Safety, Efficacy, and Dosing of Recombinant Human Bone Morphogenetic Protein-2 for Posterior Cervical and Cervicothoracic Instrumented Fusion With a Minimum 2-Year Follow-up

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BACKGROUND: Considerable attention has focused on concerns of increased complications with recombinant human bone morphogenetic protein-2 (rhBMP-2) use for anterior cervical fusion, but few reports have assessed its use for posterior cervical fusions.

OBJECTIVE: To assess the safety, efficacy, and dosing of rhBMP-2 as an adjunct for instrumented posterior cervical arthrodesis.

METHODS: All patients treated by the senior author with posterior cervical or cervicothoracic instrumented fusion using rhBMP-2 from 2003 to 2008 with a minimum of 2 years of follow-up were included. Diagnosis, levels fused, rhBMP-2 dose, complications, and fusion were assessed.

RESULTS: Fifty-three patients with a mean age of 55.7 years (range, 2-89 years) and an average follow-up of 40 months (range, 25-80 months) met inclusion criteria. Surgical indications included basilar invagination (n = 6), fracture (n = 6), atlantoaxial instability (n = 16), kyphosis/kyphoscoliosis (n = 22), osteomyelitis (n = 1), spondylolisthesis (n = 1), and cyst (n = 1). Fifteen patients had confirmed rheumatoid disease. The average rhBMP-2 dose was 1.8 mg per level, with a total of 282 levels treated (average, 5.3 levels; SD, 2.8 levels). Among 53 patients, only 2 complications (3.8%) were identified: a superficial wound infection and an adjacent-level degeneration. No cases of dysphagia or neck swelling requiring treatment were identified. At the last follow-up, all patients had achieved fusion.

CONCLUSION: Despite many of the patients in the present series having complex pathology and/or rheumatoid arthritis, a 100% fusion rate was achieved. Collectively, these data suggest that use of rhBMP-2 as an adjunct for posterior cervical fusion is safe and effective at an average dose of 1.8 mg per level.

KEY WORDS: BMP, Cervical, Complications, Dose, Fusion, Posterior, Surgery

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Bone morphogenetic proteins (BMPs) are a family of growth factors that induce bone formation.[1] Since their initial discovery, both animal and human studies have confirmed their ability to facilitate spinal fusion.[2-14] The US Food and Drug Administration (FDA) approved recombinant human BMP-2 (rhBMP-2) use with an absorbable collagen sponge scaffold (INFUSE, Medtronic Sofamor Danek, Memphis, Tennessee) for the treatment of degenerative disk disease via anterior lumber interbody fusion in an LT-CAGE (Medtronic Sofamor Danek) in skeletally mature patients in July 2002.[15] Although the on-label use of rhBMP-2 is limited, it is often used much more broadly and off-label in spinal surgery to augment fusion.

ABBREVIATIONS: BMP, bone morphogenetic protein; **FDA,** Food and Drug Administration; **ICBG,** iliac crest bone graft; **rhBMP-2,** recombinant human bone morphogenetic protein-2

Multiple studies have reported no significant increase in complications when BMP is used to augment posterolateral lumbar spine fusion.[2,6-8,12,13,16-19] After an initial FDA-sponsored trial demonstrated no increase in

complications after rhBMP-2 use in anterior cervical spine surgery,[20] a few studies predominantly using larger doses of rhBMP-2 showed an increase in soft-tissue swelling and airway compromise.[21-23] Although studies have demonstrated the safety of rhBMP-2 use at lower doses for anterior cervical fusion,[24-26] in July 2008, the FDA issued a public health notification warning of safety concerns regarding the use of rhBMP-2 in the cervical spine without clear distinction of whether applied through an anterior or posterior approach.[27]

Since the public health notification from the FDA, considerable attention has focused on concerns about increased complications with the use of rhBMP-2 for anterior cervical fusion, but few reports have assessed its use for posterior cervical fusion.[19,21,28] Our objective in the present study was to report our experience in a consecutive series of patients with rhBMP-2 to augment instrumented posterior cervical arthrodesis, including the doses of rhBMP-2 used, rates of complications, and the fusion rates achieved with a minimum 2-year follow-up.

