Surgical Neurology International

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Editor-in-Chief: **James I. Ausman**, MD, PhD University of California, Los Angeles, CA, USA

Original Article

Safety and efficacy of rhBMP2 in posterior cervical spinal fusion for subaxial degenerative spine disease: Analysis of outcomes in 204 patients

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Received: 27 April 11 Accepted: 7 July 11 Published: 13 August 11

This article may be cited as:
Xu R, Bydon M, Sciubba DM, Witham TF, Wolinsky J, Gokaslan ZL, *et al.* Safety and efficacy of rhBMP2 in posterior cervical spinal fusion for subaxial degenerative spine disease: Analysis of outcomes in 204 patients. Surg Neurol Int 2011;2:109.

Available FREE in open access from: http://www.surgicalneurologyint.com/text.asp?2011/2/1/109/83726

Abstract

Background: Many studies offer excellent demonstration of the ability of bone morphogenic protein (BMP) to enhance fusion rates in anterior as well as posterior lumbar surgery. Recently, BMP has also been shown to increase arthrodesis rates in anterior cervical surgery, albeit with concomitant increases in complication rates. To date, however, few studies have investigated the safety and efficacy of BMP in cervical surgeries approached posteriorly.

Methods: We retrospectively reviewed 204 consecutive patients with degenerative cervical spinal conditions necessitating posterior cervical fusion at a single institution over the past 4 years. The incidence of postoperative mechanical neck pain, fusion rates, as well as neurologic outcomes were compared between patients who received BMP vs those who did not receive BMP intraoperatively.

Results: There were no significant differences in preoperative variables between the non-BMP vs the BMP cohorts. Over an average follow-up of 24.2 months, there were no significant differences between the two cohorts in duration of hospitalization, cerebrospinal fluid leakage, deep vein thrombosis, pulmonary embolism, hyperostosis, infection, pneumonia, hematoma, C5 palsy, wound dehiscence, reoperation rates, or Nurick/ASIA scores. Eleven (7.1%) patients in the non-BMP group experienced instrumentation failure vs none in the BMP group (P=0.06). Patients receiving BMP had a significantly increased rate of fusion by the chi-square test (P=0.01) and the log-rank test (P=0.02). However, patients receiving BMP also had the highest rates of recurrent/persistent neck pain by the chi-square test (P=0.003) and the log-rank test (P=0.01).

Conclusions: To date, few studies have evaluated the safety and efficacy of BMP in the posterior cervical spine. Here, we show that BMP usage does not increase complication rates, but it significantly increases arthrodesis rates and also may increase the rate of recurrent/persistent neck pain.

Key Words: Arthrodesis, cervical, fusion, neck pain, non-fusion, pseudoarthrodesis

Access this article online

Website: www.surgicalneurologyint.com

DOI: 10.4103/2152-7806.83726

Quick Response Code:

INTRODUCTION

At present, there exists little data on the safety and efficacy of bone morphogenic protein (BMP) usage in posterior cervical fusion procedures. In 2009, Cahill *et al.* examined the prevalence of BMP usage in spinal fusion procedures and the complications, and cost of treatment associated with its use from 2002–2006 in the nationwide inpatient sample database and found that unlike anterior cervical fusion procedures, posterior cervical fusion procedures did not demonstrate a statistically increased risk for postoperative dysphagia/hoarseness or wound complications.[4] Nevertheless, their analysis was not able to measure definitive endpoints of BMP usage, such as success of arthrodesis, resolution of presenting symptoms, or neurologic outcome.

In this retrospective analysis, we present the outcomes of patients undergoing posterior cervical fusion for subaxial degenerative spinal pathologies at a single institution in order to better understand the benefits and potential drawbacks of BMP use in the posterior cervical spine. We compare the preoperative characteristics, intra-/perioperative factors, as well as postoperative outcomes of control patients vs patients treated with BMP.

