Ultra-Low-Dose Recombinant Human Bone Morphogenetic Protein-2 for 3-Level Anterior Cervical Diskectomy and Fusion

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Abstract: This study evaluated the safety of 3-level anterior cervical diskectomy and fusion (ACDF) with ultra-low-dose recombinant bone morphogenetic protein-2 (rhBMP-2). Thirty-seven consecutive patients with cervical spondylotic myelopathy who were treated with 3-level ACDF and rhBMP-2 were evaluated. Complications such as airway or cervical swelling or hematoma were not observed. The rate of dysphagia was no different at 1, 2, and 6 months postoperatively compared with reports in the literature without rhBMP-2. There were significant improvements in VAS neck/arm pain, Oswestry Neck Disability Index, and cervical lordosis. The use of ultra-low-dose rhBMP-2 for 3-level ACDF may be efficacious for surgically addressing 3-level spondylotic myelopathy. [Orthopedics. 2015; 38(4):241-245.]
Oswestry Neck Disability Index (ONDI); (3) mean length of hospital stay; and (4) radiographic outcomes, including cervical swelling, adjacent segment disease, hypertrophic ossification, cervical lordosis, and graft migration.

**Materials and Methods**

After obtaining appropriate institutional review board approval, the authors retrospectively reviewed the clinical and radiographic outcomes of all 3-level ACDFs with 0.26 to 0.35 mg/level of rhBMP-2 performed between 2008 and 2011. All procedures were performed by a fellowship-trained orthopedic spine surgeon (A.E.) at a single high-volume institution. The study cohort included 37 consecutive patients (20 women and 17 men) with a mean age of 55±9.7 years who were followed for a mean of 4 years (range, 2-5 years). No patient was lost to follow-up. The primary indication for surgery was symptomatic spondylotic myelopathy. Exclusion criteria were trauma cases, infections, tumors, and cases without myelopathy.

All medical records, including history and physical examinations, operative notes, discharge summaries, follow-up office visits, and all appropriate radiographs, were thoroughly reviewed (S.P, A.E.). A majority of the patients had a medical risk factor for pseudoarthrosis, including smoking (43%) and diabetes mellitus (11%). A portion of the data from these patients (n=5) at an earlier follow-up period has been published.

All patients were given a preoperative intravenous (IV) dose of methylprednisolone to decrease postoperative dysphagia and airway complications related to the prolonged retraction in a 3-level anterior surgery and due to the inflammatory response secondary to the rhBMP-2 use. All anterior fusions were performed through a Smith-Robinson approach. Recombinant human BMP-2 was prepared at a concentration of 0.26 to 0.35 mg/level (between one-eighth and one-sixth of an extra-small sponge 1.4 mL at 1.5 mg/mL) with corticocancellous allograft (VG2 allograft; DePuy Synthes Spine, Rayham, Massachusetts). The specific dosage of rhBMP-2 used, which was approximately one-third to one-fourth of that used in previously published reports, was based on the senior author’s experience and a review of the literature. Four-millimeter drill holes were made in the top and bottom of the allograft spacers, and the rhBMP-2 was placed in these holes. A fibrin sealant (Tissseel; Baxter Healthcare Corp, Deerfield, Illinois) was placed anteriorly over the grafts for containment of the rhBMP-2 from the anterior structures. Five (14%) patients had a single cervical corpectomy adjacent to an ACDF at the index surgery. In all cases, an Eagle anterior cervical locking plate (DePuy Synthes Spine) was used.

Cervical drains were used in all cases. Postoperatively, all patients were placed on an IV tapered dose of methylprednisolone while in the hospital and converted to an oral tapered dose at discharge. Patients were discharged once liquids were tolerated. A hard collar was worn for the first 2 weeks, followed by a soft collar for 2 weeks. Physical therapy was initiated approximately 6 weeks postoperatively and included bilateral shoulder girdle modalities addressing pain and stiffness.

All patients were assessed clinically by the senior author at 2 and 6 weeks and 3 and 6 months postoperatively and annually thereafter. During each visit, VAS neck, VAS pain, and ONDI scores were recorded. All patients were examined thoroughly for all potential complications. A perioperative swelling complication was defined as one that occurred within 6 weeks of the index surgery. These included swallowing dysfunction, visible swelling of the surgical site, or breathing difficulties that led to (1) a delay in discharge during hospitalization for the index surgery; (2) a premature return to the clinic or the emergency room after hospital discharge, or any otolaryngological consultation as an outpatient; or (3) readmission for observation and medical management of swelling with or without surgical intervention. Dysphagia was quantified using the Bazaz dysphagia scale.