METHODS

After obtaining approval from the University of Virginia Institutional Review Board, we reviewed charts of all patients of the senior author who had undergone posterior cervical instrumented fusion from August 2003 to March 2008, including occipitocervical, cervical, and cervicothoracic fusions (to no lower than thoracic level 4). Patient demographics, indication for surgery, number of levels fused, and amount of rhBMP-2 used were extracted. We also extracted operative, perioperative, and long-term (up to last follow-up) complications. Both inpatient and outpatient clinical records were reviewed, with particular assessment for any evidence of wound issues. Evidence of bony fusion at the last follow-up was assessed from a review of anteroposterior and dynamic (neutral/flexion/extension) lateral radiographic imaging by 2 independent neuroradiologists. Assessment of fusion was based on the criteria described by Lenke et al (Table 1).[29]

The dose of rhBMP-2 for each case was extracted from the operating room documentation of products and confirmed by the surgeon's operative report. According to 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), and large (12.0 mg). The absorbable collagen sponge carrier (INFUSE, Medtronic Sofamor Danek) was used to reconstitute the rhBMP-2 as previously described.[7,30,31] In all cases, the sponges and

TABLE 1. Lenke Classification System for Grading Spinal Fusion[29]

Fusion Grade	Description
A	Solid, big trabeculated fusions bilaterally (definitely solid)
B	Solid, big fusion mass unilaterally with a small fusion mass on the contralateral aspect (possibly solid)
C	Small, thin fusion masses bilaterally with apparent crack (probably not solid)
D	Graft resorption bilaterally or fusion mass with an obvious bilateral pseudoarthrosis (definitely not solid)

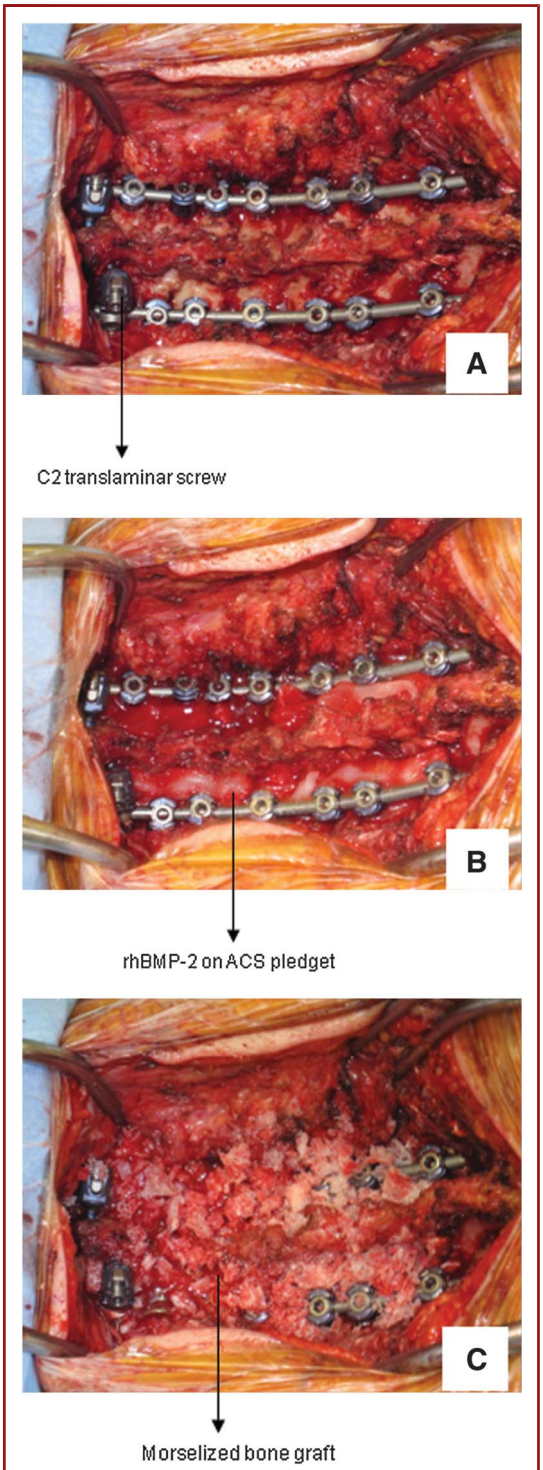

FIGURE 1. *Placement of recombinant human bone morphogenetic protein-2 (rhBMP-2) in posterior cervicothoracic fusion decortication (A) and placement of rhBMP-2–soaked absorbable collagen sponge (B) and bone allograft (C) after cervicothoracic stabilization for cervical kyphosis.*