MATERIALS AND METHODS

We reviewed patient data obtained for 204 patients undergoing posterior cervical arthrodesis for symptomatic primary degenerative cervical pathologies over the past 5 years at our institution. Patients receiving posterior cervical fusion due to trauma, tumor, or infectious etiologies were excluded, as were patients who only received C1-C2 fusion. Patients with systemic metabolic disorders that secondarily affect bone quality—such as renal osteodystrophy—were not included in our study. Patient demographics and presenting symptoms were documented, and preoperative neurologic function was assessed from clinic notes on the Nurick and ASIA scales. The age, sex, and comorbidities of patients were comparable in the treatment and control groups [Table 1]. None of the presenting preoperative symptoms or lengths of duration differed statistically between treatment vs control groups. Moreover, patients did not differ significantly in neurologic function preoperatively as assessed on both the Nurick and ASIA scales (P=0.11 and P=.10, respectively).

Operative notes were reviewed for the use of BMP, demineralized bone matrix (DBM), local autograft, allograft, and/or hydroxyapatite crystals. Intra- and perioperative data were obtained from operative, discharge, and clinic notes. Postoperative follow-up durations as well as functional outcomes were ascertained from follow-up clinical notes and telephone calls. The presence of bony fusion was determined radiographically using both plain radiographs and CT images.

Pre-, intra-, and postoperative variables were compared between the treatment cohort (patients who received BMP intraoperatively) vs the control group (patients who did not receive BMP) using the Student's *t*-test for continuous, normally distributed data, and the Mann–Whitney U test for continuous non-Gaussian data (reported as medians, with interquartile range) or non-continuous data. Categorical data were compared with the chi-squared test. Data analysis was performed using Prism 5® (GraphPad Software Inc.). Statistical significance was defined as $P<0.05$.

Kaplan-Meir curves of postoperative neck pain and presence of radiologic fusion were generated and compared between the treatment vs control groups using the log-rank (Mantel-Cox) analysis. Patients with less than 6 months follow-up were excluded. Data analysis was performed on Prism 5® (GraphPad Software Inc.). Cox proportional hazard regression models were generated for treatment vs control groups for both postoperative neck pain and fusion status. Data analysis was performed on StatView 5.0® (SAS Institute Inc.). Statistical significance for all tests and regression models was defined as $P<0.05$.

RESULTS

Intra-/perioperative outcomes

In general, for patients who do not receive BMP, it is the practice at our institution to give DBM and allograft ($P<0.0001$ for both variables) [Table 2]. The majority of patients in both cohorts received local autograft bone. Those patients who received BMP also received concomitant hydroxyapatite crystal application ($P<0.0001$). There was no statistically significant difference in the amount of intraoperative blood loss or incidental durotomies between patients in the two cohorts [Table 2].

The non-BMP treatment group experienced the only cases of CSF leakage [2 patients (1.3%)], deep vein thrombosis (DVT) [3 patients (1.9%)], and pulmonary embolism (PE) [2 patients (1.3%)], although this was not statistically significant [Table 3]. There was no significant difference between the groups in rates of infection (P=0.93), dysphagia (P=0.48), pneumonia (P=0.85), hematoma (P=0.94), C5 palsy (P=0.62), wound dehiscence (P=0.37), reoperations (P=0.36), or discharges to rehabilitation (P=0.29). Of note, 11 (7.1%) patients in the non-BMP group experienced instrumentation failure (screw pullout, instrumentation breakage, or halo sign) vs none in the BMP group. This approached but did not reach statistical significance (P=0.06).

Postoperative outcomes

Patients were followed-up for an average of 24.2±10.1

Table 1: Characteristics of all patients undergoing surgical management of degenerative cervical spinal disease via a posterior approach

