Use of Recombinant Human Bone Morphogenetic Protein-2 at the C1-C2 Lateral Articulation without Posterior Structural Bone Graft in Posterior Atlantoaxial Fusion in Adult Patients

Wataru Ishida[1], Seba Ramhmdani[1], Yuanxuan Xia[1], Thomas A. Kosztowski[2], Risheng Xu[1], John Choi[1], Rafael De la Garza Ramos[3], Benjamin D. Elder[4], Nicholas Theodore[1], Ziya L. Gokaslan[2], Daniel M. Sciubba[1], Timothy F. Witham[1], Ali Bydon[1], Jean-Paul Wolinsky[5], Sheng-Fu L. Lo[1]

■ BACKGROUND: **Posterior atlantoaxial fusion is an important armamentarium for neurosurgeons to treat several pathologies involving the craniovertebral junction. Although the potential advantages of recombinant human bone morphogenetic protein-2 (rhBMP-2) are well documented in the lumbar spine, its indication for C1-C2 fusion has not been well characterized. In our institution, we apply rhBMP-2 to the C1-C2 joint either alone or with hydroxyapatite, locally harvested autograft chips, and/or morselized allogenic bone graft for selected cases—without conventional posterior structural bone graft. We report the clinical outcomes of the surgical technique to elucidate its feasibility.**

■ METHODS: **We performed a single-center, retrospective review of data from 2008 to 2016 and identified 69 patients who had undergone posterior atlantoaxial fusion with rhBMP-2. The clinical records of these patients were reviewed, and the baseline characteristics, operative data, and postoperative complications were collected and statistically analyzed.**

■ RESULTS: **The average age of the 69 patients was 60.8 ± 4.5 years, and 55.1% were women. With an average follow-up period of 21.1 ± 4.2 months, the C1-C2 fusion rate was 94.3% (65 of 69), and the average time to fusion was 11.4 ± 2.6 months (range, 5–23). The overall reoperation rate was 10.1% (7 of 69), with instrumentation failure in 7 patients (10.1%), adjacent segment disease in 2 (2.9%), and postoperative dysphagia and dyspnea in 2 patients (2.9%). No ectopic bone formation or soft tissue edema developed.**

■ CONCLUSIONS: **Although retrospective and from a single center, our study has shown that rhBMP-2 usage at the C1-C2 joint without posterior structural bone grafting is a safe and reasonable surgical option.**

INTRODUCTION

Posterior atlantoaxial fusion (or C1-C2 fusion) is an essential element in the armamentarium for neurosurgeons to treat several pathologies involving the craniovertebral junction and upper cervical region, including degenerative disease, deformity, trauma, infection, malignancy, and basilar invagination. The bone graft options surrounding this region have included a wide variety of reported methods, such as iliac crest tricortical autograft, structural allograft, bone chips, β-tricalcium phosphate, and off-label use of recombinant human bone morphogenetic protein-2 (rhBMP-2).[1-5] The potential advantages of rhBMP-2 compared with (or noninferiority to) autograft and/or allograft alone have been well documented, especially in the lumbar spine, including decreased operative times, donor site morbidity, blood loss, infectious complications, and incidence of pseudoarthrosis.[6-8] In contrast, some concerns have been raised regarding the adverse

Key words
- Atlantoaxial fusion
- C1-C2 fusion
- Pseudoarthrosis
- rhBMP-2

Abbreviations and Acronyms
CT: Computed tomography
rhBMP-2: Recombinant human bone morphogenetic protein-2

From the [1]Department of Neurosurgery, The Johns Hopkins University, School of Medicine, Baltimore, Maryland; [2]Department of Neurosurgery, Brown University School of Medicine, Providence, Rhode Island; [3]Department of Neurological Surgery, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York; [4]Department of Neurosurgery, Mayo Clinic, Rochester, Minnesota; [5]Department of Neurological Surgery, Northwestern University, Chicago, Illinois, USA

To whom correspondence should be addressed: Sheng-Fu L. Lo, M.D. [E-mail: larrylo@jhmi.edu]

Wataru Ishida, Seba Ramhmdani, Jean-Paul Wolinsky and Sheng-Fu L. Lo contributed equally to the present report.