morselized allograft/autograft were placed laterally over the facets and transverse processes when there was a medial decompression or included laminar placement if no decompression was performed (Figure 1). Strips of rhBMP-2–soaked sponge were placed directly onto the decorticated bony surfaces, with subsequent application of morselized bone graft overlying the sponges. The amount of locally harvested bone was in general minimal and was available only in 12 cases in which significant decompression was performed. In cases in which local bone was available, the percentage of local bone used for arthordesis relative to allograft bone was consistently $< 50\%$. In general, approximately 5 cm^3 of allograft (cancellous cubes) per level was used. Fusions involving the atlantoaxial joint involved bilateral ganglionectomies and further placement of allograft/autograft with rhBMP-2 in the prepared joint space as previously described.[32] Fusions from the occiput to the cervical spine were accomplished using onlay of rhBMP-2–soaked sponge covered with morselized bone graft spanning from the occiput to the cervical spine. In no case was structural graft used. Use of instrumentation and rhBMP-2 as adjuncts for posterior cervical fusion is an off-label use of these products.

In all cases, 2 1/8-in Hemovac drains were placed before closure. The average time that drains were left in place was 2 days (range, 1-6 days). Drains were removed after 2 consecutive 8-hour shifts with < 30 cm^3 output.

RESULTS

Sixty consecutive patients treated with posterior occipitocervical, posterior cervical, or posterior cervicothoracic instrumented fusion over the time period were identified via chart review. Seven of those patients did not reach the 2-year follow-up and were unavailable for further follow-up. Four of these 7 patients were deceased: 1 died of traumatic injuries from a motor vehicle collision, and the other 3 died $>$ 1 year after surgery from kidney failure, myocardial infarction, and stroke. The remaining 3 patients who were unavailable for follow-up had not kept any appointments after surgery and could not be contacted.

Table 2 describes the 53 patients (22 men and 31 women) who were available for follow-up at the end of the study period. The average patient age was 55 years (SD, 24.6 years; range, 4-89 years) for men and 56 years (SD, 23.6 years; range, 2-87 years) for women. Surgical indications included basilar invagination (n = 6), fracture (n = 6), atlantoaxial instability (n = 16), kyphosis/kyphoscoliosis (n = 22), osteomyelitis (n = 1), spondylolisthesis (n = 1), and cervical facet joint cyst with instability

TABLE 2. Characteristics of the 53 Patients Who Underwent Instrumented Posterior Cervical Fusion With Recombinant Human Bone Morphogenetic Protein-2[a]

Diagnosis, n	Mean Age (Range), y	Sex	Procedure, (n)	Lenke Grade B, n[b]
Kyphoscoliosis, 22	54 (2-79)	7 M/15 F	6-Level O-C fusion, 1	
			2-Level cervical fusion, 1	
			4-Level cervical fusion, 1	
			5-Level cervical fusion, 1	
			4-Level C-T fusion, 1	
			5-Level C-T fusion, 2	1
			7-Level C-T fusion, 2	
			8-Level C-T fusion, 1	
			9-Level C-T fusion, 10	
			10-Level C-T fusion, 1	
			11-Level C-T fusion, 1	
Atlantoaxial instability, 16	64 (9-89)	6 M/10 F	3-Level O-C fusion, 1	
			2-Level cervical fusion, 7	1
			3-Level cervical fusion, 8	1
Basilar invagination, 6	51 (13-82)	3 M/3 F	3-Level O-C fusion, 1	
			4-Level O-C fusion, 2	
			5-Level O-C fusion, 1	
			6-Level O-C fusion, 1	
			7-Level O-C fusion, 1	
Fracture, 6	46 (4-67)	5 M/1 F	2-Level cervical fusion, 1	
			4-Level cervical fusion, 1	
			4-Level C-T fusion, 1	
			5-Level C-T fusion, 1	
			7-Level C-T fusion, 1	
			9-Level C-T fusion, 1	
Osteomyelitis, 1	41 (41)	M	8-Level C-T fusion, 1	
Spondylolisthesis, 1	65 (65)	F	7-Level C-T fusion, 1	
C8 synovial cyst, 1	82 (82)	F	2-Level cervical fusion, 1	

[a]C-T, cervicothoracic; O-C, occipitocervical.
[b]Remaining 50 cases had Lenke fusion grade A.

(n = 1). Fifteen patients (28%) had confirmed rheumatoid disease. The average follow-up was 40 months (range, 25-80 months).