Characteristics	Total Patient No.	Non-BMP	BMP	*P* value
Number of cases	204	156	48	
Age (mean)	60.7 ± 13.3	60.8 ± 12.7	60.3 ± 15.0	0.74
Sex (Male%)	123 (60.3)	100 (64.1)	23 (47.9)	0.05
Co-morbidities				
Diabetes (%)	48 (23.8)	39 (25.0)	8 (15.1)	0.12
Coronary artery disease (%)	28 (13.9)	23 (14.7)	6 (11.3)	0.57
Osteoporosis (%)	9 (4.5)	5 (3.2)	4 (8.7)	0.11
Obesity (%)	23 (11.4)	18 (11.5)	5 (9.4)	0.55
Smoking History (%)	50 (24.8)	35 (22.4)	16 (30.2)	0.35
Hypertension (%)	106 (52.5)	85 (53.8)	25 (47.2)	0.29
Previous Surgery (%)	56 (27.7)	42 (26.9)	16 (30.2)	0.86
Presenting Symptoms				
Back Pain (%)	134 (65.7)	99 (63.5)	35 (72.9)	0.15
Length of back pain symptoms (mo) Median (IQR)	12 (6, 36)	12 (4, 36)	12 (7.75, 30.75)	0.40
Radiculopathy (%)	82 (40.6)	64 (41.0)	18 (39.1)	0.55
Length of radicular symptoms (mo) Median (IQR)	9 (4, 24)	9 (3.5, 24)	9 (4.5, 12)	0.69
Motor Weakness (%)	157 (77.7)	124 (79.5)	33 (71.7)	0.12
Length of weakness symptoms (mo) Median (IQR)	6 (3, 13.5)	6 (3, 12)	8 (3, 17.3)	0.07
Sensory Deficits (%)	110 (54.5)	85 (54.5)	25 (54.4)	0.78
Length of sensory symptoms (mo) Median (IQR)	6.5 (3, 12.0)	6 (2, 13.5)	8 (3, 12)	0.32
Bowel/Bladder dysfunction (%)	44 (21.9)	36 (23.1)	8 (17.8)	0.48
Length of BB symptoms (mo) Median (IQR)	3.5 (2, 12)	4 (1.5, 12)	3 (3, 7)	0.38
Nurick Score	2.47 ± 1.39	2.51 ± 1.36	2.37 ± 1.51	0.11
ASIA Score	3.91 ± 0.74	3.88 ± 0.75	4.02 ± 0.68	0.10

BMP: Bone morphogenic protein

months (range: 1–39.6 months. During this period, 169 patients (82.8%) had radiographic follow-up times of greater than 6 months. Of these, 154 (91.1%) had spinal fusion as demonstrated by CT imaging and x-rays. While 48 (100%) patients in the BMP treatment group experienced arthrodesis, 106 (87.6%) had documented fusion in the control group [Table 3]; this was statistically significant (P=.01). Kaplan-Meier analysis showed that patients who did not receive BMP were more likely to experience non-fusion over time (P=.026) compared to patients who did receive BMP [Figure 1].

Fifty (28.9%) patients experienced recurrent neck pain during the follow-up period. Interestingly, 31 (23.3%) patients were in the non-BMP treatment group and 19 (47.5%) were in the BMP group. Thus, at last follow-up, patients who received BMP were more likely to experience neck pain (P=.003). Kaplan Meier analysis showed that when time was taken into account [Figure 2], this trend still held true (P=0.01). At last follow-up, patients improved neurologically on both the Nurick and ASIA scales, although final neurologic outcomes were not statistically significantly different between the treatment vs control groups. Notably, no patient in either cohort had clinically significant neurologic deficit attributable to hyperostosis on CT.

DISCUSSION

Although posterior cervical fusions are performed on fewer cases as compared to anterior cervical fusions, the rate of these procedures has increased markedly over the last 20 years. From 1990–2000, the number of posterior fusions increased 330%, and from 1992–2005, by 464%.[21,34] Commensurate with this rise in cervical fusions has been a large increase in the frequency of BMP usage. Cahill *et al*. reported that the national rate of BMP application increased from less than 1% of all fusions in 2002 to close to 25% of all fusions in 2006.[4] As BMP use has been associated with increases of 11%–41% in total hospital

Table 2: Intraoperative variables for surgical management of cervical degenerative disease via a posterior approach

Characteristics	Total Patient No.	Non-BMP	BMP	*P* Value
Number of cases	204	156	48	
Levels Fused (%)	5.9 ± 1.9	5.8 ± 1.8	6.3 ± 2.2	0.18
Demineralized bone matrix (%)	149 (73.0)	134 (85.9)	15 (31.3)	<0.0001
Autograft (%)	174 (85.3)	137 (87.8)	37 (77.1)	0.07
Allograft (%)	123 (60.3)	113 (72.4)	10 (20.8)	<0.0001
Hydroxyapatite crystals (%)	28 (13.9)	0 (0.0)	28 (60.9)	<0.0001
Blood Loss (mLs): Median (IQR)	300 (200, 500)	300 (200, 425)	500 (200, 700)	0.45
Incidental durotomy	4 (1.9)	4 (2.6)	0 (0.0)	0.26