All available radiographic evaluations performed preoperatively and during each follow-up visit were reviewed for adjacent segment degeneration, cervical lordosis, graft migration or subsidence, hypertrophic ossification posterior to the graft and within the spinal canal, and soft tissue swelling (at C2 and C3). Flexion/extension radiographs and/or computed tomography (CT) scans were obtained if there were concerns for pseudoarthrosis. Symptomatic adjacent segment degeneration was defined as any radiographic evidence of adjacent segment disease (ASD) if the patient had clinical symptoms related to the adjacent segment degeneration.22

Graft subsidence or migration was defined as greater than 2 mm of subsidence or migration on subsequent radiographs. Soft tissue swelling was defined as the distance from the front of the spine to the posterior edge of the trachea. The difference between preoperative and 2-week postoperative values was defined as soft tissue swelling. Radiographic fusion was defined as osseous integration of the graft on sequential postoperative radiographs.

Statistical analysis was performed by using Student’s t test to compare the pre- and postoperative changes in VAS neck pain, VAS arm pain, and ONDI scores. STATA version 11.0 statistical software (STATAcorp, College Station, Texas) was used to perform the analyses. A P value less than .05 was considered significant.

**Results**

The authors observed no airway or cervical swelling complications. Nineteen (51%) patients reported
hoarseness at 2-week follow-up, which resolved in all but 3 patients. Twelve (50%) patients reported dysphagia at 2-week follow-up (8 mild, 3 moderate, 1 severe), 19 (51%) continued to have dysphagia at 6 weeks (16 mild, 3 moderate), and 6 (16%) reported dysphagia at 6 months (6 mild). Four (11%) patients reported dysphagia at latest follow-up. One of these patients had the anterior cervical plate removed due to the dysphagia, but it did not completely resolve 6 months after removal of the plate.

There were significant improvements in VAS neck pain, VAS arm pain, and ONDI scores from preoperatively to final follow-up for all patients. Mean preoperative VAS neck pain and VAS arm pain scores improved from 7.4 and 5.6 points, respectively, to 2.3 (P=.0001) and 1.3 (P=.0001) points postoperatively, respectively. Mean preoperative ONDI score improved from 25.9 to 10.4 points (P=.0001). None of the cases were symptomatic. Six (16%) patients developed postoperative radiographic evidence of anterior segment degeneration, 2 of whom were clinically symptomatic. For these 2 patients, 1 underwent a single-level anterior cervical fusion without rhBMP-2 caudally to the fusion, and the other underwent posterior spinal fusion for dynamic instability at the cervicothoracic junction. Both patients’ symptoms resolved with no dysphagia at 6 weeks and 2 years (final follow-up). There were 4 cases of subsidence. Mean lordosis improved from 3.8° preoperatively to 16.5° postoperatively (P=.0001). None of the cases of subsidence were symptomatic. No incidence of graft migration was observed.

Mean hospital stay was 1.9 days (range, 1-4 days). No patient had a prolonged hospital stay (more than 48 hours) due to dysphagia or visible neck swelling. No patient was readmitted for either medical management or surgical irrigation and debridement of anterior neck swelling.

On radiographic evaluation, all but 1 patient fused within 6 months of surgery. Pseudoarthrosis was seen in 1 (2.7%) patient after a mean of 4 years. The pseudoarthrosis was at the C6-C7 level. Mean swelling anterior to the C2 and C3 vertebral bodies 2 weeks postoperatively was 4.8 and 9.6 mm, respectively. Seven (19%) patients developed hypertrophic ossification posterior to the graft, but it did not extend into the canal or neuroforamen and was therefore not symptomatic. Six (16%) patients developed postoperative radiographic evidence of anterior segment degeneration, 2 of whom were clinically symptomatic. For these 2 patients, 1 underwent a single-level anterior cervical fusion without rhBMP-2 caudally to the fusion, and the other underwent posterior spinal fusion for dynamic instability at the cervicothoracic junction. Both patients’ symptoms resolved with no dysphagia at 6 weeks and 2 years (final follow-up). There were 4 cases of subsidence. Mean lordosis improved from 3.8° preoperatively to 16.5° postoperatively (P=.0001). None of the cases of subsidence were symptomatic. No incidence of graft migration was observed.

**DISCUSSION**

Recombinant human BMP-2 is FDA approved for some fracture nonunions and anterior lumbar interbody fusions. The proposed mechanism of action includes induction of activating transcription factor 4 phosphorylation in chondrocytes through a COX-2/prostaglandin E2–dependent signaling pathway. The potential high fusion rates associated with the use of rhBMP-2 in 3-level ACDF have marked clinical importance, especially in patients who are at a higher risk for pseudoarthrosis. The traditional high doses of rhBMP-2 (up to 2.1 mg/level) have been associated with increased perioperative complications. The current authors hypothesized that using ultra-low-dose rhBMP-2 in 3-level ACDF may provide good fusion rates with lower complication rates than previously reported cases with higher rhBMP-2 doses. In a study of 37 consecutive 3-level ACDFs treated with ultra-low-dose rhBMP-2, there was a 97% fusion rate at 6 months postoperatively, which was maintained at a mean of 4 years postoperatively, with no cervical swelling, hematoma formation, or increased length of stay. Patients had acceptable levels of dysphagia for a 3-level ACDF (11% at latest follow-up).