Recombinant human BMP-2 was used in 3 patients under the age of 10 years. Although pediatric patients typically fuse at high rates even with allograft alone, complicating circumstances in each of these cases led to the decision to use rhBMP-2. In 1 case, rhBMP-2 was used in a 2-year-old who presented with failure above a prior thoracic fusion for severe congenital scoliosis. In the second case, rhBMP-2 was used in a 4-year-old with osteogenesis imperfecta who suffered a cervical fracture. In the third case, rhBMP-2 was used in a 9-year-old who presented with a failed fusion with wires and iliac crest bone graft (ICBG).

A total of 282 levels were fused, with an average of 5.3 levels per patient (SD, 2.8). The average dose of rhBMP-2 per fused level was 1.8 mg (Table 3). The dose of rhBMP-2 used per fused level did not differ significantly in terms of the spinal region (Table 4). There were no intraoperative complications. There was only 1 perioperative complication: a single patient with a superficial wound infection. No other wound complications were noted in a review of both inpatient and outpatient medical records.

All patients achieved fusion by the last follow-up (Lenke grade A or B; Table 2). Fifty of 53 (94%) patients achieved bilateral solid fusion (Lenke grade A). One patient with rheumatoid disease underwent a subsequent extension of instrumented fusion to the thoracic spine owing to adjacent segment disease but had solid fusion across the instrumented segments. There were no cases of implant loosening or failure in any of the patients. As part of the complications analysis, all cases were specifically evaluated for postoperative dysphagia or neck swelling requiring treatment (including use of steroids or reintubation). This was not found to have occurred. One deceased patient treated for kyphoscoliosis who was not included in the review because of a lack of follow-up had undergone preoperative gastric tube placement while undergoing traction owing to malnutrition resultant from a pre-existing mechanical swallowing failure. This was not included in the complications. Thus, the total complication rate was 3.8% (1 superficial wound infection and 1 adjacent-level degeneration requiring revision surgery). Figures 2 and 3 show illustrative case examples with postoperative fusion after the use of rhBMP-2. Although routine follow-up computed tomography imaging was not performed, in the limited number of cases in which it was available, bony overgrowth resulting in foraminal or canal compromise was not demonstrated (Figure 4).

TABLE 3. Average Recombinant Human Bone Morphogenetic Protein-2 Used Per Level Fused, Including Subsequent Fusion Grade

Levels Fused, n	Cases, n	Average Dose of BMP Per Level, mg	Fusion Grade A	Fusion Grade B
2	10	2.9	9	1
3	10	2.7	9	1
4	6	2.1	4	0
5	5	2.1	4	1
6	2	1.7	2	0
7	5	1.4	5	0
8	2	1.3	2	0
9	11	1.4	11	0
10	1	2.4	1	0
11	1	1.1	1	0

TABLE 4. Regional Differences in Average Recombinant Human Bone Morphogenetic Protein-2 Used[a]

Procedure, n	Average Levels Fused, n	Average rh-BMP2 per Level, mg	Lenke Grade A, %
Occipitocervical fusion, 8	5	2.6	100
Cervical fusion, 22	3	2.5	91
Cervicothoracic fusion, 23	8	1.6	96

[a]Differences in doses of recombinant human bone morphogenetic-2 (rhBMP-2) used based on region did not reach statistical significance ($P > .05$).

DISCUSSION

In the present study, we documented our experience with the use of rhBMP-2 for augmentation of instrumented posterior cervical fusion. The population assessed encompassed a broad range of diagnoses, including skeletally immature patients as young as 2 years of age. In addition, > 25% of the patients had a confirmed diagnosis of rheumatoid arthritis, a condition that can negatively affect fusion rates. We document the mean doses of rhBMP-2 used per patient and per level fused. Despite the relatively complex patient population assessed, only 2 complications were encountered as of the last follow-up: a single superficial wound infection and 1 case of adjacent-level degeneration that required extension of instrumentation and arthrodesis into the upper thoracic spine. Bony fusion (Lenke A or B) was documented in all patients by the time of the last follow-up. Collectively, these data support the safety of rhBMP-2 use for the augmentation of instrumented posterior cervical arthrodesis and provide a mean dose at which a fusion rate of 100% was achieved.

The present study is consistent with prior reports that have documented no significant increase in complications when rhBMP-2 is used to augment instrumented posterior spinal arthrodesis. Although the vast majority of these reports have focused on posterolateral lumbar spine fusion,[2,6-8,12,13,16-19] a limited number of reports have also demonstrated the safety of rhBMP-2 use for posterior cervical fusion.[21,28] There have been reports of adverse events associated with the use of rhBMP-2 for anterior cervical fusion, including tissue swelling and seroma formation leading to airway compromise.[21-23,33] None of these adverse events was encountered in the present series.

