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Original Article

Use of recombinant human bone morphogenetic protein-2 as an adjunct for instrumented posterior arthrodesis in the occipital cervical region: An analysis of safety, efficacy, and dosing

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Abstract

Background: There have been few reports on the use of recombinant human bone morphogenetic protein (rhBMP)-2 in posterior spine. However, no study has investigated the dosing, safety, and efficacy of its use in the posterior atlantoaxial, and/or craniovertebral junction. Recent case report of the cytokine-mediated inflammatory reaction, following off label use of rhBMP-2 as an adjunct for cervical fusion, particularly in complex cases, has increased concern about complications associated with the product. **Objective:** To assess the safety, efficacy, and dosing of rhBMP-2 as an adjunct for instrumented posterior atlantoaxial and/or craniovertebral junction arthrodesis. **Materials and Methods:** We included all patients treated by the senior author that included posterior atlantoaxial and/or craniovertebral junction instrumented fusion using rhBMP-2 from 2003 to 2008 with a minimum two year follow-up. Diagnosis, levels fused, rhBMP-2 dose, complications, and fusion were assessed. **Results:** Twenty three patients with a mean age of 60.9 years (range 4 – 89 years) and an average follow-up of 45 months (range 27 to 84 months) met inclusion criteria. The indications for surgery included, atlantoaxial instability (n = 16), basilar invagination (n = 6), and kyphoscoliosis (n = 1). The specific pathologic diagnosis included type 2 dens fracture (n = 7), complex C1 and C2 ring fracture (n = 2), chordoma (n = 2), degenerative/osteoporosis (n = 3), rheumatoid disease (n = 8), and pseudogout (n = 1). The average rhBMP-2 dose was 2.38 mg/level, with a total of 76 levels treated (average 3.3 levels, SD= 1.4 levels). There were no complications. During the most recent follow-up, all patients had achieved fusion. **Conclusions:** In a series of patients with complex pathology and/or rheumatoid arthritis, 100% fusion rate was achieved with adjunct use of rhBMP-2, with a safe and effective average rhBMP-2 dose of 2.38 mg per level.

Key words: Atlantoaxial, bone morphogenetic protein, complications, craniovertebral junction

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INTRODUCTION

Since their initial discovery as a family of growth factors that induce bone formation, bone morphogenetic proteins (BMP) have by both animal and human studies been shown to facilitate spinal fusion.[1-21] Broad off label use in spine surgery to augment fusion has occurred since the United States Food and Drug Administration (FDA) approved recombinant human bone

morphogenetic protein (rhBMP-2) use with an absorbable collagen sponge scaffold (ACS, INFUSE, Medtronic Sofamor Danek, Memphis, TN) for the treatment of degenerative disc disease via anterior lumbar interbody fusion (ALIF) in an LT-CAGE (Medtronic Sofamor Danek) in skeletally mature patients in July 2002.[22]

There have been multiple studies giving conflicting accounts on the complications and/or efficacy of rhBMP-2 in both off and on label use.[6,7,14,16,18,19,23-30] Due to concern for soft tissue swelling and airway compromise in anterior cervical spine fusion with rhBMP-2,[6,31-34] the FDA recently issued a public health notification, prompting further scrutiny of off-label use of rhBMP-2. There are few reports on the use of rhBMP-2 in the posterior atlantoaxial and craniovertebral junction,[27-29] and these are primarily case reports. There is a lack of reports on the safety or efficacious dose of rh-BMP2 used in this region of the spine.

Our objectives in the present study were to report our experience on the safety, efficacy, and dosing of rh-BMP2 used as an adjunction for arthrodesis for patients warranting posterior cervical instrumented fusion that included the occiput and/or atlantoaxial levels.

