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Clinical Evaluation of Allogeneic Growth Factor in Cervical Spine Fusion

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Abstract

Background: The initial success of recombinant human bone morphogenetic proteins (rhBMPs) in lumbar spine surgery led to its use outside the initial indication. As complications from the use of rhBMP-2 in cervical spine surgery continued to rise, the need for a safer alternative was evident. The discovery of a new allogeneic tissue processing technique has provided a way to access growth factors naturally found within bone marrow cells. This evaluation was undertaken to assess the clinical outcomes associated with the use of allogeneic morphogenetic protein in cervical spine fusion.

Methods: A retrospective analysis was conducted of one hundred and forty consecutive patients (228 levels) that underwent cervical spine fusions between C3 and T3. Patients received radiographs (x-ray and/or CT) at standard post-operative follow-up timepoints, which were generally at three, six, twelve and eighteen months post-surgical intervention. Fusion was defined as any radiographic evidence of bridging across endplates, or bridging from endplates to interspace disc plugs.

Results: Eighty percent (80%) of patients had evidence of fusions at 6 months, ninety-eight percent (98%) of patients had evidence of fusions at 12 months, and one hundred percent (100%) of patients had evidence of fusions at 18 months.

Conclusions: High fusion rate results in this report demonstrate the benefits of using an array of growth factors in cervical spine surgery and support allogeneic morphogenetic protein as a possible alternative option to rhBMP-2.

Keywords: Allogeneic growth factor; Cervical spine; Morphogenetic protein

Introduction

The use of iliac crest to assist with spine fusion has long been considered the "gold standard". Limited tissue availability, donor site morbidity, and increased surgical time have prompted the need for alternative options [1]. Since Dr. Marshal Urist's discovery of bone morphogenetic proteins (BMPs) in allograft bone, a wide range of allogeneic bone grafts has become available as an alternative or extender to autograft [2]. BMP amounts in these tissues are limited to the collagen matrix and preclinical and clinical studies have shown variability in osteoinductivity as well as questionable clinical efficacy [3]. In 2002, the FDA approved the use of a recombinant human bone morphogenetic protein-2 for single-level anterior lumbar interbody fusion (ALIF) spine surgery. The initial success of rhBMP-2 with interbody fusion soon led to its use outside of the initial indication including use in the cervical spine [4]. The widespread use of rhBMPs has raised significant controversies of late and the need for a safer, more cost effective option for the cervical spine could be beneficial.

A new allogeneic tissue processing technique has provided a way to access growth factors naturally found within bone marrow cells. OsteoAMP (Advanced Biologics, Carlsbad, CA), an allogeneic growth factor implant, utilizes this unique processing technique that exploits the angiogenic, mitogenic and osteoinductive growth factors that are within marrow cells [5-7] and makes them bioavailable. This array of growth factors may offer an alternative to rhBMP-2 or other potentially osteoinductive bone grafts for cervical spine surgery.

This evaluation was undertaken to assess the fusion rates associated with the use of allogeneic morphogenetic protein in cervical spine surgery.

Methods and Materials

A retrospective analysis was conducted at three clinical sites of one hundred and forty consecutive patients (228 levels) who underwent surgical intervention procedures in the cervical region of the spine for persistent pain symptoms. The biologic used in all cases was allogeneic morphogenetic protein in one of two main formats, granules or sponge. The biologic was used in conjunction with the centers' preferred spinal fixation system. Fusion assessments were determined by an independent radiologist using x-ray and CT images taken at follow up timepoints. Time frame between surgical intervention and positive fusion assessment was calculated and reported.

Patients received radiographs (x-ray and/or CT) at standard post-operative follow-up timepoints, which were generally at three, six, twelve and eighteen month post-surgical intervention. An independent radiologist made fusion assessments blinded to intervention, product, and surgeon information. Fusion was defined as any radiographic evidence of bridging across endplates. Any radio density that obliterates or blurs the lucency between endplates that is seen on the post-operative films is considered evidence of fusion (Figure 1). The series of radiographs from each patient were compared to postoperative x-rays and each consecutive follow up radiograph to ensure that the opacity of the biologic was not a factor in the fusion assessment.

Patient Demographics

All patients had been diagnosed with degenerative disc disease (DDD) and/or stenosis. One hundred and forty consecutive patients

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(228 levels) underwent cervical spine fusions between C3 and T3. Patients only received allogeneic morphogenetic protein in combination with morselized local autograft when available. Surgical interventions included anterior cervical discectomy and fusion (ACDF) or posterior cervical fusion (PCF). The background characteristics of this study group are provided in Table 1.

