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Multilevel anterior cervical discectomy and fusion with and without rhBMP-2: a comparison of dysphagia rates and outcomes in 150 patients

Clinical article

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Object. Reported complications of recombinant human bone morphogenetic protein–2 (rhBMP-2) use in anterior cervical discectomy and fusion (ACDF) cases include dysphagia and cervical swelling. However, dysphagia often occurs after multilevel ACDF procedures performed with allograft (without BMP) as well. To date, there has been no large study comparing the dysphagia rates of patients who have undergone multilevel ACDF using allograft spacers with those who underwent ACDF using polyetheretherketone (PEEK) cages filled with rhBMP2. The authors report one of the first such comparisons between these 2 patient cohorts.

Methods. The authors retrospectively reviewed 150 patient records. Group 1 (BMP group) consisted of 100 patients who underwent multilevel ACDF with PEEK cages filled with rhBMP-2 and instrumented with a cervical plate. Group 2 (allograft group) included a matched control cohort of 50 patients who underwent multilevel ACDF with allograft spacers and anterior plate fixation (without rhBMP-2). Patient demographics were not significantly different between the groups. Fusion was assessed by means of dynamic radiographs and/or CT at routine intervals. Complications, dysphagia incidence, standardized dysphagia score, Nurick grades, and fusion rates were assessed.

Results. The mean follow-up for the BMP group (Group 1) was 35 months while the mean follow-up for the allograft group (Group 2) was 25 months. There was a complication rate of 13% in the BMP group compared with 8% in the allograft group ($p < 0.005$). There was no significant difference in overall dysphagia incidence between the BMP group and the allograft group (40% vs 44%, respectively; $p > 0.05$). However, there was a significant difference in the severity of dysphagia (using the SWAL-QOL dysphagia scoring system) between the 2 groups: 0.757 for the BMP group versus 0.596 for the allograft group ($p < 0.005$). In subgroup analysis, the use of rhBMP-2 significantly increased the severity of dysphagia in patients undergoing 2-level ACDF ($p < 0.005$). However, the severity of dysphagia did not differ significantly between groups when 3- or 4-level ACDF cases were compared. There was no pseudarthrosis in Group 1 (the BMP group) compared with a 16% pseudarthrosis rate in Group 2 (the allograft group) ($p < 0.05$). There was a weak correlation between the total rhBMP-2 dose and the dysphagia score (Kendall tau rank correlation coefficient 0.166, $p = 0.046$).

Conclusions. The use of rhBMP-2 in patients undergoing 2-level ACDF significantly increases the severity of dysphagia (dysphagia score) without affecting the overall incidence of dysphagia. However, there is no statistically significant difference in the incidence or severity of dysphagia between patients undergoing 3-level or 4-level ACDF treated with PEEK/rhBMP-2 and those treated with only allograft. The use of rhBMP-2 appears to reduce the risk of pseudarthrosis. This benefit is most pronounced in patients who undergo 4-level ACDF and are smokers.
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Key Words • **anterior cervical discectomy and fusion** • **polyetheretherketone** • **bone morphogenetic protein**

The use of rhBMP-2 (INFUSE, Medtronic Spinal and Biologics) has been shown to be efficacious in anterior lumbar spinal fusion. In the lumbar spine, rhBMP-2 use has resulted in reduction of operating time, blood loss, and hospital stay.[3,5,7–9] Furthermore, it has precluded the need for harvest of iliac bone graft and resulted in higher fusion rates when compared with autogenous bone.[4–9] The use of rhBMP-2 in the lumbar spine has been approved by the FDA for use in anterior lumbar interbody fusions.[2] In 2008, the FDA issued a statement warning spinal surgeons to avoid use of rhBMP-2 in the anterior cervical spine until further data were available regarding efficacy and safety.

Prior to the FDA warning letter, several groups did

Abbreviations used in this paper: ACDF = anterior cervical discectomy and fusion; PEEK = polyetheretherketone; PEG = percutaneous endoscopic gastrostomy; rhBMP-2 = recombinant human bone morphogenetic protein–2; UCSF = University of California, San Francisco.