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effects associated with rhBMP-2 in spinal fusion procedures. In particular, ectopic bone formation, bony overgrowth on the fusion bed,[9] soft tissue edema, postoperative dysphagia when used in anterior cervical spine surgery,[10] effects on dura mater,[11] and a controversial increase in the incidence of neoplasms[12-15] are well-recognized sequelae of the use of rhBMP-2. However, because the atlantoaxial spine has unique anatomy and biomechanics, the indications for, efficacy of, and adverse effects from rhBMP-2 have not been well characterized to the best of our knowledge.

In our institution, for selected adult cases of posterior atlantoaxial fusion for which the risk of pseudoarthrosis has been deemed high such as revision surgery, patient age >60 years, and/or poor bone quality, we have applied rhBMP-2 to the C1-C2 joint, either alone or with hydroxyapatite, locally harvested autograft chips, and/or morselized allogenic bone graft, without conventional posterior structural bone grafting. Thus, we aimed to report our overall clinical outcomes with the use of rhBMP-2 at the C1-C2 articulation for posterior atlantoaxial fusion, with special attention to the fusion rates and complications to elucidate the feasibility of the surgical technique.

METHODS

Inclusion and Exclusion Criteria

We performed a single-center, retrospective review of data from 2008 to 2016 and identified 69 patients who had met the inclusion criteria. The inclusion criteria were 1) adult patients, 2) posterior atlantoaxial fusion with rhBMP-2 used at the C1-C2 articulation, and 3) minimum 1-year follow-up data with radiographic images, including plain radiographs, dynamic radiographs, and/or computed tomography (CT) scans available. The imaging studies were used to determine the patients' C1-C2 instability/pseudoarthrosis status. Those patients who had undergone fusion procedures spanning O—C1 and cervicothoracic junctions were excluded owing to the potential bias caused by the added biomechanical stability. The indications for posterior atlantoaxial fusion included symptomatic spinal stenosis/instability at the C1-C2 joint caused by rheumatoid arthritis, degenerative changes, os odontoideum, and C2 fracture. The use of rhBMP-2 was indicated for selected cases of posterior atlantoaxial fusion in which the estimated pseudoarthrosis rate would be relatively high, such as revision surgery ($n = 15$), patient age >60 years ($n = 36$), and/or poor bone quality (osteoporosis, $n = 12$; a history of smoking, $n = 17$). Combined anterior approaches were offered to patients who required extensive anterior decompression and stabilization. The clinical records of these 69 patients, including patient medical records, operative data, and radiographic images, were retrospectively collected. The present study was conducted in compliance with our institutional review board-approved protocol.

Surgical Procedures

The patients were placed in a prone position, and the cervical spine was exposed posteriorly in a usual fashion, depending on the region of interest. A C1 laminectomy was performed in selected cases in which direct decompression was necessary. The C2 nerve roots were transected in selected cases, depending on the surgical corridor and osseous anatomy of each patient and surgeon preference. Intra-articular decortication of C1 and C2 was achieved using either a high-speed burr or sharp curette directly into the C1-C2 lateral articulation. Next, rhBMP-2 (dose range at the C1-C2 joint, 0.8—6.0 mg) was applied on a collagen sponge (Infuse; Medtronic, Inc., Minneapolis, Minnesota, USA), which was cut into ~1-cm strips and inserted into the decorticated C1-C2 joint. Additionally, depending on the surface area of the other levels of intended fusion, rhBMP-2 was used with hydroxyapatite, local autograft chips, and/or a morselized allograft without posterior structural support. The selection of the bone graft was dependent on surgeon preference and was not randomized. Unless contraindicated, C1 lateral mass screws, C2 pedicle or pars screws, and subaxial lateral mass or pedicle screws and rods were placed in accordance with surgeon preference and the patients' bony anatomy.

