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# A Radiographic Analysis of Posterolateral Lumbar Fusion Utilizing an Allogeneic Growth Factor Compared to Recombinant Human Bone Morphogenetic Protein-2 (rhBMP-2)

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## Abstract

Posterolateral lumbar fusions have been successfully used to surgically treat mechanical back pain, low grade spondylolisthesis and other degenerative spinal conditions. The addition of biological grafts to augment available autologous bone has further improved fusion rates, yet, some of these biologics have been found to cause deleterious post-operative clinical situations and sometimes are used in an off-label manner. A biological alternative that provides equivalent fusion rates with a similar, or lower, risk profile is desirable. In this study, we report on fusion rates associated with the use of an allogeneic growth factor (OsteoAMP) to assist with lumbar spinal arthrodesis with and without augmentation with bone marrow aspirate as compared to rhBMP-2 used with and without the allogeneic growth factor. Patients having posterolateral lumbar fusion were evaluated for fusions at clinically relevant time points. A total of 302 patients (146 growth factor with BMA, 81 growth factor without BMA, 50 rhBMP-2 alone, 25 rhBMP-2 with allogeneic growth factor) were retrospectively reviewed. The growth factor with BMA group had approximately an 88% fusion rate by 12 months and 99% by 24 months. The growth factor non-BMA group had a fusion rate of 35% by 12 months and exceeding 98% at the 2 year follow up. The OsteoAMP augmented rhBMP-2 group had fusion rates of 33% at 12 months and 100% at 24 months, while the rhBMP-2 alone group only attained a 14% fusion rate at 12 months and a 32% fusion rate at 24 months. The allogeneic growth factor appears to provide a viable option to assist with the development of posterolateral spinal arthrodesis. Longer follow up and increased patient sample size is needed to further confirm these initial results.

**Keywords:** Posterolateral lumbar fusion; Bone morphogenetic protein

## Introduction

Posterolateral fusion has long been used to treat degenerative diseases of the spine such as spondylolisthesis, degenerative scoliosis and stenosis. In a meta-analysis review, Liu et al found that posterolateral fusion achieved a similar clinical satisfaction score, fusion rate and reoperation rate as compared to circumferential (interbody + posterior) fusion while reducing complication rates and operative time [1]. In addition, Christensen et al reported no difference in socioeconomic/societal benefit of transforaminal interbody fusion (TLIF) compared to posterolateral fusion (PLF) in a prospective, randomized trial of 100 patients [2]. It is obvious that the goal in posterolateral fusion is to achieve a solid inter-transverse process arthrodesis and/or solid fusion mass across the facet joints. Depending on the needs of the patient, decompressive laminectomies may be utilized and usually provide sufficient amounts of autograft to achieve fusion. In some cases sufficient local autograft is not available requiring surgeons to harvest from the iliac crest when more bone is needed. The harvest of iliac crest bone graft (ICBG) has long been associated with increased donor site morbidity and length of procedure, with many of patients reporting continued pain or numbness at 12 months post-operatively [3,4]. If autograft is not available, due to previous surgery or the desire to not harvest ICBG, the use of allograft, ceramics, recombinant human bone morphogenetic protein (rhBMP-2), demineralized bone matrix (DBM) and other alternatives are other options.

A recent alternative to autograft has been the use of an allogeneic growth factor (OsteoAMP®) that undergoes a unique process to better preserve naturally occurring angiogenic, mitogenic and osteoinductive growth factors (BMP-2, BMP-7, TGF-β1, VEGF, ANG-1, etc.) important in bone formation [5-7]. It has been previously reported that not only does OsteoAMP provide these growth factors but also at higher concentrations than other allografts tested [8]. The ideal dose of growth factor is unknown for fusion in vivo. It is likely the nanogram range in other products is not osteoinductive, while the megadose of mg range of a single rhBMP-2 might be "overkill" with potential side effects.

A previous study by Roh et al. [9] found that this allogeneic growth factor (OsteoAMP) showed higher and earlier rates of fusion as compared to rhBMP-2 with fewer complications and lower costs when used for one or two level TLIF and lateral access (LLIF type) procedures. However, it is unclear how this allogeneic growth factor may compare to bone morphegenetic protein for fusion rates and complications in the challenging biomechanical environment of a posterolateral fusion (with no interbody support). The purpose of the current study was an assessment of radiographic healing and fusion rates when using this allogeneic morphogenetic protein with or

without bone marrow aspirate (BMA) for posterolateral spinal fusions to treat single level, multi-level and deformity cases as compared to rhBMP-2 with and without augmentation with OsteoAMP.