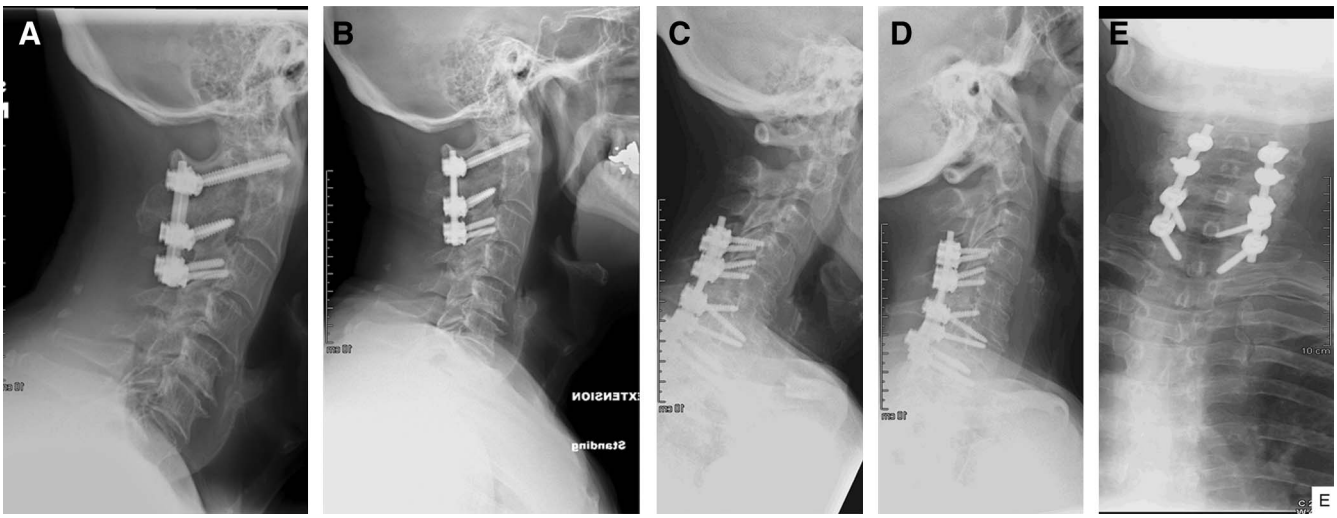

FIGURE 2. *Plain radiographs of recombinant human bone morphogenetic protein-2–augmented fusions at the 1-year follow-up.* **A** *and* **B**, *lateral flexion and extension views, respectively, of an 86-year-old man who developed a type 2 odontoid fracture after a ground-level fall.* **C** *and* **D**, *flexion and extension radiographs of a 70-year-old woman with rheumatoid arthritis.* **E**, *the corresponding anteroposterior radiograph. Note the extensive posterior lateral bony fusion.*

Recent reports have noted specific complications associated with the use of rhBMP-2. Chen et al[34] reported the occurrence of symptomatic heterotopic bone formation in association with rhBMP-2 use for transforaminal lumbar interbody fusion. No evidence of symptomatic ectopic bone formation was identified at $\geq$ 2 years after surgery in the present study. The occurrence of symptomatic ectopic bone formation in the report by Chen et al may relate to the dose of rhBMP-2 used (12 mg for each of the 4 reported cases of single-level transforaminal lumbar interbody fusion) or could relate to the proximity of rhBMP-2 placement in relation to the exposed nerve root.[34]

Garrett et al[35] have also recently reported painful seroma formation and swelling in association with rhBMP-2 use for posterolateral lumbar. In their report, 6 of 130 patients developed postoperative seromas that required a return to the operating room for evacuation. Unfortunately, although 3 of the 6 patients had durotomies during the surgery (primarily repaired), none had an objective evaluation for the presence of cerebrospinal fluid during revision/washout. In addition, only 2 patients had drains placed at their initial surgery. It has been our practice, particularly when using osteoinductive products, to routinely place drains and to leave them in place until output falls below 30 cm^3 for 2 consecutive 8-hour shifts. It is possible that our more liberal use of drains prevented the occurrence of painful seroma or swelling.