Patient Data Collection

The baseline characteristics of the 69 patients, including age, gender, smoking history, comorbidities, body mass index, and diagnosis, were retrospectively collected. Also, the operative data, such as operative time, total estimated blood loss, a history of cervical surgery in the same region, operated levels, combined anterior approaches, the dosage of rhBMP-2 placed into the C1-C2 joints, and total length of hospitalization and intensive care unit stay were reviewed. Furthermore, postoperative complications including pseudoarthrosis C1-C2, overall reoperation, surgical site infection, wound dehiscence, adjacent segment disease, instrumentation failure, dysphagia, difficulty in phonation or airway, incidental durotomy, vertebral artery injury, soft tissue edema, and ectopic bone formation, were reviewed. A reoperation was defined as any unplanned surgery required to treat pseudarthrosis, device failure, adjacent segment disease, infection, hematoma, and wound dehiscence. C1-C2 instability and/or pseudoarthrosis and instrumentation failure were diagnosed by each attending physician on an outpatient basis, who evaluated the plain radiographs, dynamic radiographs, and/or CT scans at 3, 6, and 12 months postoperatively. Finally, patient functional status, including improvement in neck pain, motor deficits, sensory deficits, and ambulatory status[16] (rated as 4, independently ambulatory; 3, requiring a cane; 2, requiring a walker; and 1, wheelchair-bound), was collected both preoperatively and postoperatively at the last follow-up examination.

Statistical Analysis

Data are presented as the mean ± standard deviation, unless specified otherwise. The perioperative changes in ambulatory status were analyzed using the Wilcoxon signed rank test. Kaplan-Meier curves were drawn to depict the time to fusion in our cohort. All reported P values are 2-sided, and $P < 0.05$ was considered to indicate statistical significance. All statistical analyses were conducted using JMP Pro, version 12.2 (SAS Institute Inc., Cary, North Carolina, USA).

RESULTS

Baseline Characteristics

The average age of the 69 patients was 60.8 ± 4.5 years, and 55.1% were women (Table 1). Regarding the risk factors for pseudoarthrosis, which prompted the use of rhBMP-2, 36

Table 1. Baseline Characteristics ($n = 69$)

Characteristic	Value
Age (years)	60.8 ± 4.5
Female gender	55.1 (38)
BMI (kg/m^2)	28.8 ± 4.3
Smoking	24.6 (17)
Diabetes mellitus	11.6 (8)
Osteoporosis	17.4 (12)
Previous surgery at operated levels	21.7 (15)
Preoperative diagnosis	
Rheumatoid arthritis	49.2 (34)
Degenerative disease	26.1 (18)
Trauma	13.0 (9)
Os odontoideum	4.3 (3)
Other	7.2 (5)
Preoperative symptoms	
Neck pain	79.7 (55)
Motor deficit	53.6 (37)
Sensory deficit	40.6 (28)
Gait disturbance	52.2 (36)
Bladder/bowel dysfunction	14.5 (10)

Data presented as mean ± standard deviation or % (*n*).
BMI, body mass index.

Table 2. Operative Data ($n = 69$)

Variable	Value
Operative time (minutes)	298.1 ± 55.6
Estimated blood loss (mL)	346.8 ± 66.8
Operated level	3.1 ± 1.6
Combined anterior approach	21.7 (15)
Dosage of rhBMP-2 at C1-C2 (mg)	2.5 ± 0.9
Bone graft options	
rhBMP-2 only	21.7 (15)
rhBMP-2 plus hydroxyapatite	18.8 (13)
rhBMP-2 plus local autograft chips	24.6 (17)
rhBMP-2 plus local autograft and allograft chips	34.8 (24)
Length of stay (days)	8.2 ± 2.6
Length of ICU stay (days)	2.3 ± 1.1

Data presented as mean ± standard deviation or % (*n*).
rhBMP-2, recombinant human bone morphogenetic protein-2; ICU, intensive care unit.

patients were aged >60 years (52.2%), 17 (24.6%) had a history of smoking, 12 had osteoporosis (17.4%), and 15 patients (21.7%) had undergone previous surgery at the same level. The preoperative diagnosis was rheumatoid arthritis in 34 patients (49.2%), degenerative spine disease in 18 (26.1%), trauma in 9 (13.0%), and os odontoideum in 3 patients (4.3%).

Operative Data

The operative data of the included patients are summarized in Table 2. The average operative time was 298.1 ± 55.6 minutes, the estimated blood loss was 346.8 ± 66.8 mL, and the operated level was 3.1 ± 1.6. The bone graft options used in these 69 patients were with rhBMP-2 only in 15 patients (21.7%), rhBMP-2 plus hydroxyapatite in 13 (18.8%), rhBMP-2 plus locally harvested autograft chips in 17 (24.6%), and local autograft chips and morselized allograft in 24 patients (34.8%). Representative images of an illustrative case are shown in Figure 1.