## Methods

This was a retrospective review from a multi-center study of 302 patients receiving either an allogeneic growth factor (OsteoAMP, Advanced Biologics, Carlsbad, CA) combined with local autologous bone (when available) with/without bone marrow aspirate (BMA) or bone morphogenetic protein-2 (rhBMP-2) (Infuse, Medtronic, Memphis, TN) with/without the allogeneic growth factor to achieve posterolateral arthrodesis with autologous bone when available. The use of the allogeneic growth factor with or without BMA is considered an "on label" indication for posterolateral spinal fusion. However, the use of the rhBMP-2, regardless of a biological supplementation, is considered an "off label" indication as the regulatory approval for rhBMP-2 is specifically for anterior lumbar interbody fusion when used with a particular manufacturer's interbody fusion device. The conditions listed for the treatment of degenerative disc disease, spondylolisthesis, scoliosis (not greater than 20°) and other spinal diseases. Table 1 describes the pathology breakdown for each the OsteoAMP and rhBMP-2 groups (note: some patients had multiple pathologies and these pathologies were included for each patient). Table 2 describes the sample sizes, gender rate and age at surgery and the number of levels treated per subgroup.

| OsteoAMP PATHOLOGY BREAKDOWN (227 patients total): | N | % |
|---|---|---|
| DDD | 62 | 27% |
| herniated disc | 61 | 27% |
| pseudoarthrosis/nonunion/hardware failure/revision | 12 | 5% |
| post laminectomy/fusion syndrome | 67 | 30% |
| radiculitis/radiculopathy | 131 | 58% |
| scoliosis | 25 | 11.% |
| spondylosis | 28 | 12% |
| spondylolisthesis | 167 | 74% |
| stenosis | 139 | 61% |
| rhBMP-2 PATHOLOGY BREAKDOWN: (75 patients total) | N | % |
| DDD | 13 | 17% |
| herniated disc | 1 | 1% |
| pseudoarthrosis/nonunion/hardware failure/revision | 3 | 4% |
| post laminectomy/fusion syndrome | 0 | 0% |
| radiculitis/radiculopathy | 0 | 0% |
| scoliosis | 3 | 4% |
| spondylosis | 0 | 0% |
| spondylolisthesis | 63 | 84% |
| stenosis | 9 | 12% |

**Table 1:** Pathology Breakdown for Each Treatment Group

| Group | N | % female | Avg Age | Avg # of treated levels |
|---|---|---|---|---|
| OsteoAMP with BMA | 146 | 58% | 61.9 | 1.6 |
| OsteoAMP without BMA | 81 | 56% | 58.8 | 1.6 |
| rhBMP-2 with OsteoAMP | 25 | 64% | 49.1 | 1.6 |
| rhBMP-2 without OsteoAMP | 50 | 58% | 56.1 | 1.5 |

**Table 2:** Patient demographics

Patients were assessed for bridging bone between the transverse processes or the facet joints via anterior-posterior and lateral x-rays and flexion/extension films when available by a radiologist blinded to the osteobiologic used or the treating physicians. Patients were evaluated for fusion at 3 months, 6 months, 12 months, 18 months and 24 months. The percentages between both groups at each time point were compared using a chi-square test ($p<0.05$).

## Results

Table 3 shows the fusion rates reported for each subgroup at each time point. Figure 1 demonstrates a stepwise increase in the percentage of patients demonstrating fusion at each subsequent time point for each group although the time to fusion appears to differ between groups. The statistical analysis for four sub-group comparisons is shown in Table 4. It appears that the augmentation of BMA to the OsteoAMP group had a significant benefit to aid in fusion at 12 months and was equivalent at 24 months compared to OsteoAMP without BMA. When comparing the OsteoAMP with BMA group to rhBMP-2 with OsteoAMP group, significantly higher fusion rates were found at the intermediate time points for the OsteoAMP with BMA group but without a significant difference at 24 months. OsteoAMP without BMA compared to rhBMP-2 with OsteoAMP demonstrated no statistical differences in fusion rates at any time point. Finally, OsteoAMP without BMA compared to rhBMP-2 without OsteoAMP reported similar fusion rates at the early time points but with significantly greater fusion rates for OsteoAMP without BMA at the later time points.

| | 3m | 6m | 12m | 18m | 24m |
|---|---|---|---|---|---|
| OsteoAMP with BMA | 22% | 53% | 88% | 97% | 99% |
| OsteoAMP without BMA | 9% | 20% | 35% | 74% | 100% |
| rhBMP-2 with OsteoAMP | 8% | 13% | 33% | 56% | 100% |
| rhBMP-2 without OsteoAMP | 4% | 9% | 14% | 24% | 32% |