In the present study, we provide the mean dose of rhBMP-2 that was used to achieve a 100% fusion rate. Two previous reports have documented the doses of rhBMP-2 used for cases of instrumented posterior cervical fusions.[21,28] Hiremath et al[28] reported 16 cases of posterior cervical fusion in which the average dose of rhBMP-2 used was 1.3 mL (range, 0.5-2.7 mL). Presuming that this was reconstituted at the standard concentration of 1.5 mg/mL, this would be a mean dose of 2.0 mg per level, which is comparable to the 1.8-mg dose per level used in the present study. However, the mean follow-up was relatively short (5.7 months), and there was no assessment of fusion rates. Crawford et al[21] also provided doses of rhBMP-2 used for 41 cases of posterior cervical fusion. The mean dose of rhBMP-2 per level was 3.6 mg (range, 1.05-6.0 mg). No assessment of fusion rates was provided. However, 6 wound complications (15%; 2 prolonged drainage and 4 presumed deep infection) were reported. It is possible that this relatively high rate of wound complications may be related to their routine removal of wound drains on postoperative day 2. It is also possible that it could relate to the dose of rhBMP-2 used, which is twice the dose used in the present study.

Because we were limited to the dosages per package size, it may appear that there was intent to use a higher dose of rhBMP-2 per level for shorter fusions (Table 3). However, this was not intentional but instead reflects the constraints of dosage by packaging.

Another important benefit of using rhBMP to augment fusion is the reduced need to harvest ICBG. Prior reports suggest an iliac crest donor site morbidity rate as high as 29%.[36-38] In the present study, ICBG was not harvested for any of the patients; thus, this source of potential morbidity was completely avoided.

Historical comparison of fusion rates with similar rod-and-screw constructs indicates a higher fusion rate with respect to the use of rhBMP for posterior cervical fusion. Heller et al,[39] in an independent matched cohort analysis comparing laminectomy and fusion with laminoplasty for multilevel cervical myelopathy, had a pseudoarthrosis rate of 38.5% with laminectomy and fusion using ICBG for arthrodesis. Subsequent studies using a mixture of local bone and allograft have improved results. Nockels et al[40]