This article contains some figures that are displayed in color online but in black-and-white in the print edition.

report on the use of rhBMP-2 for ACDF in patients at risk for pseudarthrosis (for example, those with osteoporosis, cervical kyphotic deformity, revision fusion surgery, multilevel surgery, or a history of smoking). The rhBMP-2 was used to enhance fusion while avoiding the morbidity involved in autograft iliac crest harvest. Furthermore, rhBMP-2 use avoided the potential for disease transmission from allograft bone. This issue arose in 2005, when an allograft source in New Jersey was found to not be screening cadavers appropriately for transmissible disease.[10,11,17,20]

Recently, several reports of complications associated with the use of high-dose rhBMP-2 in ACDF procedures have appeared in the literature.[15,16,18,19] These complications included postoperative hematoma and soft-tissue edema without hematoma.[16,18,19]

We retrospectively reviewed 100 cases involving patients treated with multilevel (2 or more levels) ACDF augmented with rhBMP-2 within a PEEK cage with plate placement and compared this cohort to 50 cases involving profile-matched patients treated with standard ACDF with structural allograft (without BMP) and plating. We specifically compared the parameters of dysphagia, pseudarthrosis, and clinical outcome.

Methods

Patient Population

We retrospectively reviewed 100 consecutive cases in which a multilevel (2 or more levels) ACDF was performed using a PEEK spacer filled with rhBMP-2 on a Type I collagen carrier sponge (0.7–2 mg of rhBMP-2 per level) along with plate fixation between 2002 and 2006 in one institution (Emory University). As a 2:1–ratio control cohort, 50 patients who had undergone multilevel ACDF were matched in surgical levels, number of levels, smoking status, and age to the study population. Patients in the rhBMP-2 cohort were consecutively chosen. The patients in the control cohorts were matched for the number of levels of ACDF performed and by the date of operation. The patients in the control allograft cohort underwent surgery at UCSF between 2005 and 2007. The clinical and radiographic records of these cases were reviewed. All patients in both cohorts had anterior fixation procedures only (no posterior fixation).

There were no statistically significant demographic differences between the control allograft cohort and the BMP group when analyzed for age, sex, or smoking status (Table 1).

TABLE 1: Summary of characteristics of patients undergoing ACDF with rhBMP-2 or allograft*

Variable	Group 1 (BMP)	Group 2 (allograft)
no. of pts	100	50
mean age (yrs)	51	55
sex (% female)	55	54
smokers (%)	18	16
FU (mos)	35	25

* There was no statistically significant difference between groups with respect to age, sex, or smoking status. Abbreviations: FU = follow-up; pts = patients.

Surgical Technique

All patients underwent anterior cervical fusions via the Smith-Robinson approach and received 10 mg of dexamethasone prior to incision. For the BMP group (Group 1), we used a PEEK cage filled with a portion of an rhBMP-2–soaked collagen sponge (Fig. 1 left) and supplemented with an anterior cervical plate. The initial 10 patients in the BMP cohort had a total dose of 2.1 mg of rhBMP-2 per level (one-half of a small INFUSE kit).[3] In the subsequent 48 patients, we reduced the amount of rhBMP-2 to one-half of a small sponge (1.05 mg of rhBMP-2 or one-fourth of a small INFUSE kit) embedded into a PEEK spacer. Subsequently, we again reduced the amount of sponge placed into the PEEK spacer to one-third of a small sponge (0.7 mg of rhBMP-2 or one-sixth of a small INFUSE kit) for the final 42 patients in this series after reviewing the work of Lanman and Hopkins.[13] With each of these doses, the collagen sponge was soaked in the reconstituted rhBMP-2 for a minimum of 30 minutes and then placed into the PEEK spacer. We did not irrigate after the placement of the rhBMP-2–filled PEEK spacer to avoid diluting the rhBMP-2 concentration and to minimize exposing surrounding tissues to washed rhBMP-2. No BMP sponges were placed outside the PEEK spacer. All patients had an anterior cervical titanium plate placed.

In the control allograft group (Group 2), all patients were treated with a machined structural allograft spacer packed with local bone shaving and supplemented with anterior cervical plate fixation (Fig. 1 right). The plating system for both cohorts includes both semiconstrained rotational and translational plates.