This study has some limitations, including the small sample size. The retrospective design of the study could have introduced potential biases. Patient satisfaction and broader quality of life measures were not evaluated. The authors did not use a comparison cohort of 3-level ACDF without rhBMP-2. The reliability of plain radiographs to assess for asymptomatic pseudoarthrosis is limited compared with CT scans. Also, the authors did not use CT scans to further confirm the fusion rates. Nevertheless, the authors believe that the outcomes are valuable. Although the safety profile of rhBMP-2 in anterior lumbar interbody fusion has been documented, the safety and efficacy of its off-label use in anterior cervical spine surgery is not FDA approved and is black labeled due to lack of evidence regarding results of various doses of this agent.

Previous studies of rhBMP-2 in ACDF reported a higher incidence of airway complications and dysphagia when compared with patients who did not receive rhBMP-2. However, these complications are dose dependent and were not observed in the current study for this reason. In this study, the rate of dysphagia was no different at 1, 2, and 6 months postoperatively compared with reports in the literature of 3-level ACDF without rhBMP-2 (with rhBMP-2=50%, 51%, 16%, respectively; without rhBMP-2=60%, 39%, and 24%, respectively). Shields et al retrospective reviewed 51 patients who underwent ACDF (n=138) or anterior cervical corpectomy and fusion (n=13) augmented with high-dose rhBMP-2 (up to 2.1 mg/level). They reported that 35 (23.2%) patients had complications, including 15 patients diagnosed with a hematoma, 8 of which were surgically evacuated. Thirteen patients had either a prolonged hospital stay (more than 48 hours) or hospital readmission because of swelling/breathing difficulties or dramatic swelling without hematoma. Smucker et al used 1.5 mg/mL of rhBMP-2 in 69 ACDFs and compared their outcomes with 165 patients who did not receive this agent. They reported that the rhBMP-2 group had a 27.5% complication rate (vs 3.6% in the comp-
Patients in the current study received doses of rhBMP-2 that were one-third to one-fourth the level of the lowest reported doses in the literature. However, the authors previously reported their experience with similar ultralow-dose rhBMP-2 during single-level cervical corpectomies in high-risk patients for pseudoarthrosis. Pourtaheri et al. evaluated 24 consecutive patients with cervical spondylosis who had diabetes mellitus or who were tobacco smokers and who were treated with cervical corpectomy and rhBMP-2 (0.25 to 0.36 mg/level) with stand-alone anterior cervical surgery. Mean number of levels fused was 2.4±0.58. At a mean follow-up of 5 years (range, 3.5-6 years), a 100% fusion rate was observed, with no apparent airway or cervical swelling or hematoma complications. Mean hospital stay was 1.1±0.34 days. However, 4 (16.5%) patients had dysphagia at final follow-up. There were significant improvements in pre- vs postoperative VAS neck pain scores (mean, 7.5 vs 2.0, respectively [P=0.001]), VAS arm pain scores (mean, 5.3 vs 0.92, respectively [P=0.001]), ONDI scores (mean, 28.8 vs 13.4, respectively [P=0.001]), and cervical lordosis (mean, 4.5° vs 11.2°, respectively [P=0.001]). Four (16.7%) patients developed heterotopic ossification posterior to the graft (which was not clinically significant), 4 (16.7%) developed postoperative ASD, 1 (4%) required reoperation, and 4 (16.7%) had subsidence greater than 2 mm.20

In the current study, the dysphagia rates were similar to those in other reports that have not used rhBMP-2. According to a systemic review, the rate of postoperative dysphagia after anterior cervical surgery without rhBMP-2 ranges from 13% to 21% at 1 year.25 Bazaz and Jung prospectively evaluated 221 patients undergoing anterior cervical surgery specifically for 3-level fusions or more, and their dysphagia rates were 60%, 39%, and 24% at 1, 2, and 6 months, respectively.14,23 The current study had similar rates of dysphagia in the early postoperative period and in the long term when compared with ACDF without rhBMP-2, which is encouraging.

CONCLUSION

The authors found that the use of 0.26 to 0.35 mg/mL/level of rhBMP-2 in their cohort resulted in successful fusions (97%) and was associated with fewer complications for 3-level ACDFs than previously reported with rhBMP-2. The authors believe that their outcomes may be considered as a pilot report for future studies. The optimal dosage of rhBMP-2 for 3-level ACDF needs to be validated by a prospective, randomized study.

REFERENCES


