



Clinical commentary

Recombinant human bone morphogenetic protein-2 versus iliac crest bone graft in anterior cervical discectomy and fusion: Dysphagia and dysphonia rates in the early postoperative period with review of the literature



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ABSTRACT

Recombinant human bone morphogenetic protein-2 (rhBMP-2) is a growth factor utilized to stimulate bone development in several clinical scenarios. Although the U.S. Food and Drug Administration approved this therapeutic modality for only two applications, it is frequently used off-label in anterior cervical discectomy and fusion (ACDF) procedures as an alternative to iliac crest bone graft (ICBG), the prior standard of care. This usage has been a source of controversy in the medical community due to evidence of increased rates of postoperative edema and dysphagia. This retrospective cohort study investigates two groups of 200 patients having undergone ACDF, one using rhBMP-2 and the other using ICBG, to evaluate the incidence of complications in the early postoperative period. A significant reduction in average length of stay was found in the rhBMP-2 cohort (1.40 days) compared to the ICBG cohort (1.85 days) as well as a significantly increased rate of dysphagia (25.5% in rhBMP-2 vs. 15% in ICBG; $p = 0.01$). An increased rate of dysphonia was observed among patients undergoing revision surgery (25.0%) compared to primary surgery (1.6%), but stratification by number of levels, gender, and smoking status yielded no differences in complication rates. Our evaluation of two large cohorts along with review of the literature on the topic sheds light on potential benefits and risks of rhBMP-2 in ACDF procedures. Further investigation is warranted to determine if clinical gains outweigh the potential harms of rhBMP-2 use in this setting.

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1. Introduction

Bone morphogenetic proteins (BMPs) are a large family of signaling molecules recognized as essential mediators of bone, cartilage, and blood vessel formation [1]. Of particular interest to spine surgeons is recombinant human bone morphogenetic protein-2 (rhBMP-2), which has been shown to be a potent stimulator of bone formation [2].

Currently, rhBMP-2 has just two indications approved by the U.S. Food and Drug Administration (FDA): for single-level anterior

lumbar interbody fusion (ALIF) and for open tibial fractures treated with an intramedullary nail within 14 days of injury [3]. rhBMP-2 is used off-label for a number of additional indications, notably as an alternative or supplement to bone graft in anterior cervical discectomy and fusion (ACDF) procedures.

Currently, the gold standard for osteogenic supplementation in ACDF procedures is autogenous iliac crest bone graft (ICBG); however, rhBMP-2 has the advantage of eliminating the need for graft harvest from the iliac crest and the morbidity associated with this procedure [2]. Furthermore, rhBMP-2 has been shown to provide similar or better fusion rates compared to ICBG in lumbar and cervical fusion procedures [4–7]. Unfortunately, rhBMP-2 use in ACDF has been associated with relatively high complication rates, specifically postoperative edema and dysphagia [7–17]. In July 2008, the FDA released a Public Health Notification to practitioners, alerting

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them to the association between certain life-threatening complications and the use of BMPs in the cervical spine.

This study aims to assess the association of rhBMP-2 in ACDF procedures with significant early postoperative complications, with a specific focus on dysphagia, and to compare early ACDF complications with rhBMP-2 to those encountered following ACDF with ICBG.

2. Methods

Four-hundred patients who underwent ACDF with a single surgeon at a single surgical center were assessed retrospectively for early postoperative complications. The first group of 200 patients was identified and treated consecutively with an ACDF procedure using iliac crest autograft from November of 1996 to September of 2001. A second group of 200 patients was identified and treated consecutively with an ACDF procedure using rhBMP-2 (INFUSE[®]; extra small pack; Medtronic Sofamor Danek, Minneapolis, MN) and freeze-dried allograft bone (Cornerstone[®] bone) from June 2007 to April 2012. Oncologic cases and cases involving a corpectomy were excluded.