Dysphagia Calculation

The incidence of dysphagia was retrospectively assessed with the SWAL-QOL scale, which is a 5-point scale assessing difficulty with eating, drinking, and having food stick in the throat.[14] A score of 1 indicates the patient almost always had difficulty; a score of 2 indicates the patient often had difficulty; a score of 3 indicates the patient sometimes had difficulty; a score of 4 indicates that the patient hardly ever has difficulty; and a score of 5 indicates the patient never had difficulty. For the dysphagia incidence calculation, the patient was considered "positive for dysphagia" if the SWAL-QOL score was less than 4 in any of the categories during the 7-day postoperative period.

During hospitalization, patients were asked if they had dysphagia on a daily basis. The patients' subjective responses were recorded in the chart. These responses were retrospectively rated with the SWAL-QOL scoring system. After discharge, all patients were followed up in clinic and were asked about dysphagia at 2 weeks, 6 weeks, 3 months, 6 months, 12 months, and 24 months after surgery. Their subjective responses were recorded in the chart and also retrospectively rated with the

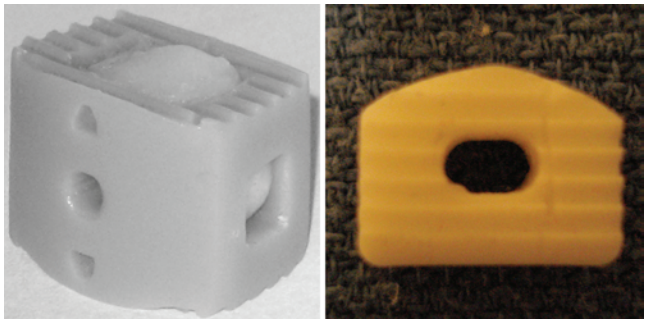

Fig. 1. Photographs of a PEEK cage filled with a sponge soaked in rhBMP-2 **(left)** and structural allograft spacer **(right)**.

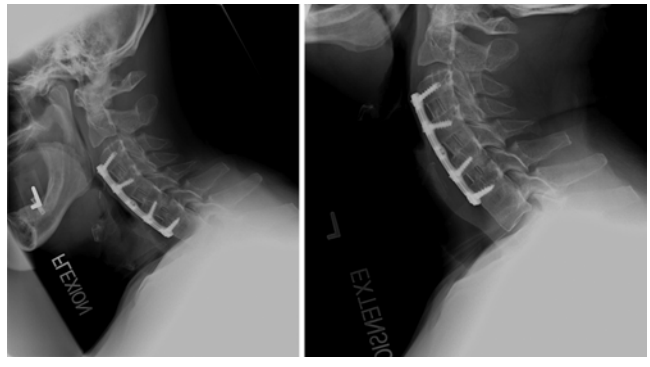

Fig. 2. Lateral dynamic flexion **(left)** and extension **(right)** radiographs demonstrating solid fusion at 6 months subsequent to a 3-level ACDF procedure with PEEK cages and rhBMP-2.

SWAL-QOL scoring system. Clinically significant dysphagia was defined as dysphagia that created difficulty with swallowing soft food. In patients with clinically significant dysphagia, the disorder was stratified as mild, moderate, or severe. Patients with mild dysphagia were those who were identified to have subjective swallowing difficulty that prolonged their hospitalization by 48 hours or more. Patients with moderate dysphagia were those who were identified to have swallowing difficulty that delayed their discharge 72 hours or more and required a speech therapy evaluation and/or modification of diet. Patients with severe dysphagia were those who were unable to sustain adequate nutrition by swallowing and required supplemental nutrition by a nasal feeding tube or PEG tube. For statistical calculation, numerical values were assigned to none (0), mild (1), moderate (2), and severe (3) dysphagia. Averages of these scores were computed within the cohorts and comparisons were made.

The total dose of rhBMP-2 was compared with the dysphagia score to assess a correlation. The total dose of rhBMP-2 used was obtained by multiplying the dose of rhBMP-2 per level by the number of levels treated.

Fusion

Fusion was assessed by flexion-extension lateral radiographs at clinic follow-up, as described in the Cervical Guidelines,[12] for evidence of motion within the construct and lucency within the interface of the bone graft and vertebral body (Fig. 2). Thin-cut CT was performed if the radiographic findings were equivocal (no abnormal motion but persistent lucency at bone and graft interfaces or difficult to assess levels by plain radiograph; Fig. 3). At 1 year after the ACDF procedure, if fusion was not observed, the individual was deemed to have pseudarthrosis.