BMP: Bone morphogenic protein

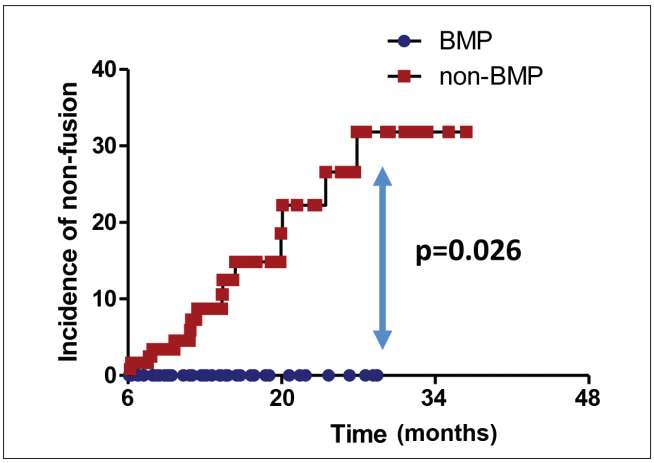

Figure 1: Kaplan-Meier plots of postoperative nonfusion. Patients who did not receive bone morphogenic protein had a significantly higher chance of non-fusion over time (*P*=0.026) when compared with patients who received bone morphogenic protein

Table 3: Perioperative variables for surgical management of cervical degenerative disease via a posterior approach

Characteristics	Total Patient No.	Non-BMP	BMP	*P* Value
Number of cases	204	156	48	
Length of Hospitalization	7.1 ± 6.4	7.4 ± 6.9	6.1 ± 4.7	0.23
CSF Leakage (%)	2 (0.1)	2 (1.3)	0 (0.0)	0.43
DVT (%)	3 (1.5)	3 (1.9)	0 (0.0)	0.33
PE (%)	2 (0.1)	2 (1.3)	0 (0.0)	0.43
Hyperostosis (%)	0 (0.0)	0 (0.0)	0 (0.0)	1.00
Infection (%)	22 (10.9)	17 (10.9)	5 (10.9)	0.93
Pneumonia (%)	5 (2.5)	4 (2.0)	1 (2.2)	0.85
Dysphagia (%)	9 (4.4)	6 (3.8)	3 (6.3)	0.48
Hematoma (%)	4 (2.0)	3 (1.9)	1 (2.2)	0.94
C5 Palsy (%)	10 (5.0)	7 (4.5)	3 (6.5)	0.62
Wound Dehiscence (%)	9 (4.5)	8 (5.1)	1 (2.2)	0.37
Instrumentation Failure (%)	11 (5.4)	11 (7.1)	0 (0.0)	0.06
Reoperation (%)	39 (19.3)	32 (20.5)	7 (15.2)	0.36
Discharge to Rehabilitation (%)	68 (33.8)	55 (35.4)	13 (28.3)	0.29
Fusion (%)	154 (91.1)	106 (87.6)	48 (100.0)	0.01
Neck pain at last follow up (%)	50 (28.9)	31 (23.3)	19 (47.5)	0.003
Nurick score at last follow up (%)	1.34 ± 1.51	1.34 ± 1.49	1.30 ± 1.15	0.61
ASIA score at last follow up (%)	4.39 ± 0.78	4.39 ± 0.78	4.39 ± 0.80	0.96