MATERIALS AND METHODS

We identified all patients of the senior author who had undergone posterior cervical instrumented fusion from August 2003 to March 2008 following approval by the University of Virginia Institutional Review Board. The study cohort was narrowed to those who had undergone posterior occipito-cervical and/or atlantoaxial fusions with the use of rh-BMP2. Patient demographics, indications for surgery, number of levels fused, and amount of rhBMP-2 used were extracted. Both inpatient and outpatient clinical records were reviewed, with particular assessment for any evidence of wound issues. Bony fusion at last follow-up was assessed based on review of anteroposterior and dynamic (neutral/flexion/extension) lateral radiographic imaging by two independent neuroradiologists. Fusion grade was based on the criteria described by Lenke *et al.*[35] [Table 1].

For each case, the dose of rhBMP-2 was extracted based on the product documentation from the operating room log and matched with the surgeon's operative report. Based on the package insert from the manufacturer (Medtronic Sofamor Danek), doses of rhBMP-2 for each kit size were as follows: XX small (1.05 mg), X small (2.10 mg), small (4.2 mg), medium (8.4 mg), large (12.0 mg). The absorbable collagen sponge carrier (ACS; INFUSE, Medtronic Sofamor Danek) was used to reconstitute the rhBMP-2 as previously described.[21,36,37]

Placement of sponges and morselized allograft/ autograft was done laterally over the facets and transverse processes when there was a medial decompression, or laminar placement, if no decompression was performed. The amount of locally harvested bone was minimal and we typically used 5 cc of allograft (cancellous cubes) per level. In all adult patients, bilateral ganglionectomies and further placement of allograft/autograft

Table 1: Lenke posterior fusion grade/score with descriptions

Fusion grade	Description of fusion
A	Solid, big trabeculated fusions bilaterally
B	Solid unilateral fusion with small contralateral aspect
C	Small thin fusion masses bilaterally with possible crack
D	Graft resorption bilaterally or bilateral pseudoarthrosis

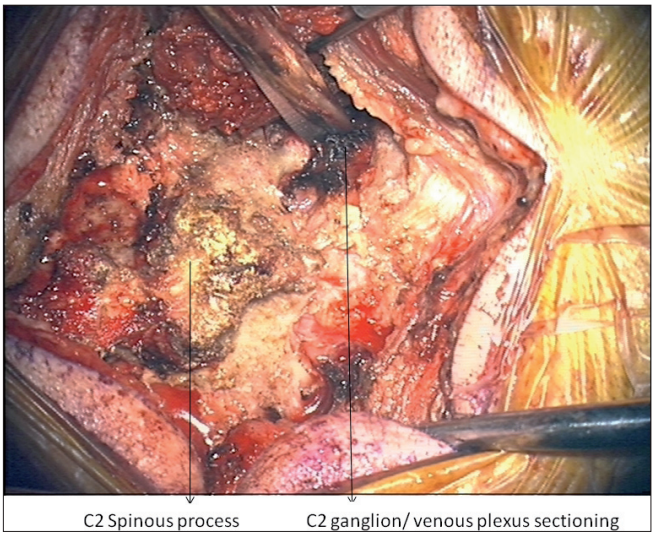

Figure 1: Intraoperative image of C2 nerve/ganglionectectomy following coagulation of nerve/venous plexus.