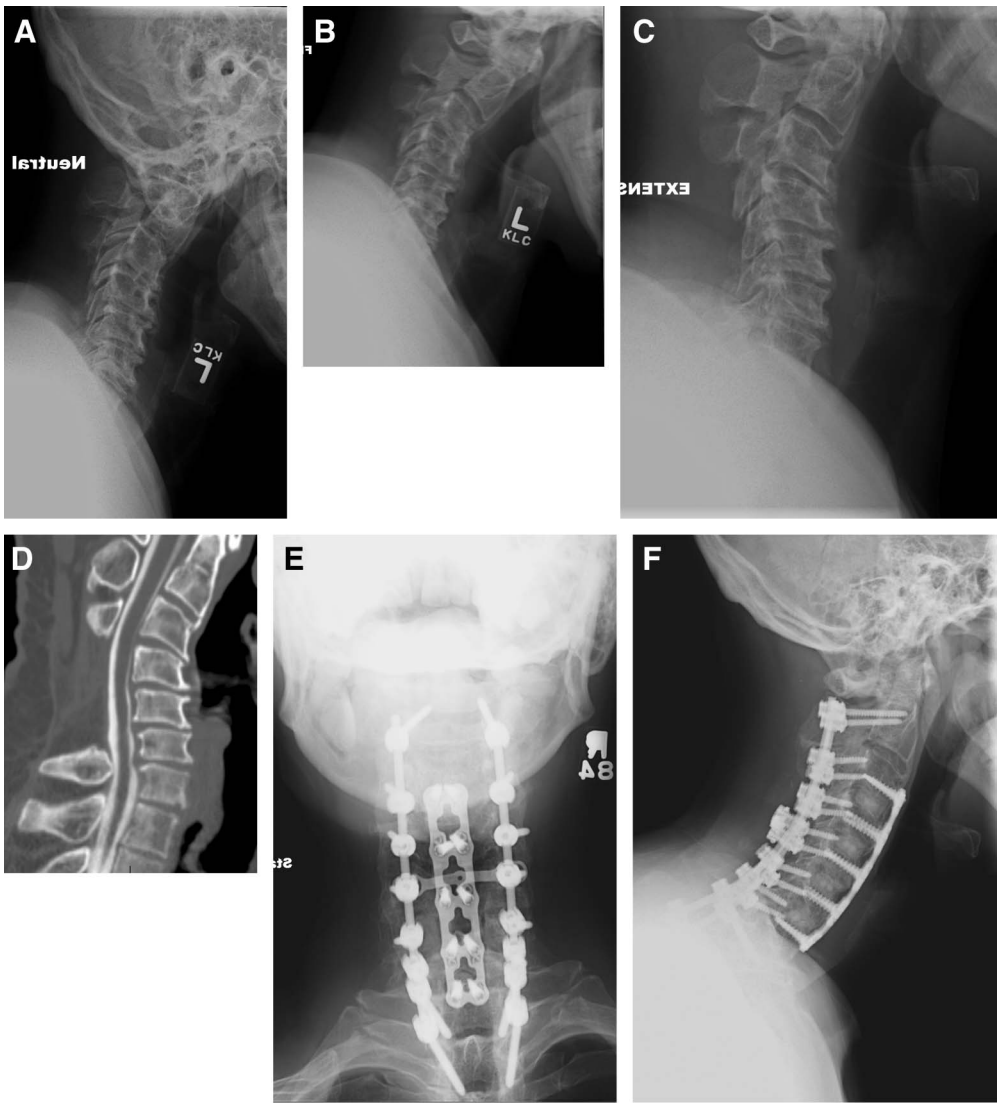

FIGURE 3. *A 57-year-old man with progressive upper- and lower-extremity weakness caused by cervical spondylotic myelopathy and progressive cervical kyphosis. Preoperative imaging, including neutral (**A**), flexion (**B**), and extension (**C**) lateral plain radiographs and a sagittally reconstructed image from a computed tomography myelogram (**D**), shows fixed kyphosis and evidence of prior laminectomies. The patient was treated with C3-C4, C4-C5, C5-C6, and C6-C7 anterior cervical diskectomies and fusions with cancellous allograft spacers and a plate spanning C3 to C7, followed by posterior C2-T2 posterior instrumented arthrodesis using a combination of recombinant human bone morphogenetic protein-2, cancellous allograft, and local bone graft. Two years after surgery, plain radiographs, anteroposterior (**E**) and lateral (**F**), and computed tomography imaging (**G**, coronal reconstruction) demonstrate brisk arthrodesis. Note the facet fusion mass in **G** (arrow).*

reported a large occipital-cervical fusion series (69 patients), with 33% of patients receiving ICBG. They reported a fusion rate of 97%, with a graft site infection in 1 patient. In a recent systematic review of occipital cervical fusion outcomes, Winegar et al[41] noted an occipital cervical fusion rate ranging from 84% to 100% among 11 studies that used only rod-and-screw or plate-and-screw constructs. In the present series, 8 patients underwent occipital-cervical fusion without ICBG harvest, and all achieved Lenke grade A fusion.

The primary limitation of this study is the retrospective design. In addition, we did not assess clinical outcomes using standardized measures. Although fine-cut computed tomography