Results

Thirty-one percent (30.7%) of patients had evidence of fusion at 3 months, eighty percent (80.3%) of patients had evidence of fusion at 6 months, ninety-eight percent (97.6%) of patients had evidence of fusions at 12 months, and one hundred percent (100%) of patients had evidence of fusions at 18 months. Fusion rates are summarized in Figure 2. Average time to fusion was 5.4 ± 3.0 months. 69% of patients fused within one standard deviation (2.4 to 8.4 months). Patients who received sponges fused faster (157.9 ± 83.8 days) than patients who received granules (192.3 ± 113.0 days), but the difference was not statistically significant (p=0.09). No persistent dysphagia or swelling was reported in the cohort.

Discussion

The evolution of bone graft materials, spinal implants and surgical techniques have greatly improved clinical outcomes of spine surgery [8-10]. The clinical success of ACDF and PCF is well documented and range from 70% to 98% for a single level fusion as reported in literature [11-13]. However, as the number of surgical levels increases, the decrease in clinical success rates becomes more prevalent [14]. Early results of rhBMP-2 in the lumbar spine prompted the increase in off label use, including the use in cervical cases. This led to an increase in complications [4,15] but the evidence that growth factors improve bone regeneration was substantial [16].

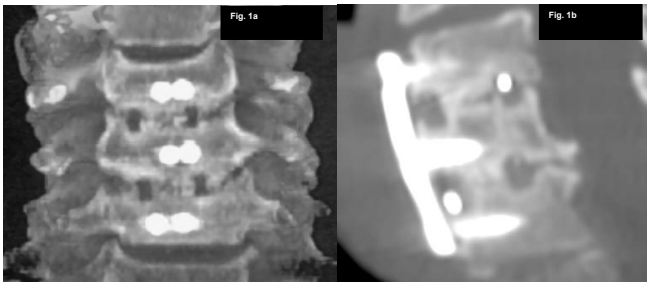

Figure 1: Radiologic examples of fusion.
a: 3 month follow-up CT, 54 year old male year smoker, C4-6.
b: 12 month follow-up CT, 40 year old male, C5-7.

Characteristic	**Value** (n=140)
Age, *mean ± SD, y*	**52.4 ± 10.8**
Female, *n (%)*	**71** (51%)
Affected Levels, *n(%)*	
One	**74** (52.9%)
Two	**51** (36.4%)
Three	**11** (7.9%)
Four	**3** (2.1%)
Seven	**1** (0.7%)
Surgical Interventions, *n(%)*	
ACDF	**132** (94.3%)
PCF	**14** (10.0%)
OsteoAMP Format, *n(%)*	
Granules	**28** (20.0%)
Sponge	**103**(73.6%)
Cervical spacer	**4** (2.9%)
Unknown	**5** (3.6%)

Table 1: Patient baseline characteristics

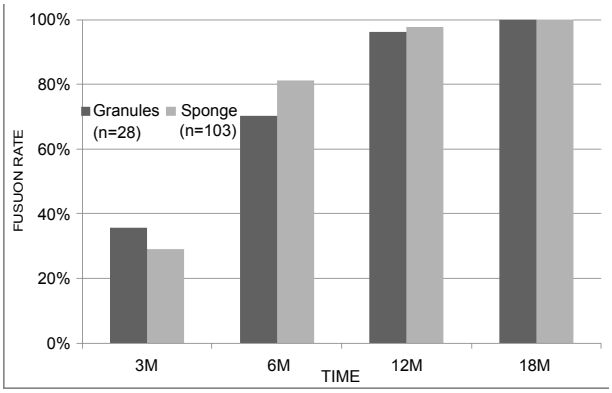

Figure 2: Allogeneic morphogenetic protein fusion rates.
Fusion rates at 3, 6, 12, and 18 months for both cervical fusion procedure types.

The introduction of allogeneic morphogenetic protein made available the naturally occurring growth factors and BMPs found within bone marrow. A recent retrospective analysis reported fusion rate results of 98% at 18 months when allogeneic morphogenetic protein was used in transforaminal lumbar inter-body fusion (TLIF) [17]. This analysis showed similar fusion results when used in cervical spine surgery supporting the benefits of having an array of growth factors. In addition, fusion rates of 97.6% at 12 months and 100% at 18 months when allogeneic morphogenetic protein when used exceeds fusion rates reported in literature.

As with all retrospective studies, there was a number of potential shortcomings in this analysis. There was no control used in the study and clinical outcomes were not evaluated. In addition, follow-up CTs as well as x-rays were used to assess fusion over each time point. Despite these limitations, results in this report demonstrate that allogeneic morphogenetic protein may be a viable alternative to rhBMP-2 with encouraging clinical results for use in the cervical spine. Multicenter randomized controlled studies will be necessary to confirm the clinical efficacy and results of this analysis.

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Disclosure

Authors CY, JF, and JR are unpaid consultants for Advanced Biologics and hold shares in the company. An acquisition of the OsteoAMP product was made by Bioventus after the time of publication. No authors have financial ties to Bioventus.

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