Postoperative Complications

The complications observed in our cohort are listed in Table 3. The average follow-up period was 21.1 ± 4.2 months. Overall, C1-C2 instability/pseudoarthrosis was observed in 4 patients (5.7%), with an average time to fusion of 11.4 ± 2.6 months (range, 5–23). The Kaplan-Meier curve for the time to fusion is depicted in Figure 2. Pseudoarthrosis in other joints was not identified in any of the 69 patients. The overall reoperation rate was 10.1%, which was attributable to 7 cases of instrumentation failure, 2 cases of adjacent segment disease, and 2 cases of postoperative dysphagia and dyspnea.

Functional Outcomes

The proportions of patients who had experienced symptom relief postoperatively at the final follow-up evaluation, including neck pain and motor and sensory deficits, are listed in Table 4. The comparison between pre- and postoperative ambulatory status demonstrated that the functional status had improved, with a statistically significant difference (2.9 ± 0.4 vs. 3.5 ± 0.4; $P = 0.02$).

DISCUSSION

Although adult anterior interbody lumbar fusion is the only Food and Drug Administration–approved usage of rhBMP-2 plus collagen sponges, a wide variety of "off-label" indications have been extensively reviewed in reported studies.[8,17,18] However, for posterior atlantoaxial fusion, the scientific evidence has been surprisingly sparse, aside from several studies of pediatric populations or patients with Down syndrome.[19,20] Only a few studies have specifically focused on the use of rhBMP-2 for posterior atlantoaxial fusion in adult patients. Hood et al.[21] retrospectively reviewed the data from 48 adult patients and 4 pediatric patients, who had undergone posterior C1-C2 fusion with posterior structural allografts, morselized allografts, rhBMP-2, and screw fixation. They reported a fusion rate of 100%, without any significant adverse effects.[21] Furthermore, although dozens of clinical or review reports have compared different instrumentation methods for posterior C1-C2 fusion,[2,22-25] those comparing different bone graft options in the region were substantially limited.[26-28]