Statistical Analysis

Statistical analysis was performed by GraphPad Instat 3.0 (GraphPad Software). For categorical or nominal data, the Fisher exact test was used; and for continuous measurements, the Student t-test was used. The Kendall tau rank correlation test was used to assess the correlation between total rhBMP-2 dose and dysphagia score. A p value < 0.05 was deemed statistically significant.

Results

The mean duration of follow-up was 35 months in the BMP group (Group 1) and 25 months in the allograft group (Group 2).

Overall, there was an increased rate of short-term complications with the use of rhBMP-2, with complications noted in 13 (13%) of the 100 patients in the BMP group and 4 (8%) of the 50 patients in the control group ($p < 0.005$, Table 2). Of the 13 patients treated with rhBMP-2 who had complications, 5 required further surgery for evacuation of either a postoperative hematoma (2 patients) or seroma (2 patients, Fig. 4), or repair of a CSF leak (1 patient). An additional 3 of the 13 patients required readmission within 1 week of the initial surgery for difficulty swallowing or breathing. They were treated with a brief course of intravenous dexamethasone and then discharged within 2–3 days. Three patients had transient recurrent laryngeal nerve palsies that ultimately resolved. One patient suffered from aspiration pneumonia and required a temporary tracheostomy tube placement. One patient had transient C-5 nerve root palsy that resolved upon follow-up at 4 months.

Of the 4 patients with short-term complications in the control cohort, 3 had superficial wound erythema and/or infection that resolved with oral antibiotics. One patient had a transient C-5 nerve root palsy.

There was no statistically significant difference in the overall incidence of dysphagia between the BMP group (40%) and the control allograft group (44%, Table 2). However, when comparing the severity of dysphagia, there was an increase in severity in the BMP cohort (dysphagia score of 0.757 for the BMP group vs 0.596 for the allograft group, $p < 0.005$). In subgroup analysis stratified by number of surgery levels, there was a significant difference in the severity of dysphagia for patients undergoing 2-level ACDF (dysphagia score of 0.778 for the BMP group vs 0.318 for the allograft group, $p < 0.05$; Table 3). For patients treated with 3-level and 4-level ACDF, however, there were no significant differences in dysphagia rate or severity of dysphagia when comparing the control and rhBMP-2 group ($p > 0.05$; Tables 4 and 5).

We found that 4% of the rhBMP-2 treated patients underwent PEG tube placement, but none of the control cohort had PEG tube placement. Of the 4 patients in the

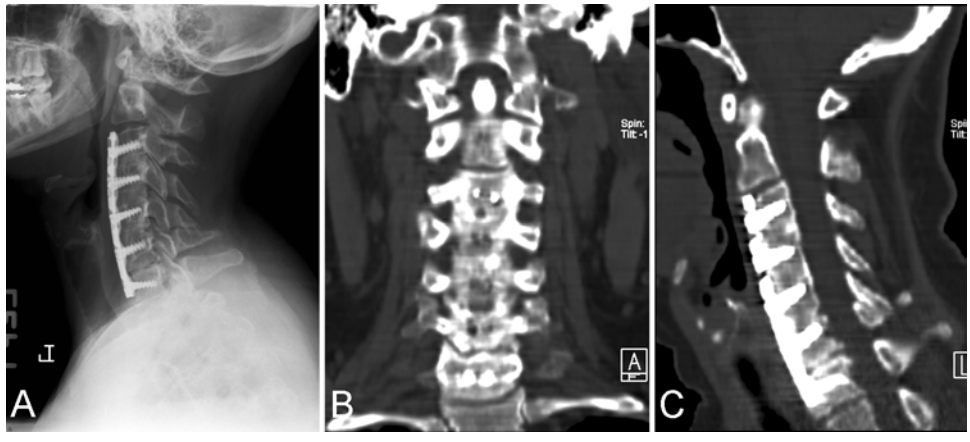

Fig. 3. Radiographs obtained 1 year postoperatively in a patient who underwent a 4-level ACDF procedure. **A:** Lateral radiograph demonstrating a 4-level ACDF with possible pseudarthrosis at C6–7. **B and C:** Coronal (B) and sagittal (C) CT reconstructions confirming the pseudarthrosis at C6–7.

