I\textbf{t is well known that pseudarthrosis remains a major limitation of instrumented, multilevel anterior cervical fusions. In 2002, Barnes et al.\textsuperscript{1} reported on a series of 77 patients who had undergone anterior cervical discectomy and fusion using the Atlantis cervical plating system (Medtronic Sofamor-Danek) with fibular allograft; the authors reported satisfactory outcomes in only 65\% of patients who had undergone multilevel procedures, with an overall fusion rate of only 90\%. Other recent studies have shown that while anterior cervical plating can improve the fusion rate of 2-level fusions to approximately that of uninstrumented single-level procedures, there is still an unacceptably high rate of pseudarthrosis in 3- and 4-level fusions.\textsuperscript{6,12}

Given these high rates of pseudarthrosis, there is an important need for new techniques and materials that can help decrease the rate of pseudarthrosis in multilevel fusions. One strategy that is commonly used is to supplement multilevel anterior fusion with posterior instrumentation to increase the rigidity of the construct. This strategy, however, adds to the morbidity of the procedure and increases surgical time.\textsuperscript{11} Alternatively, one innovative technique aimed at decreasing the pseudarthrosis rate in cases of multilevel fusion is the adjuvant use of BMP as a fusion enhancer. Although currently an FDA “off-label” use, there have been numerous articles on rhBMP-2 use in anterior cervical fusion.\textsuperscript{2,4,8,10,13–17} These reports have indicated that successful fusion can be achieved with BMP, but there have been safety concerns due to complications that

Fusion rates in multilevel, instrumented anterior cervical fusion for degenerative disease with and without the use of bone morphogenetic protein

\textbf{Clinical article}

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\textit{Object.} The goal of this study was to compare the rates of solid arthrodesis and complications following multilevel, instrumented anterior cervical fusion in patients treated with and without bone morphogenetic protein (BMP).

\textit{Methods.} The authors conducted a retrospective cohort study of patients who underwent multilevel (2+ level) anterior cervical fusions performed for degenerative disc disease with or without the concurrent use of BMP-2 from 1997 to 2012. The dosage throughout the study ranged from 2.1 to 0.26 mg/level (mean 1.0 mg/level). All patients were evaluated postoperatively by means of radiographs and CT scans to determine fusion status.

\textit{Results.} The overall fusion rate for the patients treated without BMP (n = 23) was 82.6\% compared with a 100\% fusion rate in the group treated with BMP (n = 22) (p = 0.04). The pseudarthrosis rates increased with number of fusion levels in patients who did not receive BMP, whereas all patients in the group treated with BMP had solid arthrodesis. Furthermore, there were 2 instrumentation failures in the non-BMP group. There was a direct correlation between the incidence of complications and the dosage of BMP used per level, with no complications reported at doses equal to or less than 1.1 mg/level.

\textit{Conclusions.} The overall rate of bony arthrodesis was increased following the use of BMP in multilevel anterior cervical fusion. Traditional methods without BMP had a high rate of pseudarthrosis. The complications associated with the use of BMP appeared to be dose related and of low incidence when BMP is used in doses equal to or less than 1.1 mg/level.

(key Words) • bone morphogenetic protein • cervical spine • fusion • instrumentation

Abbreviations used in this paper: ACDF = anterior cervical discectomy and fusion; BMP = bone morphogenetic protein; rhBMP-2 = recombinant human BMP-2.

This article contains some figures that are displayed in color online but in black-and-white in the print edition.
have been associated with its use. Many of the earlier reported cases were performed with high doses of BMP, and the effectiveness and complication profile of lower dose versus higher dose BMP has not been determined. Given the uncertainties associated with BMP use in the anterior cervical spine, the goal of this study was to examine the effectiveness of BMP as a fusion enhancer in multilevel (2- to 4-level) anterior cervical fusion with fibular allograft and an anterior cervical plating system.

**Methods**

Patients were identified by means of retrospective chart review. Patients over the age of 18 who underwent a 2-, 3-, or 4-level ACDF performed by the senior author (A.D.L.) between January 1997 and January 2012 at the University of Miami/Jackson Memorial Medical Center were included. Patients were categorized into the BMP group if BMP was used and into the non-BMP group if BMP was not used. Only patients who underwent a stand-alone procedure (without a concurrent posterior procedure) and had no prior cervical surgery were included.

