with rhBMP-2 compared with those treated with autologous iliac crest bone grafting

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(ICBG) [3,4].

The effects of rhBMP-2 on perioperative blood loss during thoracic and lumbar fusions remain controversial. Several studies have reported reduced blood loss with the use of rhBMP-2 compared with that of ICBG [5,6] with reductions ranging from 97 to 192 mL [7]. However, other studies have not shown statistically significant differences in blood loss [8-10]. Additionally, studies have generally focused on the intraoperative blood loss alone and have not specifically analyzed the postoperative drain output. Both thoracic and lumbar fusions can incur significant intraoperative blood loss and additional loss via the postoperative drain output. Therefore, information on the expected reduction in blood loss when utilizing rhBMP-2 would assist spine surgeons when counseling patients and developing surgical plans, particularly when determining whether to place a subfascial drain at the conclusion of the surgical case.

Therefore, in this study, we aimed to use a retrospective cohort design to examine the impact of rhBMP-2 on the total perioperative blood loss (intraoperative estimated blood loss and postoperative drain output) following lumbar and thoracic spinal fusions involving the placement of a subfascial drain. Our study sought to empirically test the hypothesis that the use of rhBMP-2 during spinal fusion procedures reduces intraoperative and postoperative blood loss relative to the use of ICBG. As secondary endpoints, we attempted to determine the effects of rhBMP-2 on the operative times, transfusion rates, hospital stays, reoperation rates, and intensive care unit (ICU) admission rates. To our knowledge, this was the first study to specifically address the effect of rhBMP-2 on the total perioperative blood loss during lumbar and thoracic fusions.

Methods

1. Study population

We analyzed 617 consecutive adult patients (311 males and 306 females) undergoing posterior lumbar and/or thoracic fusions involving subfascial drain placement to treat degenerative conditions of the spine between January 2009 and December 2016. The average patient age was 63.5 years (range, 18–91 years). The procedures were performed by seven surgeons at a single institution. Patients who were younger than 18 years and those who did not undergo drain placement were excluded. Patients who underwent concurrent cervical operations, surgery for infection, or tumor resection were also excluded. The Institutional Review Board approval of Mayo Clinic was

Table 1. Demographic data

Characteristic	Total (N=617)	No BMP (N=467)	BMP (N=150)
Age (yr)	63.5±14.1	63.8±14.1	62.5±14.3
Female	311 (50.4)	231 (49.5)	80 (53.3)
Male	306 (49.6)	236 (50.5)	70 (46.7)
Height (cm)	168.4±11.0	168.8±11.0	167.3±10.8
Weight (kg)	84.6±20.3	85.5±20.1	82.0±20.6
Body mass index (kg/m^2)	29.8±6.3	30.0±6.2	29.3±6.7
Preoperative hemoglobin level (Hgb)	13.0±1.9	13.1±1.8	12.6±2.0
Preoperative blood thinners	65 (10.5)	54 (11.5)	11 (7.3)
Cancer history	126 (20.4)	366 (78.4)	125 (83.3)
Myocardial infarction history	25 (4.1)	445 (95.3)	147 (98.0)
Cerebrovascular accident history	42 (6.8)	436 (93.4)	139 (92.7)
Peripheral vascular disease	14 (2.3)	455 (97.4)	148 (98.7)
Diabetes	102 (16.5)	388 (83.1)	127 (84.7)
Smoking (current or former)	253 (41.0)	191 (40.9)	62 (41.3)
Prior spine surgery	190 (30.8)	122 (26.1)	68 (45.3)

Values are presented as mean±standard deviation or number (%).
BMP, bone morphogenic protein.

obtained for this study, which included reviewer approved waiver of the requirement to obtain informed as a low-risk retrospective review (IRB approval no., 10-002852).

Within the study population, 41% of subjects (n=253) were current or former smokers, 16.5% (n=102) had diabetes, and 30.8% (n=190) had undergone prior spine surgery. Additionally, 10.5% (n=65) were using preoperative blood thinners and 2.3% (n=14) had peripheral vascular disease. Of the 617 patients, 150 (24.3%) had received BMP (in an off-label use of this product) and 467 (75.7%) had not received BMP. No patient in the BMP group received both BMP and harvested ICBG. The groups differed significantly in terms of the preoperative hemoglobin levels (12.6 Hgb in the BMP group versus 13.1 Hgb in the non-BMP group, p=0.02) and rate of previous spine surgery (45.3% in the BMP group versus 26.1% in the non-BMP group, p=0.005) (Table 1). There were no other significant demographic differences between the BMP and non-BMP groups.