BMP group who had PEG tubes, 2 had prior cervical surgery and were treated with ACDF with BMP in a revision setting, whereas the remaining 2 had no previous surgery. Also, among the patients with PEG tubes, 1 had undergone a 4-level ACDF with BMP, 2 had undergone 3-level ACDFs with BMP, and 1 had a 2-level operation with BMP (but this patient had a comorbidity of amyotrophic lateral sclerosis).

In analyzing the relationship between the total dose of BMP used and dysphagia score, we performed a rank correlation analysis by utilizing the Kendall tau rank correlation test and found a weak correlation (correlation coefficient 0.166, $p = 0.046$).

Nurick Scores

When comparing Nurick scores between groups, we found there was no significant difference in the postoperative Nurick outcome score between the rhBMP-2 group and the allograft group (Table 2).

Pseudarthrosis

Pseudarthrosis was assessed with dynamic cervical radiographs at 6-month intervals. Computed tomography was used to assess for pseudarthrosis in only those patients whose radiographs were indeterminate. There was a significant difference in the rate of pseudarthrosis between the groups. Fusion was achieved in all the patients in the BMP group (0% pseudarthrosis), whereas 16% of patients in the allograft control group had pseudarthrosis ($p < 0.0001$).

Subgroup analysis was done to assess pseudarthrosis by number of surgical levels. For 2-level cases, there was an 18% rate of pseudarthrosis in the allograft group. For 3-level cases, there was a 6% rate of pseudarthrosis in the

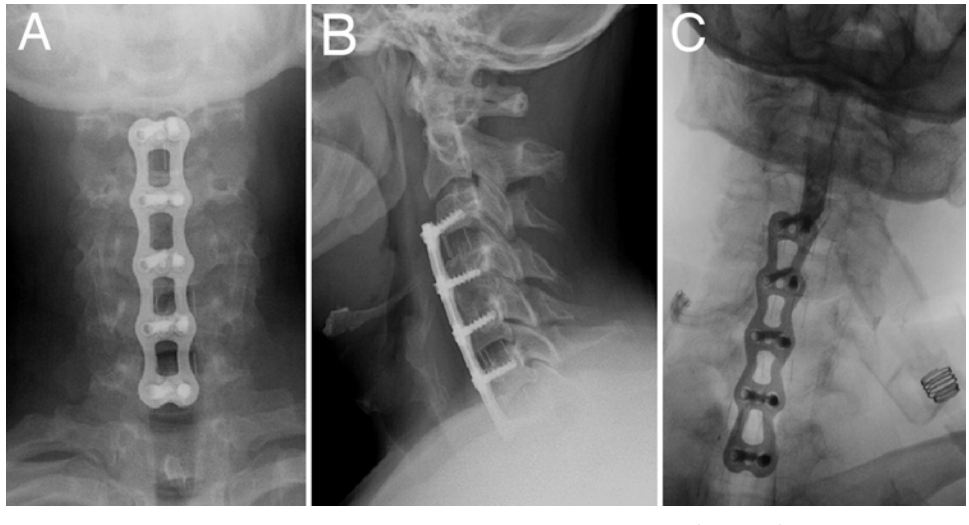

Fig. 4. Anteroposterior **(A)** and lateral **(B)** radiographs obtained in a patient with a 4-level ACDF associated with dysphagia and cervical swelling. This patient required reexploration of the surgical site on the 5th postoperative day for drainage of a seroma. A subsequent anteroposterior radiograph of an esophagram demonstrated dysmotility related to swelling **(C)**. Note the blockage of dye at the upper portion of the construct. Despite this swelling-induced dysmotility, the patient did not require a PEG and had complete resolution of his dysphagia 6 weeks after his initial surgery.

TABLE 2: Summary of clinical outcomes for ACDF with and without rhBMP-2

Variable	Group 1 (BMP)	Group 2 (allograft)
complication rate (%)	13*	8
dysphagia		
incidence	40	44
mean score	0.757*	0.596
Nurick grade		
preop	0.933*	1.288
postop	0.238	0.268
pseudarthrosis rate (%)	0*	16

* $p < 0.005$.

allograft group. For 4-level cases, there was a 40% rate of pseudarthrosis in the allograft group (Table 5).