All patients underwent a standard exposure of the anterior cervical spine. Decompressions involved removal of disc material as well as burring of the endplates to promote fusion at the graft-host interface. Decompression varied from 2 levels to 4 levels. A 1-level corpectomy would span by definition a minimum of 2 interspaces and would be calculated in the data as a 2-level fusion as the allograft would have to fuse with only 2 endplates. The numbers of levels were added when discectomies and corpectomies were combined (for example, a 1-level discectomy and 1-level corpectomy would be calculated as 2 levels). Bone morphogenetic protein was offered beginning in 2003 to those patients who the senior author felt had a high likelihood of developing pseudarthrosis. Each fibular allograft in the non-BMP group was supplemented by vertebral autograft from the burred endplates. In the BMP group, INFUSE (Medtronic) rhBMP-2 strips were packed inside fibular allografts. The size of INFUSE kit and amount of BMP placed varied from patient to patient (range 0.26–2.1 mg/level, mean 1.0 mg/level). In patients from both groups, an Atlantis cervical plate (Medtronic Sofamor-Danek) was affixed to the anterior cervical spine with variable-angle screws and screw placement was unicortical. Intraoperative fluoroscopic guidance was used in all cases, with a special emphasis on placement of parallel screws within each of the vertebral bodies.

Patients were specifically asked if they had suffered any neck pain or dysphagia for liquids and solids during follow-up examinations, and clinical outcome was divided into clinically worse, unchanged, or improved based on patient-related questionnaires and self-assessments. Two sets of radiographs were reviewed by the principal investigators and an independent radiologist: 3-month postoperative and remote (minimum 1-year) postoperative anteroposterior, lateral, flexion, and extension radiographs or fine-cut CT scan. The radiographs were reviewed for fusion and instrumentation failure. Principal investigators were not blinded in reviewing the films, but the independent radiologists had no knowledge of BMP status. Instrumentation failure was defined as plate and/or screw backout, fracture of plate and/or screw, or telescoping of construct. Pseudarthrosis was defined by multiple criteria. Primary among these was the presence of motion on flexion-extension radiographs. In the absence of motion, a failure of fusion was diagnosed by the presence of lucency at the graft-endplate interface and absence of bony trabeculations across the graft-endplate interface. If the principal investigators or the independent radiologists observed motion on flexion/extension, lucency at the graft-endplate interface, or lack of bony trabeculations across the graft-endplate interface, the patient was considered to have a pseudarthrosis (Fig. 1). Patients were included in the study only if they 1) had follow-up imaging studies from at least 12 weeks after surgery showing solid fusion according to the criteria described above, and/or 2) had follow-up imaging from at least 12 weeks after surgery showing a lack of fusion as well as additional imaging from more than 1 year after surgery.

**Results**

There was a total of 45 patients meeting the defined criteria for inclusion. Twenty-two of these patients were in the BMP group and 23 were in the non-BMP group (Table 1). The average patient age was 52 years in the non-BMP group and 48 years in the BMP group. There were no significant differences between groups with respect to age, sex, or smoking history (Table 1). The average length of follow-up was 54 months for the non-BMP group (range 14–161 months) and 35 months for the BMP group (range 3–117 months). In the non-BMP group, one patient was treated for traumatic C-5 fracture resulting in incomplete quadriplegia (fusion success). All other patients in both groups underwent surgery for either radiculopathy and/or myelopathy caused by degenerative changes (cervical spondylosis).

The overall fusion rate was 91.1% for all patients combined. There was a significantly higher overall rate of fusion in patients who underwent procedures with BMP compared with fusion performed without BMP. In the patients who underwent fusion without BMP, the fusion rate was 83%, compared with 100% in patients who underwent fusion with BMP (Pearson chi-square, p = 0.040).

In the 23 patients in the non-BMP group, there was an overall 83% fusion rate, with an 87.5% fusion rate for patients who underwent 2-level procedures (Fig. 2). In the non-BMP group, 16 patients underwent fusion at 2 levels, 4 underwent fusion at 3 levels, and 3 underwent fusion at 4 levels. There were 2 instrumentation failures in the entire non-BMP group (a 2-level case and a 4-level case).

In the 22 patients in the BMP group, there was a 100% fusion rate (Fig. 2). Twelve patients underwent fusion at 2 levels, 9 underwent fusion at 3 levels, and 1 underwent fusion at 4 levels. There were no instances of instrumentation failure in this group.

There were no significant differences between fusion rates for patients in the non-BMP and BMP groups when comparing patients based on the number of fusion levels performed (that is, 3-level BMP vs 3-level non-BMP) due to the relatively small numbers (Fig. 3).

The cases in the BMP group were also analyzed by the dose of BMP used per level of fusion. A total of 5

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patients received a dose of 2.1 mg/level; 3 received 1.4 mg/level; 5 received between 1.1 and 0.5 mg/level, and 9 received less than 0.5 mg/level.