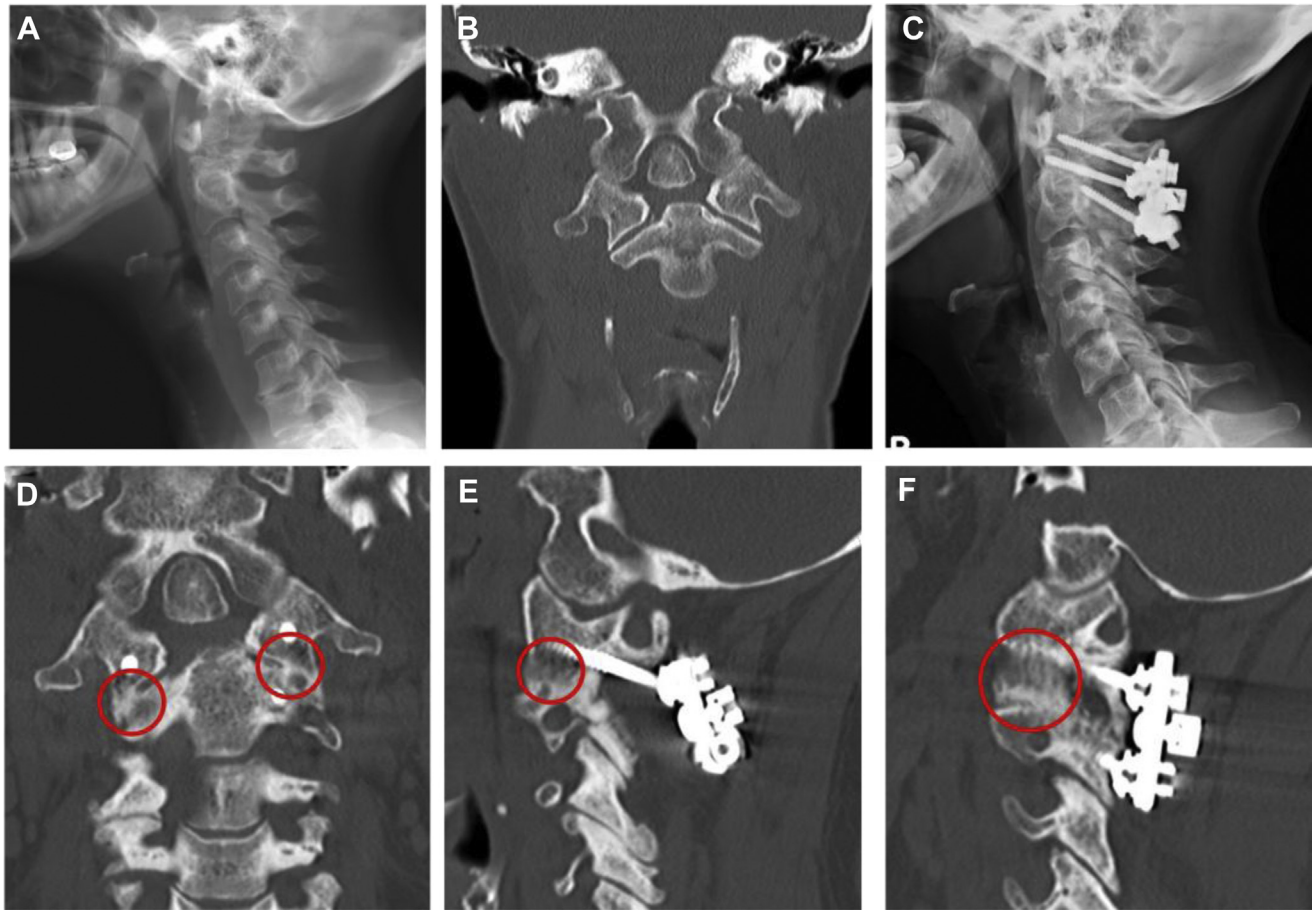

Figure 1. A 52-year-old woman with osteoporosis had presented with hand clumsiness. Preoperative (**A**) lateral radiograph and (**B**) reconstructed computed tomography scan at presentation had revealed instability at the C1-C2 joint caused by os odontoideum. She underwent posterior instrumented arthrodesis from C1 to C2 with bilateral C1 lateral mass screws, C2 right translaminar screw, and C2 left pedicle screw, in addition to recombinant human bone morphogenetic protein-2 at the C1-C2 lateral articulation. At 1 year postoperatively, a (**C**) lateral radiograph and (**D**–**F**) reconstructed computed tomography scans demonstrated instrumentation in adequate positions and solid bony fusion at the C1-C2 joint. *Red circles* indicate arthrodesis across C1-2 articulation.

To the best of our knowledge, our study is the first to report the use of rhBMP-2 at the C1-C2 lateral articulation without posterior structural support for posterior atlantoaxial fusion procedures and to elaborate its clinical outcomes in adult patients. The key findings of the present study were as follows. First, the use of rhBMP-2 at the C1-C2 joint either alone or with hydroxyapatite, locally harvested autograft chips, and/or morselized allogenic bone graft without posterior structural bone graft resulted in an acceptable C1-C2 fusion rate of 94.3%. Second, the overall reoperation rate was 10.1%. Third, the long- and short-term complications included 7 cases of instrumentation failure, 2 of adjacent segment disease, and 2 of postoperative dysphagia and dyspnea, which prompted reoperation. Finally, no adverse effects from rhBMP-2 were observed in the present study.

C1-C2 Pseudoarthrosis Rate

First, our technique yielded an overall fusion rate of 94.3%, which was deemed acceptable. The reported fusion rates for conventional posterior atlantoaxial fusion procedures without rhBMP-2 in adult patients, such as structural autograft/allograft alone, morselized autograft/allograft, other bone graft extenders, or combinations of any of these, have ranged from ~90% to 100%.[1-3,29-31] Our patient selection criteria included cases considered predisposed to postoperative pseudoarthrosis such as revision surgery, age >60 years, and/or poor bone quality (e.g., osteoporosis, osteopenia, a history of smoking). Presumably owing to the negative-result biases in the reported data, the clinical outcomes of conventional posterior C1-C2 fusion techniques in this specific high-risk cohort have been underreported.[32-35] Yan et al.[35] elaborated on the clinical outcomes of posterior C1-C2 fusion in patients aged >60 years, comparing rhBMP-2 with autologous iliac bone graft. They reported that the fusion rate of the rhBMP-2 group was greater than that of the autologous iliac bone graft group (82.4% [56 of 68] vs. 78.7% [52 of 66], respectively; $P = 0.782$).[35] They also reported that the time to fusion in the rhBMP-2 group was 11 days shorter ($P = 0.034$).[35]