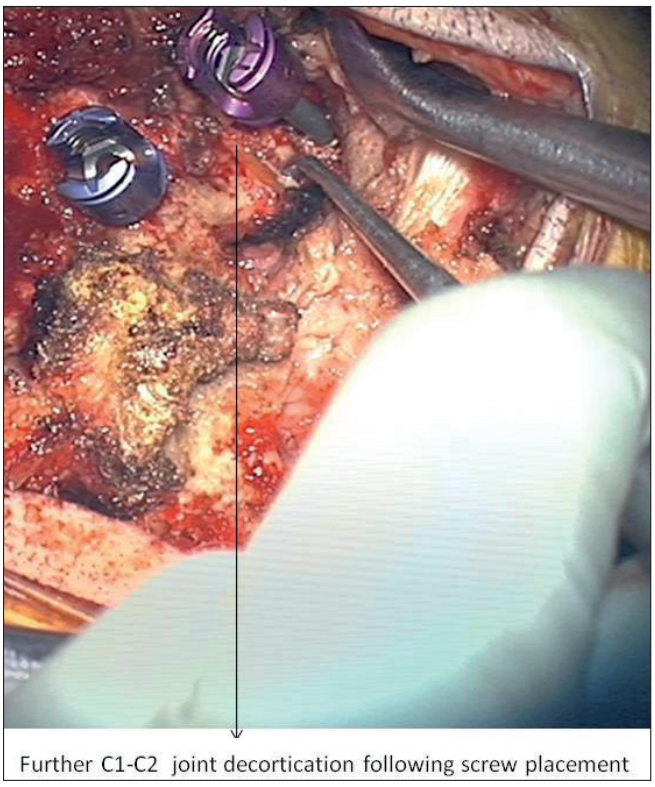

Figure 2: Further decortication of C1-C2 joint following arthrodesis.

with rhBMP-2 in the prepared joint space was performed in the following manner: first, the friable and often prominent epidural venous complex surrounding the C2 nerve complex was coagulated with bipolar electrocautery and divided. Upon isolation of the C2 nerve complex, bipolar electrocautery was again applied to the proximal and distal end of the C2 dorsal root ganglion prior to sharp division of the C2 nerve root (C2 dorsal root ganglion) as seen in Figure 1. C2 nerve root sectioning was first documented by Goel *et al*.[38,39] and further described with outcomes by Hamilton *et al*. With the visualization of the C1-C2 facets and joint space, decortication was performed as shown in Figure 2, and rh-BMP2-soaked sponge with morsellized allograft was subsequently placed bilaterally. Placement of instrumentation done as described by Goel and Lahiri in 1994.[38, 39, 40]

In no case was structural bone graft used. In occiput to cervical spine fusions, rhBMP-2 soaked sponge was covered with morselized bone graft as an onlay spanning the fusion bed. All