2. Study design

This ambispective study used a retrospective cohort design, in which all data from the prospectively maintained electronic medical record were abstracted. In the primary analysis, all patients with spinal fusion identified during the study period were classified into the BMP cohort if they received rhBMP-2 or into the non-BMP cohort if they did not receive rhBMP-2. Patients in the latter group received ICBG. The outcomes of interest were intraoperative blood loss, as documented by the anesthesia team, postoperative blood loss collected through subfascial drains via suctioning at various postoperative timepoints, total perioperative blood loss (intraoperative blood loss+postoperative blood loss through the subfascial drain), minimum postoperative hemoglobin level, and transfusion rate. We also compared the operative times, transfusion rates, ICU admission rates, stay lengths, and reoperation rates. Finally, we evaluated the incidence of venous thromboembolism in patients who did and did not receive BMP and also in those who did and did not receive tranexamic acid (TXA).

3. Statistical analysis

The data are summarized as means±standard deviations for continuous variables and counts (percentages) for categorical variables, unless otherwise noted. The analysis was conducted using a propensity score to account for the between-group differences because the subgroup of patients who received BMP differed from those who did not receive BMP with respect to demographics, medical history, and surgical factors. The propensity score was calculated using a logistic regression model, in which the response variable was BMP versus no BMP, and the independent variables included patient demographics, medical history, baseline clinical data, and surgical information (including the number of vertebral levels fused). The results of this model represent the likelihood that a patient received BMP given their demographic profile, past medical history, baseline clinical data, and surgical factors. The propensity score was included as an adjusting covariate in models examining the effects of BMP on the study outcomes, such as the postoperative drain output, intraoperative blood loss, total blood loss, and the need for transfusion. The inclusion of the propensity score minimized the potential bias between the BMP and non-BMP subgroups.

The outcomes of postoperative drain output, intraoperative blood loss, and total blood loss were analyzed using linear regression, whereas the transfusion rates were analyzed using logistic regression. All models included the propensity score and operative time as adjusting covariates. All statistical tests were two-sided with a threshold of statistical significance set at p<0.05. All analyses were conducted using SAS ver. 9.4 (SAS Institute Inc., Cary, NC, USA).

Table 2. Number of levels fused

No. of levels	Total	No BMP	BMP
1	176 (28.6)	156 (33.4)	20 (13.4)
2	133 (21.6)	98 (21.0)	35 (23.5)
3	73 (11.9)	57 (12.2)	16 (10.7)
4	54 (8.8)	38 (8.1)	16 (10.7)
5	38 (6.2)	30 (6.4)	8 (5.4)
6	29 (4.7)	23 (4.9)	6 (4.0)
7	29 (4.7)	19 (4.1)	10 (6.7)
8	23 (3.7)	11 (2.4)	12 (8.1)
9	18 (2.9)	11 (2.4)	7 (4.7)
≥10	43 (7.0)	24 (5.1)	19 (12.7)

Values are presented as number (%).
BMP, bone morphogenic protein.

Results

The mean number of fused levels was higher in the BMP group than in the non-BMP group (5.1 versus 3.4, $p<0.001$) (Table 2); 63.1% and 45.4% of procedures in the BMP group than in the non-BMP groups, respectively, involved fusions of ≥3 levels ($p<0.001$). Not unexpectedly, the significantly increased number of levels fused in the BMP group led to a trend in a longer overall surgery duration in this group relative to the non-BMP group, although this trend was not statistically significant (410.5 minutes versus 378.4 minutes, $p=0.093$). However, there was a significant reduction in the time spent per level (surgical time divided by number of levels fused) in the BMP group compared with that in the non-BMP group (131.7 minutes versus 187.9 minutes, $p<0.001$). The two groups did not differ significantly with respect to the length of stay (BMP versus non-BMP, 8.5 days versus 10.4 days; $p=0.62$), reoperation rate (odds ratio [OR], 1.37; 95% confidence interval [CI], 0.62–3.00; $p=0.43$), or the mean minimum postoperative hemoglobin level (BMP versus non-BMP, 9.4 versus 9.5; $p=0.88$).

At a per-level fused basis, the BMP group exhibited significant reductions relative to the non-BMP group in intraoperative (66.1 mL per-level fused basis; 95% CI, 127.9–4.25 mL; $p=0.036$) and total blood perioperative blood loss (100.7 mL per-level fused basis; 95% CI, 200.9–0.5 mL; $p=0.049$). However, no significant difference was observed when the analysis was not controlled for the number of levels or if the postoperative drain output alone was evaluated (Table 3). Significantly higher rates of blood (OR, 1.81; 95% CI, 1.1–2.98; $p=0.02$) and platelet transfusions were observed in the BMP group (OR, 3.55; 95% CI, 1.55–8.15; $p=0.003$), however, cases in which BMP was used involved significantly higher number of levels fused.