Table 3. Postoperative Complications ($n = 69$)

Variable	Value
Follow-up period (months)	21.1 ± 4.2
Time to fusion (months)	11.4 ± 2.6
Long-term complications	
C1-C2 instability/pseudoarthrosis	5.7 (4)
Reoperation	10.1 (7)
Surgical site infection	0.0 (0)
Wound dehiscence	0.0 (0)
Adjacent segment disease	2.9 (2)
Instrumentation breakage	10.1 (7)
Short-term complications	
Postoperative dysphagia	2.9 (2)
Postoperative dyspnea	2.9 (2)
Postoperative difficulty in phonation	1.5 (1)
Incidental durotomy	1.5 (1)
Vertebral artery injury	0.0 (0)
Soft tissue edema	0.0 (0)
Ectopic bone formation	0.0 (0)

Data presented as mean ± standard deviation or % (*n*).

To the best of our knowledge, the present study is the first to date that has specifically focused on the use of rhBMP-2 in this high-risk cohort. Hence, we could not find enough adequate historical control data with which we could compare our results. However, it can be estimated that the fusion rate in this cohort with conventional techniques would be less than that of the general population (range, 90%–100%), as identified in the study by Yan et al.[35] (78.7% rate with structural autografting), which could justify the efficacy and utility of our novel technique.

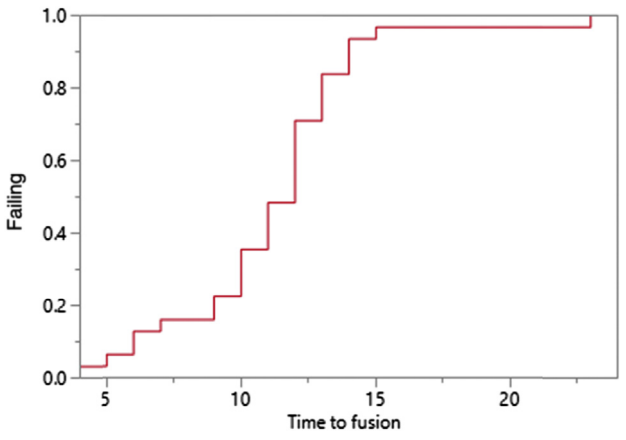

Figure 2. Time-to-fusion analysis using Kaplan-Meier curve.

Table 4. Functional Outcomes ($n = 69$)

Outcome	% (*n*/*N*) or Mean ± Standard Deviation
Improved neck pain	70.9 (39/55)
Improved motor function	83.8 (31/37)
Improved sensory function	79.2 (19/28)
Improved gait disturbance	77.8 (28/36)
Ambulatory status score*†	
Preoperative	2.9 ± 0.4
Postoperative	3.5 ± 0.4
Change	0.57 ± 0.32

*Ambulatory status score: 4, independently ambulatory; 3, requiring a cane; 2, requiring a walker; and 1, wheelchair-bound.
†Comparison between preoperative and postoperative functional outcomes using the Wilcoxon signed rank test ($P = 0.02$).

This limitation in patient selection can also be applied to our retrospective data review. Ideally, the clinical outcomes of patients who have undergone conventional structural autograft or allograft alone in our institution should also have been compared with those of the rhBMP-2 cohort included in the present study. However, this was not feasible owing to the substantial bias present in the patient selection processes. More specifically, the baseline characteristics of those who had undergone conventional techniques (age <60 years, trauma etiology, better bone quality, and/or first surgery) were strikingly different from those of the rhBMP-2 cohort (age >60 years, degenerative disease, rheumatoid arthritis, poor bone quality, smoking, and/or revision surgery). This difference limited the direct intra-institutional comparison between the current standard care and our novel technique. Thus, future prospective, randomized studies that include general population cohorts and high-risk cohorts are warranted to further investigate its validity.