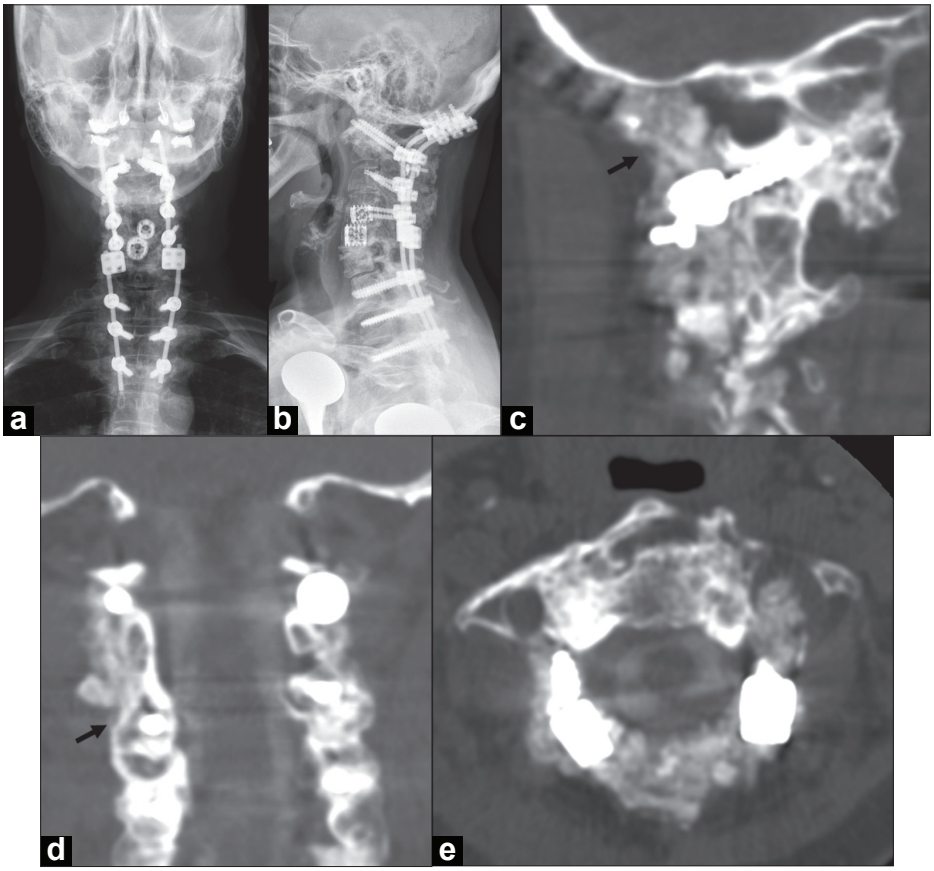

Figure 3: A 52-year-old woman with severe rheumatoid arthritis and basilar invagination. She had previously undergone multiple prior cervical procedures done at another hospital, including placement of anterior interbody cages at C4-C6. She subsequently required occipital-cervical instrumented arthrodesis and decompression using rhBMP-2 and cancellous allograft for treatment of basilar invagination. Postoperative AP and lateral radiographs are shown in panels a and b, respectively. CT imaging with sagittal (panel c) and coronal reconstructions (panel d) performed 19 months following surgery demonstrates brisk bony fusion extending from the occipital to C1 (panel c, arrow) and along the lateral masses (panel d, arrow). Axial CT imaging at the interspace of C1-C2 does not demonstrate canal encroachment (panel e).

Table 2: Characteristics of 23 patients who underwent instrumented posterior occipito-cervical fusion using rhBMP-2

Diagnosis (n)	Mean age (range) (years)	Sex	Procedure (n)	Lenke B*
Atlantoaxial instability	64 (4-89)	6 M / 10 F	2 level fusion (7)	Lenke B (1)
			3 level fusion (9)	Lenke B (1)
Basilar invagination	51 (13-82)	3 M / 3 F	3 level fusion (1)	
			4 level fusion (2)	
			5 level fusion (1)	
			6 level fusion (1)	
			7 level fusion (1)	
Kyphoscoliosis	74	1 M	6 level fusion	