Overall, the percentage of patients in each group who were smokers was 18% in the BMP group and 16% in the allograft group (this difference was not statistically significant). In the BMP group, 20% of the patients treated with 2-level ACDF were smokers, compared with 15% in the allograft group ($p > 0.05$). In the BMP group, 14% of the patients treated with 3-level ACDF were smokers, compared with 16% in allograft group ($p > 0.05$). In the BMP group, 14% of the patients treated with 4-level ACDF were smokers, compared with 20% allograft group ($p > 0.05$). There were no statistically significant differences in the percentage of smokers in each subgroup. However, it is interesting to note that a majority (63%) of the allograft cohort patients who exhibited pseudarthrosis were smokers, whereas all the patients who were in the BMP group had a solid fusion regardless of smoking status.

Discussion

Recombinant human BMP-2 is approved by the FDA for use as an osteoinductive protein in anterior lumbar interbody fusion procedures. Its use in the cervical spine is considered off-label by the FDA. The most notable complication reported in the literature regarding the use of rhBMP-2 in the anterior cervical spine has been dysphagia associated with retropharyngeal cervical soft-tissue swelling.[18,19] However, there is an inherent risk of dysphagia and cervical swelling associated with ACDF procedures without rhBMP-2 that increases with the number of surgical levels.[1] This is one of the first works to compare the risk of dysphagia with and without the use of rhBMP-2 in patients treated with multilevel ACDF.

We had previously reported on a series of 200 patients who underwent ACDF (1–4 levels) with rhBMP-2.[21] All patients in this cohort achieved solid radiographic fusion, and the rate of clinically significant dysphagia was 7%. In this prior publication we found 4% of patients requiring repeated operation for hematoma or seroma.

The present analysis served to advance our previous work by matching a control cohort of 50 profile-matched patients who underwent multilevel ACDF (with allograft and plating) and did not receive rhBMP-2 with 100 patients who underwent multilevel ACDF (with BMP) to compare the complication rates. We sought to differentiate the effect of the number of surgery levels versus the use of rhBMP-2 on the dysphagia rate. Additionally, we compared other clinical parameters such as fusion, complications, and Nurick score.

Over the years, we progressively decreased the dose of rhBMP-2 during this study (from 2.1 to 0.7 mg per level) in an attempt to minimize the complications of rhBMP-2 use (dysphagia and edema) while still achieving the osteoinductive effects of rhBMP-2.

We observed a dysphagia incidence of 40% in the BMP group (Group 1) versus 44% in the allograft group (Group 2) (no statistically significant difference). These rates are higher than in our previously published study since we excluded all 1-level cases and used the more sensitive SWAL-QOL scale to detect dysphagia. Although the overall dysphagia incidence was slightly higher in the

TABLE 3: Summary of clinical outcomes for 2-level ACDF procedures

Variable	Group 1 (BMP)	Group 2 (allograft)
no. of pts	59	27
complications	12*	0
Nurick grade		
preop	0.821	1.09
postop	0.179	0.136
dysphagia		
mean score	0.778*	0.318
incidence (%)	29	32
pseudarthrosis rate (%)	0*	18
smokers		
% of pts w/ pseudarthrosis	0*	75
% of group	20	15

* $p < 0.05$.

TABLE 4: Summary of clinical outcomes for 3-level ACDF procedures

Variable	Group 1 (BMP)	Group 2 (allograft)
no. of pts	35	18
complications	14	19
Nurick grade		
preop	1.05*	1.75
postop	0.318	0.25
dysphagia		
mean score	0.730	0.714
incidence (%)	46	50
pseudarthrosis rate (%)	0	6
smokers		
% of pts w/ pseudarthrosis	0	0
% of group	14	16

* $p < 0.05$.

TABLE 5: Summary of clinical outcomes for 4-level ACDF procedures

Variable	Group 1 (BMP)	Group 2 (allograft)
no. of pts	7	5
complications	28.6	20
Nurick grade		
preop	1.29	2
postop	0.33	0.8
dysphagia		
mean score	1.167	1.2
incidence (%)	71	80
pseudarthrosis rate (%)	0	40
smokers		
% of pts w/ pseudarthrosis	0*	50
% of group	14	20

* $p < 0.05$.

allograft group (Group 2) ($p > 0.05$), the severity of the dysphagia in the BMP group (Group 1) was greater than in the allograft group. In subgroup analysis, we found the greatest increase in the severity of dysphagia in the 2-level ACDF subgroup treated with rhBMP-2. This increase in severity of dysphagia was not seen when comparing the 3- or 4-level ACDF subgroups. This analysis suggests that the dysphagia effect observed in patients in the BMP group who had undergone 3- and 4-level ACDFs is likely mostly attributable to the surgical exposure, retraction, and duration of the surgery.