Exclusion of Patients with Structural Autogenic/Allogenic Bone Grafts

Another limitation of our study was that we excluded patients who had received a structural bone graft as posterior biomechanical support from the study, because only 9 such patients were found. These 9 patients had received a structural iliac autograft ($n = 2$) or an allograft ($n = 7$). Thus, we were unable to statistically compare the clinical outcomes between those with versus without a structural bone graft because those who had received rhBMP-2 plus a structural tricortical autograft might have resulted in an improved fusion outcome compared with rhBMP-2 alone. Although a paucity of studies has compared the different bone graft options for posterior C1-C2 fusion in adult patients, Zhang et al.[28] recently

reported that the use of structural autografts compared with structural allografts did not increase the overall fusion rate (100% for autografts vs. 94% for allografts). Also, the time to fusion was 3 months longer in the allograft group ($P < 0.05$). In contrast, a recent report from Huang et al.[27] concluded that structural allografts are unreliable for posterior atlantoaxial fusion and that the use of structural autografts should remain the reference standard despite the occurrence of donor site morbidities (8.3% fusion rate vs. 88.2%, respectively, as determined from CT scans).

The clinical evidence from pediatric populations is more abundant. A recent systematic review by Reintjes et al.[36] maintained that the overall fusion rates of autografts and allografts for pediatric posterior C1-C2 fusion were 94% and 80%, respectively. They concluded that "further study of the use of allograft as a viable alternative to autograft bone fusion is warranted because limited data are available regarding the use of allograft in combination with more rigid internal fixation techniques and osteoinductive substances, both of which may enhance fusion rates with allograft."[36] In our study, it is also plausible that the osteoinductivity of rhBMP-2 dominated the effect of other modalities and that posterior structural autografts or allografts might not always be necessary in these cases, given our favorable fusion rate of 94.3%. This strategy would enable us to eliminate the potential complications associated with bone grafting such as donor site morbidities[4,37,38] and, although exceedingly rare, transmission of infection from allografts.[39,40]

Other Long- and Short-Term Outcomes

Other long-term complication outcomes, including reoperation (10.1%), surgical site infection (0.0%), wound dehiscence (0.0%), adjacent segment disease (2.9%), and instrumentation failure (10.1%), were acceptable. In our cohort, 2 cases of postoperative dysphagia and dyspnea were identified. They were attributed to the instrumentation construct and postoperative spinal alignment, which had resulted in subsequent narrowing of the oropharyngeal space, and not to soft tissue edema at the C1-C2 level induced by rhBMP-2. We determined this because the patients' symptoms had resolved quickly after instrumentation and spinal alignment revision. These postoperative issues in the oropharyngeal area are one of the most crucial complications of upper cervical surgery, including occipitocervical fusion and C1-C2 fusion.[41-43] As such, more thorough discussion is necessary for us to further address the safety of the use of rhBMP-2 in this area.

Furthermore, none of our patients developed ectopic bone formation, one of the notorious complications related to the use of rhBMP-2.[9,44,45] Singh et al.[44] addressed the clinical sequelae after rhBMP-2 use for minimally invasive transforaminal lumbar interbody fusion and reported that 10 of 573 patients (1.7%) had experienced nerve root impingement due to neuroforaminal bone overgrowth at 1 year postoperatively. Therefore, close follow-up of patient symptoms and radiographic studies is necessary to address the safety issues of rhBMP-2 in posterior C1-C2 fusion pertinent to ectopic bone formation. However, in our case series, the C2 nerve roots were transected in those patients in whom C1 and/or C2 screw insertion would not have been safely executed otherwise (43.4%; 30 of 69). This could result in another intriguing clinical question of whether these nerve roots should be preserved or sacrificed, as discussed extensively in reported studies,[46-48] especially in the setting of rhBMP-2 usage.

Finally, it is of paramount importance that the surgical technique we have described led to a statistically significant increase in ambulatory status scores and improvement in neck pain and motor and sensory symptoms. Overall, the efficacy and potential adverse effects of rhBMP-2 in this region has not yet been well characterized. Thus, we hope that the favorable outcomes reported in our study will result in exploration and documentation of the use of rhBMP-2 in this area in the near future.

Other Study Limitations

The present study also had other general limitations. These included its relatively small sample size and single-center, retrospective nature. Thus, the results of the present study should be interpreted cautiously and warrant future prospective studies with larger patient cohorts in multicenter studies to better elucidate the strengths and weaknesses of this novel surgical technique.

CONCLUSIONS

Although the present report was a retrospective and single-center study, we found that the use of rhBMP-2 at the C1-C2 joint without a conventional posterior structural bone graft was a safe and reasonable option. Future prospective, multicenter studies are necessary to further scrutinize the efficacy and safety profile of this surgical strategy.

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