* Remaining 21 cases Lenke A fusion grade

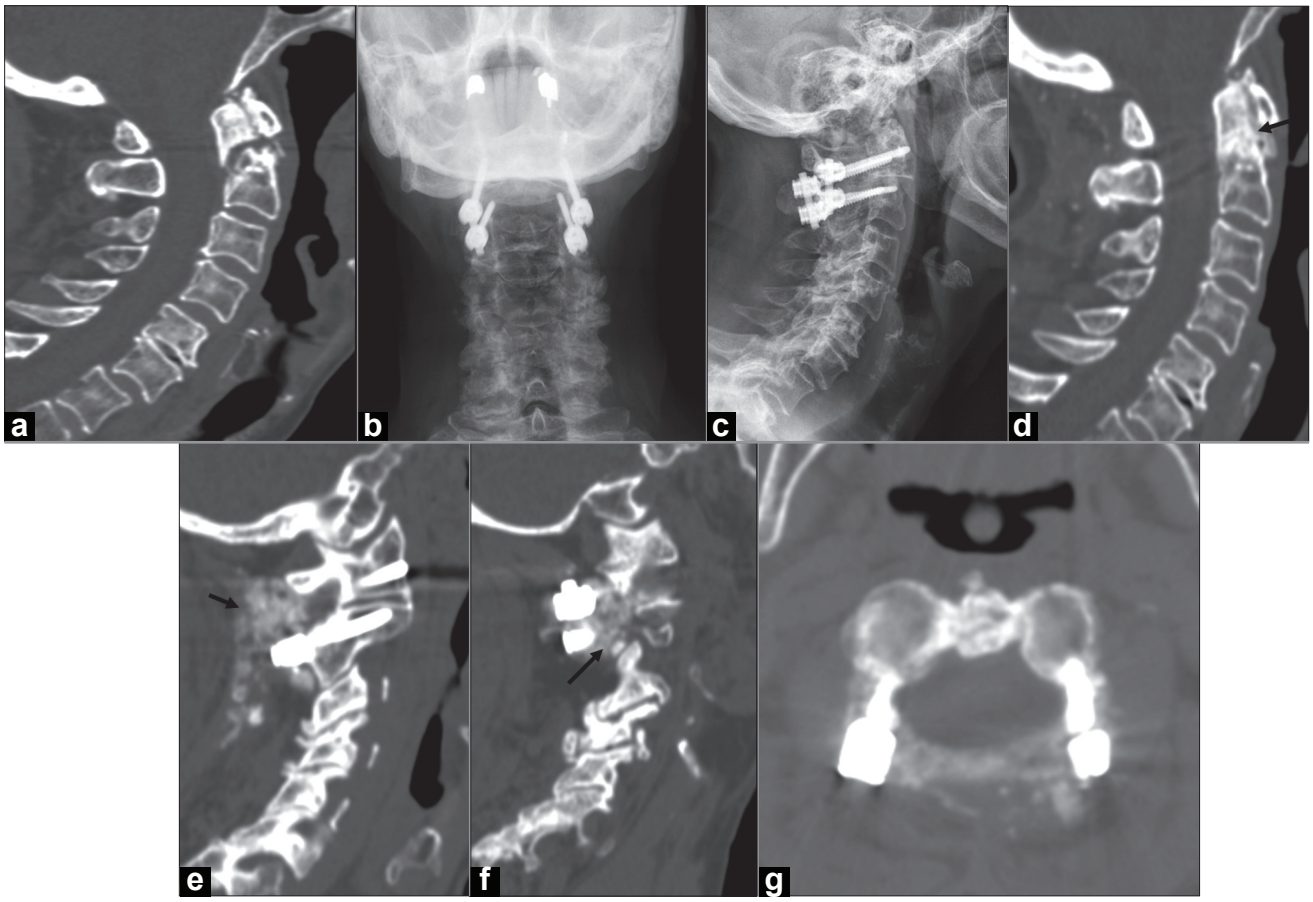

Figure 4: A 78-year-old woman with nonunion of a Type II odontoid fracture. Preoperative CT imaging with sagittal reconstruction demonstrates a Type II odontoid fracture (panel a). Postoperative plain AP (panel b) and lateral (panel c) radiographs following C1-C2 instrumented arthrodesis with C1 lateral mass and C2 pedicle screws, rhBMP-2 and cancellous allograft. CT imaging with sagittal reconstructions at one-year follow-up demonstrates healing of the odonoid fracture (panel d, arrow) and brisk bony fusion (panels E and f, arrows). Axial CT imaging at the interspace of C1-C2 does not demonstrate canal encroachment (panel g).

Table 3: Specific pathological diagnosis

	Atlantoaxial instability	Basilar invagination
Odontoid fracture†	7	0
C_1 ring and C_2 pars fracture	1	1
Tumor‡	1	1
Degenerative/Osteoporosis	3	0
Rheumatoid disease	4	4
Pseudogout	0	1

† Type 2 dens fracture ‡ Chordoma in both cases

cases had two 1/8th inch hemovac drains placed prior to closure, and these were left in place for an average of 2 days (range 1–6 days). Removal of drains required two consecutive 8-hour shifts of less than 30 cc of output. Use of instrumentation and rhBMP-2 as adjuncts for posterior craniovertebral and atlantoaxial cervical fusion are off-label uses of these products.

RESULTS

We identified 28 patients with posterior craniovertebral junction and/or atlantoaxial instrumented arthrodesis over the time period via chart review. Five of those patients were not available for follow-up. One of the patients never returned for follow-up and provided inaccurate contact information following trauma admission. The other four patients were deceased more than a year after surgery from unrelated causes like: myocardial infarction, stroke, and kidney failure (x2). None of the patients lost to follow-up experienced an operative or peri-operative complication.

Table 2 describes the 23 patients (10 men and 13 women) available for follow-up. The average patient age was 60.9 years (standard deviation [SD] =27.4 years, range: 4–89 years). The gender breakdown, diagnosis and level of fusion with Lenke fusion grade is seen in Table 1. Specific pathological diagnosis for the 23 patients with follow-up is summarized in Table 3. Figures 3 and 4 demonstrates an illustrative cases in which computed tomography (CT) was obtained during follow-up.

The average rhBMP-2 used per level fused with subsequent fusion grade is shown in Table 4. The average rhBMP-2 dose was 2.38 mg/level, with a total of 76 levels treated (average 3.3 levels, SD= 1.4 levels). By last follow-up, all patients had achieved solid fusion, with all but two patients having Lenke Grade A fusion.