Confirming our previous report of a possible correlation between the total rhBMP-2 dose and the incidence of dysphagia, we did observe a weak correlation between total rhBMP-2 dose and dysphagia (correlation coefficient 0.166, $p = 0.046$). This suggests that while the total dose of rhBMP-2 used probably does impact the severity of dysphagia, it is only one of the many possible contributors (others likely being duration of surgery, number of exposed levels, and the patient's body habitus).

We observed a 16% pseudarthrosis rate in the multilevel allograft control cohort (compared with no pseudarthrosis in the multilevel BMP group). Our criterion for fusion was stringent (use of dynamic radiographs and/or CT evaluation demonstrating bridging bone). Of note, only 1 patient with radiographic pseudarthrosis (Group 2) underwent a posterior cervical fusion during the follow-up period. The remaining individuals with radiographic pseudarthrosis (all in Group 2) were followed. Three patients in this pseudarthrosis group with significant symptoms are being medically managed and may require revision surgery in the future. Additionally, 63% of the allograft group (Group 2) patients who had pseudarthrosis were smokers.

Although the economics of rhBMP-2 use is not the focus of this paper, we performed a preliminary economic analysis. As of this writing, the current average cost of an XX Small INFUSE kit at the study institutions is $800, which allows for up to 4 levels of ACDF (note that this XX Small INFUSE kit was not available until 2008). The average cost for the Medtronic Cornerstone PEEK spacer is $990, and the average cost of the Cornerstone bone allograft spacer is $890. Therefore, there is an approximate $900 differential in instrumentation/substrate cost between the cases with rhBMP-2 compared with those without. For a pseudarthrosis that requires surgical intervention, a posterior cervical fusion is often elected. The hardware cost of a posterior cervical fusion with a 1-level construct averaged $5492.50 at the study institutions (drill bit × 1 = $375.00; lateral mass screws × 4 = $3858.40; rods = $286.30; setscrews × 4 = $436.80; allograft cancellous bone chips [30 cm^3] = $536.00).

Depending on the hospital and type of insurance, the cost of the surgeon's fee, operating room time, imaging, and a single day of hospitalization in a regular ward would increase the total cost to approximate $22,000 at our study institutions. So, based on such crude financial analysis, the use of rhBMP-2 would make sense if the operative pseudarthrosis rate exceeds 4.1% (cost of rhBMP-2 use in ACDF/cost of posterior cervical fusion for pseudarthrosis × 100). Our current operative pseudarthrosis rate is 2%, which does not economically justify the use of rhBMP-2 in patients undergoing multilevel ACDF. However, we believe that our follow-up of 2 years is not adequate to effectively assess operative pseudarthrosis rate. Based on our study, if all current symptomatic pseudarthrosis patients progress to surgery, our operative pseudarthrosis rate would be 8%, thus exceeding the economic threshold of rhBMP-2 use. Such economic study of rhBMP-2 use would require a larger cohort with longer follow-up.

There were no cases of pseudarthrosis in the BMP group regardless of the patients' smoking status or the number of levels treated. This data suggests the use of rhBMP-2 in patients undergoing multilevel ACDF who are smokers may be of benefit and may merit further investigation.

Conclusions

The use of rhBMP-2 in patients undergoing 2-level ACDF significantly increases the severity of dysphagia (dysphagia score) without affecting the overall incidence of dysphagia. However, with respect to the incidence or severity of dysphagia in patients who have undergone 3- or 4-level ACDF, there is no statistically significant difference between patients treated with a PEEK cage filled with BMP and those treated with an allograft spacer. The use of rhBMP-2 appears to reduce the risk of pseudarthrosis. This benefit is most pronounced in patients treated with 4-level ACDF who are smokers.

Disclosure

Dr. Chou is a consultant for Stryker Spine.

Author contributions to the study and manuscript preparation include the following. Conception and design: all authors. Acquisition of data: all authors. Analysis and interpretation of data: all authors. Drafting the article: Lu, Chou. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors:

Lu. Statistical analysis: Lu, Tumialán. Administrative/technical/material support: Lu. Study supervision: Lu, Chou.

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