BMP: Bone morphogenic protein

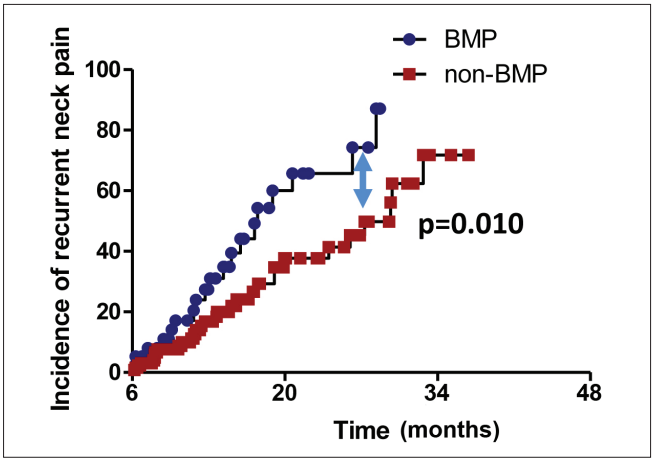

Figure 2: Kaplan-Meier plots of postoperative recurrent neck pain over time. Patients who received bone morphogenic protein had a significantly higher chance of recurrent neck pain (*P*=0.010) compared to patients who did not receive bone morphogenic protein

charges, as well as longer lengths of hospitalization for patients,[3,6–8,15–16,21,24,26,31] it is imperative to fully understand the risks and benefits of BMP.

To the best of our knowledge, our manuscript is the first to summarize the outcomes of patients treated with BMP in posterior cervical fusions, and to compare these results with a control group. Like Cahill *et al.* we found no statistically significant difference in total complications between BMP vs non-BMP (autograft, allograft, and/or DBM)-treated patients undergoing posterior cervical fusion. In our series we specifically looked at blood loss, incidental durotomy, CSF leakage, DVT, PE, wound infection, pneumonia, dysphagia, hematoma, C5 palsy, wound dehiscence, instrumentation failure (11 in the non-BMP group vs 0 in the BMP group; this approached, but did not reach significance), and reoperation rates; we found no statistically significant difference between

the two groups.[4] Our control group had complications comparable with that reported in other cervical fusion case series.[1-5,8-14,17-20,22-35] Unlike Cahill *et al*. who found a 12.1% increase in length of hospitalization for posterior cervical fusions, we found that patients who received BMP had approximately the same — if not slightly shorter — length of hospitalization (BMP vs non-BMP, 6.1±4.7 days vs 7.4±6.9 days; P=0.23).

Importantly, patients who received BMP with instrumented fusion had a statistically higher rate of arthrodesis compared with those receiving DBM, autograft, and/or allograft alone, both over time and at last follow-up [Figure 1]. In addition, with our maximum dose of 8 cc/12 mg (standard large kit of INFUSE®, Medtronic), neither the BMP treatment group nor the control group experienced symptomatic spinal cord compression due to hyperostosis within the spinal canal. However, it is important to keep in mind that those who received BMP also had the highest recurrence rate for neck pain [Figure 2]. As this neck pain is not due to pseudarthrosis or instability, it is likely that this pain is multifactorial in etiology. Although no inflammatory radiculitis was noted in patients receiving BMP, it is possible that the increased inflammation associated with BMP may play a contributory role in the postoperative neck pain.[26] BMP dosage has been proposed as a factor contributing to unwanted side effects, and future studies need to explore the possibility that BMP dose is correlated to persistent/recurrent postoperative neck pain.

One must acknowledge that as with all retrospective studies, the patient cohorts in this study are nonrandomized and thus subject to selection bias. Nonetheless, we attempted to minimize bias by only including patients with degenerative cervical disease and only those with subaxial pathologies. Moreover, by demonstrating that the two cohorts were not significantly different with regard to comorbidities or presenting symptoms, we hoped to control for such biases during data analysis.

CONCLUSIONS

We conducted a retrospective analysis of 204 who underwent instrumented posterior fusion, with or without BMP, for degenerative cervical pathologies. Patients were followed up for 24.2±10.1 months and, during this time, patients who underwent fusion with BMP were statistically more likely to undergo arthrodesis compared to the non-BMP treatment group. However, patients who underwent fusion with BMP were also statistically more likely to experience postoperative persistent/recurrent neck pain. Equally important is the finding that BMP use in posterior cervical fusions does not increase complication rates compared with non-BMP control patients. This is one of the first retrospective studies to quantitatively examine the risks and benefits of BMP use in the posterior cervical spine. Additional prospective studies should be performed to corroborate our findings.

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