Table 4: Average rhBMP-2 used per level fused including subsequent fusion grade

Number of levels fused	Number of cases	Average dose of BMP used (mg)	Average dose of BMP used per level (mg)	Fusion grade	
				A	B
2	7	5.4	2.7	6	1
3	10	8.2	2.7	9	1
4	2	10.2	2.6	2	0
5	1	8.4	1.7	1	0
6	2	10.2	1.7	2	0
7	1	12	1.7	1	0

The use of rhBMP-2 in pediatric patients under 10 years occurred in 2 patients due to special circumstances. One was a 4-year-old with osteogenesis imperfecta who suffered a cervical fracture and a 9-year-old who presented with failed fusion with wires and iliac crest bone graft.

The complications were assessed by reviewing both inpatient and outpatient charts. There were no cases of implant loosening or failure in any of the patients. All cases were evaluated for postoperative dysphagia or neck swelling requiring treatment (including steroids or reintubation). There were none found. In limited number of cases, in which routine follow-up included computed tomographic imaging, canal compromise from bony overgrowth was not identified. No patient reported discomfort with ganglionectomies performed based on direct assessment at clinical follow-up.

DISCUSSION

Interest in performing this review study arose from the current conflicting reports of complications versus increased fusion rates in the use of rhBMP-2 for cervical and craniovertebral junction surgery.[5-8,10,11,16,21,26,27,34,41] Reports have included painful seroma requiring return to the operating room for evacuation.[41] There have also been reports of tissue swelling and airway compromise, particularly in the anterior cervical spine.[31-33,42] The use of surgical wound drains in cases using osteoinductive products as adjuncts to fusion was not consistently documented in all patients in the above studies. Use of drains (left in place until output falls below 30 cc for 2 consecutive 8-hour shifts) in our practice greatly reduces the occurrence of painful seroma or swelling. In a report by Crawford *et al*.[6] a 15% wound complications rate was reported with the use of rh-BMP2. This may be related to the routine postoperative day 2 removal of drains. It is also possible that it could relate to the dosage of rh-BMP2 used per level, which was twice as high as that used in the present study.

In the present study, which included a high proportion of patients with significant risk factors for pseudoarthosis (e.g., rheumatoid arthritis), we achieved a 100% fusion rate without complications. In addition, we have documented and reported the dosage of rh-BMP2 used per level. The non-linear relationship between the milligrams of rhBMP-2 used per level is a limitation/constraint of dosage by packaging.

In reviewing our cases involving C2 nerve (ganglion) resection, we have reported that sectioning of the C2 nerve root improves visibility, mitigates the risk of postoperative neuralgia from screw irritation, helps to treat pre-existing occipital neuralgia, and mitigates blood loss and operative time.[43]

We avoided the donor site morbidity[23,44,45] of iliac crest bone graft (ICBG) with rhBMp-2 augmented fusion. ICBG site infections and complications can be as high as 29% from the above studies. In comparing our series with a cohort of patients by Nockels,[46] who used ICBG in one-third of his patients (occipital-cervical fusion, n = 69), a 97% fusion rate was achieved with one donor site infection, while in our current series using rhBMP-2, 100% fusion rate was achieved without any donor site morbidity.

The limitations of this study include the retrospective design. In addition, standardized measures were not used in assessing clinical outcomes. Flexion/extension and anterior-posterior plain radiographs were used for assessment of fusion as opposed to fine cut computed tomography. Although the latter has been shown to have a greater degree of interobserver and intraobserver agreement, Carreon *et al*.[47,48] have demonstrated that this difference is minimized when fusion is solid. However, an underestimation of pseudoarthrosis remains a possibility.

CONCLUSION

In augmenting posterior craniovertebral and atlantoaxial instrumented fusion with rhBMP-2, a 100% fusion rate was achieved in a series of patients with complex pathology and/or rheumatoid arthritis. From our data, a safe and effective average dose was found to be 2.38 mg per level.

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