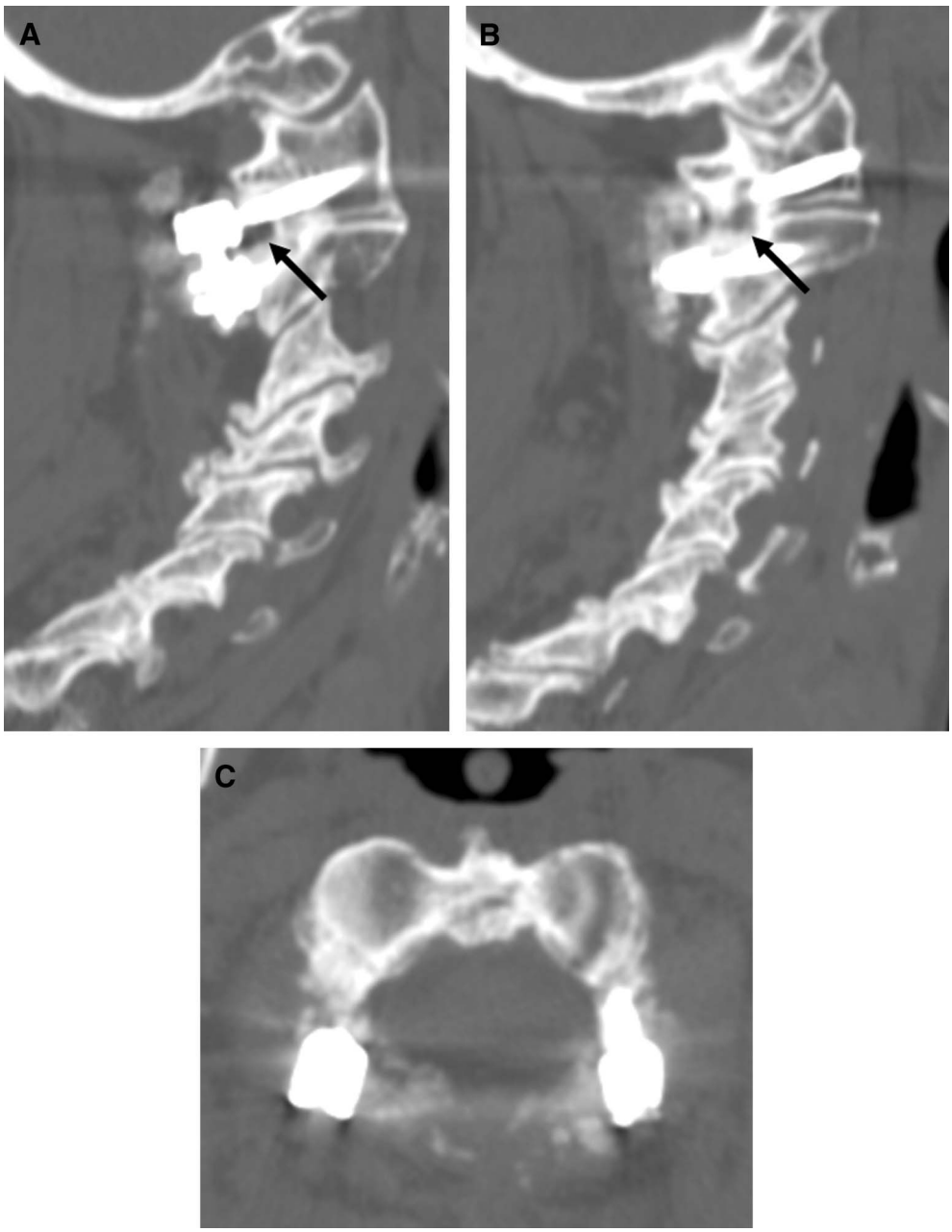

FIGURE 4. *Computed tomography imaging 1 year after C1-C2 posterior instrumented arthrodesis with recombinant human bone morphogenetic protein-2 and cancellous allograft in a 78-year-old man who presented with nonunion of a type 2 odontoid fracture. Although brisk fusion was achieved, reconstructed sagittal images do not show significant bony overgrowth in the left (**A**, arrow) or right (**B**, arrow) C1-C2 foramen, and a reconstructed axial image at the level of the C1 lateral masses (**C**) does not demonstrate canal encroachment.*

has been shown to have a greater degree of interobserver and intraobserver agreement compared with flexion/extension and anteroposterior plain radiographs, when fusion is solid, per Carreon et al,[42,43] these differences in assessment are minimized. Nevertheless, it is a limitation of this study that assessment of fusion was not performed with computed tomography imaging, and underestimation of pseudoarthrosis remains a possibility.

CONCLUSION

Use of rhBMP-2 to augment posterior cervical fusion appears to be safe with a very low associated complication rate. Despite many of the patients in the present series having complex pathology and/or rheumatoid arthritis, a 100% fusion rate was achieved. Collectively, these data suggest that use of rhBMP-2 as an adjunct for posterior cervical fusion is safe and effective at an average dose of 1.8 mg per level.

Disclosure

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENT

Hamilton et al report a series of 53 patients who underwent posterior cervical or cervicothoracic instrumented fusion with recombinant human bone morphogenetic protein type 2 (rhBMP-2) with morselized allograft/autograft. They found a 100% fusion rate at the 2-year follow-up, which is higher than the reported rate of fusion with allograft or local autograft alone. It appears the authors used rhBMP-2 to avoid pseudoarthrosis, which often leads to repeat surgeries (especially at the cervicothoracic junction). It is important to note that the use of rhBMP-2 other than for anterior lumbar interbody fusion is a Food and Drug Administration off-label application. The Food and Drug Administration issued a warning letter to surgeons last year to avoid the use of rhBMP-2 in the anterior cervical spine because of reports of dysphagia, seroma, and ectopic bone formation. These complications are likely dose related and have not been reported with posterior spine procedures.[1]

The authors have found that the use of rhBMP-2 appears to be effective in achieving a posterior cervical fusion, and they did not find complications similar to those reported with use of this substance in the anterior cervical spine. Still, it is important to note that complications are possible in the posterior cervical spine (seroma or bone formation in the neural foramen). It is important to recognize that the optimal dosage for applying rhBMP-2 in posterior spinal fusion remains uncertain. This well-written report sheds some light on the dosing of this substance in the posterior cervical spine.

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