There was a total of 9 complications in the study. There was a nonsignificant trend toward higher rates of complications in the patients who underwent fusion with BMP (22.7% vs 17.4%, p > 0.05). In the BMP group, a total of 5 patients complained of complications. These included 4 instances of dysphagia (resulting in 1 emergency room visit), 1 of which was accompanied by neck pain, and 1 instance of cervical swelling. In the non-BMP group there were 4 complications, including 1 instance of Horner syndrome, 1 episode of tracheal swelling requiring urgent reintubation, and 2 instances of dysphagia, 1 of which required placement of a Dobhoff tube for 1 week.

On follow-up examination, 21 of 22 patients in the BMP group reported an improvement in their symptoms, while 1 patient reported that the symptoms remained unchanged. In the non-BMP group, 20 of 23 patients reported an improvement in their symptoms and 3 reported that the symptoms remained unchanged. No patient in either group reported worsening of symptoms.

There was a direct correlation between the incidence of complications and the dosage of BMP used per level (Pearson correlation 0.753, p < 0.01) (Fig. 3), with 4 of the 5 patients in the 2.1 mg/level group and 1 of the 3 patients in the 1.4 mg/level group complaining of complications. There were no complications reported at any doses less than 1.4 mg/level (Fig. 3). There were 2 instances of dysphagia (1 in a 2-level patient, 1 in a 3-level) and 2 instances of instrumentation failure (1 in a 2-level patient, 1 in a 4-level) in the non-BMP group.

**Discussion**

There were several key findings from this retrospective analysis of fusion rates in anterior cervical discectomy with and without BMP. First, this analysis highlights the high rates of pseudarthrosis seen in multilevel cervical discectomy using traditional techniques. In fact, almost 20% of patients who underwent multilevel cervical fusion without BMP developed a pseudarthrosis. This finding is consistent with prior reports in the literature. In 1993, Bohlman et al. found that the risk of pseudarthrosis using traditional techniques was significantly greater after a multilevel fusion than a single-level fusion (p < 0.01). In fact, pseudarthrosis was seen in 7 (11%) of 62 patients who had a single-level fusion compared with 13 (27%) of 48 who had a 2-level procedure, 3 of 11 who had a 3-level procedure, and the only patient (1 of 1) who had a 4-level procedure. Likewise, Bolesta et al. found solid arthrodesis at all levels in only 7 (47%) of 15 patients who underwent 3- and 4-level fusions using plate fixation.

Importantly, the current study also demonstrated that the use of BMP resulted in a dramatic increase in solid arthrodesis rates (100%, regardless of levels) for multilevel, instrumented cervical fusions. Unfortunately, due to

**TABLE 1: Demographic characteristics of patients treated with and without the use of BMP**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BMP (n = 22)</th>
<th>No BMP (n = 23)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>average age (yrs)</td>
<td>48</td>
<td>52</td>
<td>0.311</td>
</tr>
<tr>
<td>male</td>
<td>14 (63.6)</td>
<td>12 (52.2)</td>
<td>0.436</td>
</tr>
<tr>
<td>smoking history</td>
<td>7 (31.8)</td>
<td>6 (26.1)</td>
<td>0.672</td>
</tr>
</tbody>
</table>

* Values represent numbers of patients (%) unless otherwise indicated.
the relatively small number of patients in this study, subgroup comparisons based on the number of levels of fusion performed did not reach statistical significance. This analysis showed no instance of pseudarthrosis for 2-level fusions in the BMP group, and 1 instance in the non-BMP group, resulting in 100% and 87.5% fusion rates, respectively. These findings are similar to those of Baskin et al., who found a 100% fusion rate in a randomized trial of BMP for single-level anterior cervical fusion.

Unfortunately, due to the nonrandom, retrospective nature of this study, there is a degree of selection bias present, as the senior author preferentially offered BMP to patients who he believed to be at higher risk for nonfusion, and the majority of these patients were treated at a later time than those in the non-BMP group. This bias should have had the effect of decreasing the fusion rates in patients in the BMP group, and because of this, combined with the high rates of fusion in that group relative to the non-BMP group, makes the current findings more compelling. The reason for the relatively shorter duration of follow-up in the BMP group relates to the use of BMP at higher doses early in 2003 and then suspension of the practice of using BMP until it was better understood, many years later, that our early experience with postoperative dysphagia and hospital readmission was most likely due to the higher doses.