All ACDF procedures were accomplished using the same surgical protocol with the exception of the use of iliac crest autograft versus rhBMP-2 in the two respective cohorts. The iliac crest bone grafting was accomplished with a standard approach to the iliac crest for harvesting. For patients treated with rhBMP-2, an extra small INFUSE[®] pack of rhBMP-2 was opened. For each level fused, one-third of an extra small INFUSE[®] pack (2.1 mg rhBMP-2 total) was used, amounting to 0.7 mg of rhBMP-2 per level. For all patients, the fusion site was reinforced with an ACDF plate (ICBG patients were plated with either the Medtronic Atlantis Translational[®] anterior cervical plate system or the Medtronic Orion[®] plate system; rhBMP-2 patients were plated with the DePuy Skyline[®] plate system). All wounds were irrigated with 100–200 mL of an antibiotic solution prior to closure over a Penrose drain.

The primary outcomes gathered were early postoperative complications. Secondary outcomes gathered were length of stay postoperatively and need for postoperative steroids.

All statistical analyses were performed using R version 3.3.2 (The R Foundation for Statistical Computing, <https://www.r-project.org/>). Two-tailed Student *t* tests were used to compare quanti-

Table 1
Patient Demographics.

Demographic	rhBMP-2	ICBG	P-value
Number of Patients	200	200	
Mean age (range)	52.4 (28–87)	44.9 (22–79)	<0.01 ^a
Sex			
Male	112 (56%)	118 (59%)	0.61
Female	88	82	
Smoking History			
Yes	36 (18%)	21 (10.5%)	0.045 ^a
No	164	179	
Indication			
Disk Herniation	143	139	0.74
Spondylosis	44	44	1
Spondylolisthesis	5	4	1
Revision (Adjacent Segment Disease)	5	7	0.77
Revision (Pseudarthrosis)	3	6	0.5
Levels Instrumented			
Single-Level	104 (52%)	124 (62%)	0.05 ^a
Multiple-Level	96	76	

rhBMP-2: recombinant human bone morphogenetic protein-2; ICBG: iliac crest bone graft.

^a Indicates statistically significant difference.

Table 2
Distribution of Operative Levels.

Operative Levels	rhBMP-2	ICBG	P-value
Single Level	104	124	
C3-4	18	11	
C4-5	11	13	
C5-6	40	56	
C6-7	28	41	
C7-T1	7	3	
Multiple Level	96	76	
2 Level	75	68	
C3-5	3	5	
C4-6	18	15	
C5-7	51	44	
C6-T1	1	0	
C3-4, C5-6	0	4	
C3-4, C6-7	1	0	
C4-5, C6-7	1	0	
3 Level	20	8	
C3-6	5	1	
C4-7	14	6	
C5-T1	1	1	
4 Level	1	0	
C3-7	1	0	
Mean # of Levels	1.59 ± 0.05	1.42 ± 0.04	<0.01 ^a

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^a Indicates statistically significant difference.

Table 3
Complication Rates for rhBMP-2 vs. ICBG.

Cohort	rhBMP-2 (n = 200)	ICBG (n = 200)	P-Value
Dysphagia	51 (25.5%)	30 (15%)	0.01 ^a
Dysphonia	5 (2.5%)	9 (4.5%)	0.41
Postoperative Steroids	21 (10.5%)	12 (6%)	0.15
Postoperative Length of Stay (days)	1.40	1.85	<0.01 ^a

rhBMP-2: recombinant human bone morphogenetic protein-2; ICBG: iliac crest bone graft.

^a Indicates statistically significant difference.

tative data. A chi-square test for the homogeneity of proportions was used for categorical data. A Fisher exact test was utilized for those categorical data exhibiting observed cell counts of less than five.

3. Results

3.1. Demographics

Both cohorts had similar proportions of males (56% for rhBMP-2, 59% for ICBG; $p = 0.61$) and distribution of indications for surgery ($p = 0.86$). Patients in the rhBMP-2 group were older on average (52.4 years old for rhBMP-2, 44.9 years old for ICBG; $p < 0.01$) and more likely to be smokers (18% for rhBMP-2, 10.5% for ICBG; $p = 0.05$). Most patients in both cohorts underwent a single-level ACDF (57%), while 35.5% underwent a 2-level fusion, 7% underwent a 3-level fusion, and 0.5% underwent a 4-level fusion. The most common level fused in both groups was C5/6, followed by C6/7, then C4/5, and finally C3/4. Patients in the rhBMP-2 cohort were more likely to have undergone a multilevel fusion (48% for rhBMP-2, 38% for ICBG; $p = 0.05$). These results are summarized in Table 1. See Table 2 for the distribution of operative levels in both groups.

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