Twenty-two instances of VTE were observed in the study population during a 6-week postoperative period; of these, 11 cases (1.8%) involved only acute deep venous thrombosis and 11 (1.8%) developed pulmonary embolism. In the BMP group, three patients with deep vein thrombosis (DVT, 2%) and three with pulmonary embolism (PE, 2%) received BMP compared with 1.7% of patients in the non-BMP group who developed either a DVT or a PE. No allergic reactions to BMP were documented.

Twenty-one reoperations (4.5%) were performed within 30 days of the index surgery in the non-BMP group versus 10 (6.6%) in the BMP group ($p=0.64$). The reasons for reoperation included infection (13 in non-BMP and six in BMP), implant malposition or inadequate decompression

Table 3. BMP versus no BMP, adjusted for propensity score and length of surgery

Outcome	Propensity as covariate		
	Estimate or odds ratio	95% confidence interval	*p*-value
Intraoperative blood loss	80.9[a]	-90.0 to 251.3	0.35
Drain blood loss	140.8[a]	-8.8 to 290.3	0.065
Total blood loss	211.2[a]	-46.5 to 468.9	0.11
Intraoperative blood loss per level	-66.1[a]	-127.9 to -4.25	0.036
Drain blood loss per level	-32.4[a]	-85.5 to 20.7	0.23
Total blood loss per level	-100.7[a]	-200.9 to -0.5	0.049
Got red blood cells	1.81[b]	1.10 to 2.98	0.020
Got fresh-frozen plasma	2.40[b]	0.81 to 7.08	0.11
Got cryoprecipitate	1.27[b]	0.32 to 4.97	0.73
Got platelets	3.55[b]	1.55 to 8.15	0.003
Got cell saver	0.99[b]	0.61 to 1.58	0.95
Got transfusion	0.995[b]	0.57 to 1.75	0.98
Admitted to intensive care unit	1.62[b]	0.96 to 2.72	0.070
Reoperation	1.37[b]	0.62 to 3.00	0.43

BMP, bone morphogenic protein.
[a]BMP–no BMP. [b]BMP vs. no BMP.

(three in non-BMP and one in BMP), postoperative hematoma (two in the non-BMP group), hernia (two in the BMP group), dura leakage (two in non-BMP and one in BMP), and pelvic fracture (one in the non-BMP group).

Discussion

RhBMP-2 is widely used as an osteoinductive adjuvant to promote fusion during spinal surgery. The literature contains a significant number of studies pertaining to its use (both on- and off-label uses) relative to ICBG and evaluating fusion rates, surgery durations, hospital stay lengths, complication rates, and patient outcome scores [1,3,5,6,8-20]. However, there is a relative dearth of information in the literature regarding the effects of the use of rhBMP-2 on perioperative blood loss. Indeed, few studies have specifically addressed intraoperative blood losses in their analyses of BMP [5,6,8-10] and none have specifically examined postoperative blood losses via drain output.

Our study findings indicate that the use of rhBMP-2 reduced the intraoperative and total blood losses on a per-level fused basis. This pragmatic review of cases performed at a single quaternary academic center is primarily limited by a bias toward the use of BMP in fusion surgeries involving more than 3 levels ($p<0.001$). Therefore, to truly assess the effect of the use of BMP on the total blood loss in this study, we were required to control for the number of levels fused. Without controlling for this parameter, we observed no significant difference in intraoperative, postoperative, or total blood loss. In contrast, when we controlled for the number of levels fused, we observed clear reductions in the intraoperative and total blood losses but not in the postoperative drain output. We also observed a per-level fused reduction in the surgical duration when BMP was used. These findings are probably best explained by the increased time and bleeding associated with ICBG harvesting because the authors are unaware of any intrinsic properties of BMP that would reduce blood losses. In our attempt to exclude potential confounders, we did not identify any other aspects of the surgical or anesthetic technique with known hemostatic effects (i.e., the use of TXA or topical thrombin mixed with collagen powder) that differed significantly between the two groups. We previously evaluated the effect of the use of TXA in this patient cohort and found that this agent (administered as a bolus and then via continuous infusion until skin closure) independently reduced intraoperative, postoperative, and total perioperative blood loss [21]. However, we observed higher risks of blood and platelet transfusion in the BMP group along with a non-significant increase in the ICU admission rate. These findings may be attributable to the higher proportions of 10+ level fusions and patients with a history of spinal surgery in the BMP group.