This study adds to the relatively small volume of literature on BMP use in the cervical spine. The use of BMP in the anterior cervical spine has been evaluated in a single prospective, randomized clinical trial involving 33 patients with 1- or 2-level disease, using an anterior plating system. This study found a 100% fusion rate in the BMP group as well as the non-BMP group, with no device-related adverse events reported. Other authors have concluded that using a PEEK spacer filled with low-dose (0.7 mg/level) rhBMP-2 leads to solid fusion, with rare complications, even in multilevel cases. Finally, an additional study compared the outcome of ACDF performed with BMP and allograft against iliac crest bone graft and found that “ACDF with BMP seemed to have a higher fusion rate for multilevel cases as compared with most recent ACDF with allograft reports,” but the authors also noticed an increased incidence of neck swelling in the BMP group—a known complication of using high doses of BMP.

Of note, we chose not to perform any single-level fusions with the use of BMP. This decision was made by comparing the low risk of pseudarthrosis in these cases with the potential added monetary cost of the use of BMP. We previously examined 29 sequential single-level ACDF cases in which BMP was not used and found a 100% fusion rate in all of these cases with a 1-year follow-up (unpublished data), which is a rate consistent with the available literature. It was thus felt that any added benefit of the use of BMP in these cases would be negligible.

We also examined the dosage of BMP used per level in this report and examined its relationship with the rate of complications such as dysphagia. The risk of adverse effects secondary to the use of BMP has been well documented. Tumialán et al. found a direct correlation between dose of BMP administered and the incidence of dysphagia, ranging from 2-level fusions using a total dose of 0.7–1.05 mg being associated with a 1% incidence, to 3- and 4-level fusions using a total dose of 2.8–4.2 mg being associated with an incidence of 66%. While dosage increased in this study in 2- versus 3- and 4-level fusions, part of the increased risk of dysphagia may be related to the performance of a multilevel fusion in itself.

There has been widespread recognition of the complications associated with BMP use in the cervical spine. The FDA has issued a public health notification of life-threatening complications associated with the use of rhBMP in cervical spine fusion. Citing reports of swelling of the neck and throat, which resulted in compression of the airway and/or neurological structures in the neck, the FDA noted that “the safety and effectiveness of rhBMP in the cervical spine have not been demonstrated and these products are not approved by the FDA for this use.” Many of these adverse effects were likely due to high doses of BMP, and by using lower doses of BMP, the benefit of decreased pseudarthrosis rates may be obtained without an increase in complication rates.

In our cases performed with BMP prior to 2007, higher doses of BMP per level (2.1 mg/level) were used than in later operations. This is largely because safety concerns about the usage of BMP were not as widely reported in the literature until approximately this time. There was a total of 5 patients who received this dosage, all of whom had 2-level fusions. Of these 5 patients, 4 reported complications (dysphagia, cervical swelling, neck pain). Three patients treated in 2008 (all 3-level fusions) also received higher doses of BMP than were used in subsequent cases (1.4 mg/level), and of these patients, one reported dysphagia resulting in an emergency room visit. Of the 14 patients treated subsequently in the BMP group, all received less than 1.4 mg/level, and none reported complications.

There has also been significant discussion regarding the costs associated with the use of BMP. Given the high rate of pseudarthrosis without BMP documented in this report, it is feasible that a reduction in the need for revision surgery or posterior supplementations would improve the overall cost profile of BMP. Furthermore, the smaller doses used in this analysis are less costly than higher doses of BMP. Unfortunately, no papers have specifically examined the cost of using low-dose BMP for multilevel cervical fusions. Another study found that the use of BMP was associated with more frequent complications in anterior cervical fusions and thus with greater hospital charges,
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but the authors did not consider the delayed costs of revision surgery and other treatments of pseudoarthrosis. We would also add that an anecdotally observed acceleration of the fusion process was seen when comparing 3-month follow-up imaging studies between groups, with fusion appearing to progress faster in the BMP group than in the non-BMP group. This finding may ultimately translate into a faster recovery process for the patient resulting in cost savings in the postoperative period.

In conclusion, the results of this retrospective cohort study suggest that there may be a substantial benefit to the use of BMP in multilevel cervical fusions given the extremely high rate of pseudoarthrosis seen with traditional techniques. A similar benefit is unlikely to be seen with the use of BMP in single-level cervical fusions, given the already high fusion rate observed in such procedures. Significant dysphagia and airway problems may occur with any multilevel anterior cervical fusion procedure, even in the absence of BMP. Although the complications associated with BMP use appeared to be small when it was used in doses equal to or less than 1.1 mg/level, the individual surgeon must determine the risk-benefit profile for BMP use for any given patient.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Levi, Javahary, Zacur, Green. Acquisition of data: Levi, Cahill, Javahary, Zacur, Green. Analysis and interpretation of data: all authors. Drafting the article: all authors. 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: Levi. Statistical analysis: Levi, Frenkel.

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