One particularly interesting finding is the lack of difference in the total and per-level fused postoperative drain outputs in contrast to the expectation that the reduction in intraoperative blood loss would continue postoperatively. Although the reason for this finding is unclear, BMP may cause a delayed bleeding response that would offset the reduction in bone graft harvest-related bleeding. This tendency toward delayed bleeding is consistent with that reported in a previous report by Shields et al. [20], who observed a high rate of postoperative hematoma among patients with anterior cervical discectomy and fusion who received high-dose rhBMP-2 therapy. Specifically, 11 of the 15 patients were diagnosed with a hematoma on postoperative day 4–5, suggesting an element of delayed bleeding with the use of rhBMP. Alternatively, this postoperative drain output may represent seromatous fluid, a consequence of the proinflammatory effects of rhBMP [22]. Although at best, the potential cause of the postoperative drain output following the use of rhBMP is conjecture, this topic has clinical relevance. Anecdotal experience at Mayo Clinic indicates that the off-label use of BMP during posterior spinal fusion surgery can lead to symptomatic seromas, which may require reoperation. The fact that the use of BMP does not reduce postoperative drain output, despite intraoperative reductions in blood losses and surgical time, emphasizes the need for subfascial drain placement after all open posterior spinal fusion surgeries in which BMP is used. At our institution, these drains are routinely placed for at least 2–3 days.

Several studies have also shown reductions in intraoperative blood loss with the use of rhBMP-2. Burkus et al. [5] published a prospective randomized multicenter study with 131 patients undergoing single-level anterior lumbar interbody arthrodesis, in which they compared rhBMP-2 with ICBG. The authors reported an average intraoperative blood loss of 87.4 mL in the rhBMP-2 group compared with 184.7 mL in the ICBG group ($p<0.001$). This single-level reduction in blood loss is within the range predicted by our analysis. Dimar et al. [6] published a prospective randomized study, in which ICBG and rhBMP-2

were compared in the context of single-level posterolateral fusions. The authors investigated a range of outcomes and found an average blood loss of 273 mL in the rhBMP-2 group versus 465 mL in the ICBG group (p<0.001), which was a larger reduction than that observed in our study [6].

We note that the literature does not universally report a reduction in blood loss with the use of rhBMP-2. Boden et al. [8,9] published two prospective randomized trials comparing ICBG and rhBMP-2 in single-level fusions and did not find a statistically significant difference in blood losses between the groups in either study, although the average blood loss was lower in the rhBMP-2 groups in both studies. Haid et al. [10] published a large (14-center) prospective randomized trial of single-level fusions and also failed to identify a statistically significant reduction in blood loss with rhBMP-2. However, all three of these studies specifically evaluated intraoperative blood loss and did not consider postoperative blood loss. Given these limitations, our study was the first to our knowledge to examine the intraoperative and postoperative blood losses and blood losses during multi-level fusions in the context of the use of rhBMP-2. These findings allowed us to generate an estimated blood loss reduction with the use of rhBMP-2 on a per-level fused basis, which is unique in the literature.

However, our study had several limitations. First, our study exhibited a relatively high degree of heterogeneity in terms of surgical procedures because all thoracic and lumbar fusion procedures at our institutions that met the inclusion criteria were included. The most significant form of heterogeneity involved the number of levels fused. We controlled for this heterogeneity by normalizing the output values by the number of levels fused. Second, although we attempted to statistically control for demographic factors in our propensity scores, our demographic review could not fully capture all the clinical factors that may have factored into the surgeons' decisions to use rhBMP-2 as opposed to ICBG and may therefore have confounded our results. Third, the blood salvage effect identified in this study may have been negated or at least reduced if local autograft and allograft bone were used in lieu of the ICBG harvest.

Conclusions

In conclusion, the use of rhBMP-2 reduced intraoperative and total blood loss relative to the use of ICBG during lumbar and thoracic fusions when examined on a per-level fused basis in an analysis controlled for operative time. However, rhBMP-2 did not appear to reduce the postoperative drain output. Although we observed no differences in the postoperative drain output volumes between the BMP and non-BMP groups, we recommend that postoperative subfascial drains remain a standard practice to protect against symptomatic compressive seroma when performing posterior thoracic or lumbar fusion together with an off-label application of rhBMP-2. Finally, although we observed higher rates of blood and platelet transfusions with rhBMP-2, we consider this likely secondary to the higher proportion of large fusions in the rhBMP-2 group.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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