**Table 3:** Fusion rates for all patients at the various time points

| | 3m | 6m | 12m | 18m | 24m |
|---|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| OsteoAMP with BMA vs OsteoAMP w/o BMA | p<0.015 | p<0.001 | p<0.001 | p<0.001 | p=0.7 |
| OsteoAMP with BMA vs rhBMP-2 with OsteoAMP | p=0.1 | p<0.001 | p<0.001 | p<0.001 | p=0.8 |
| OsteoAMP w/o BMA vs rhBMP-2 with OsteoAMP | p=0.9 | p=0.5 | p=0.9 | p=0.3 | NA |
| OsteoAMP w/o BMA vs rhBMP-2 w/o OsteoAMP | p=0.3 | p=0.1 | p<0.025 | p<0.001 | p<0.001 |

**Table 4:** Statistical results between the various subgroups at each time point

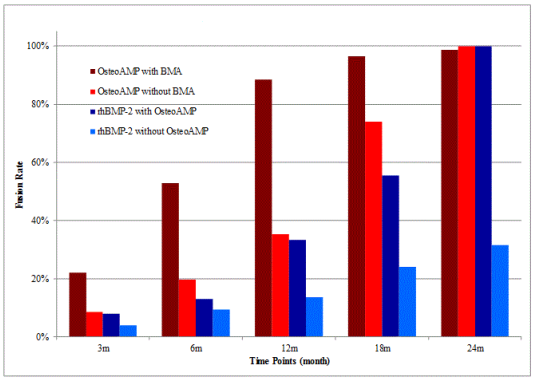


**Figure 1:** Fusion Rates of PLF patients

## Case Examples

Case 1 (Figure 2) (below) is a CT scan at 12 months of a 66 year old male being treated for primary canal stenosis via laminectomies and instrumentation from L2-L5 with the use of the allogeneic growth factor with BMA (OsteoAMP). The patient presents with bridging bone across the facet joints for a successful three level fusion.

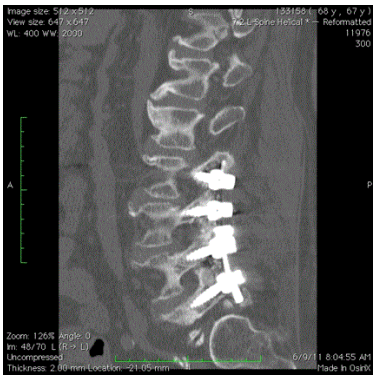

**Figure 2:** Patient with Primary Canal Stenosis

Case 2 (Figure 3) (below) is a CT at 6 months of a 37 year old female being treated for single level stenosis at L4-L5, with a previous surgery for interbody grafting at L5-S1. The allogeneic growth factor (OsteoAMP) with BMA was used and bridging bone between the transverse processes of L4-L5 is clearly visible confirming successful arthrodesis.

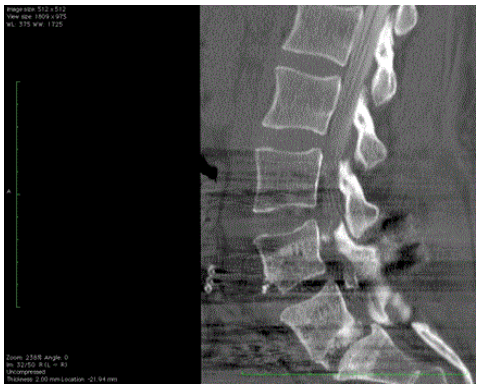

**Figure 3:** Patient with Single level stenosis

Case 3 (Figure 4) (below) are anterior-posterior (AP) and lateral radiographs at sequential time points for a 66 year old male patient being treated for central canal stenosis and grade 1 spondylolisthesis at L4-L5. The surgery involved a 2-level laminectomy and posterior instrumented lumbar fusion (without interbody) from L4 to S1 with OsteoAMP mixed with morselized local bone and placed in the lateral gutters. At 2 weeks (middle figure), the radiographs show initial graft incorporation. At 4 months (right figure), the radiographs demonstrate solid fusion. CT scans (bottom figures) were also performed with a volume density measurement scale (UCLA Color Lookup Table) which confirmed the radiodensity of the fusion mass as compared to the local pedicle/lamina region.

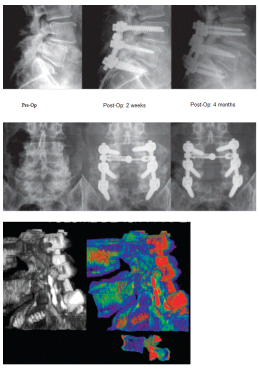

**Figure 4:** Patient with central canal stenosis and grade 1 spondylolisthesis

## Discussion

Lumbar spinal arthrodesis is a desirable surgical outcome as part of the clinical treatment plan for patients with degenerative disc disease (DDD), scoliosis, spondylolisthesis and other conditions. Autograft has long been considered the "gold standard" to achieve arthrodesis due to its inherent osteogenic, osteoconductive and osteoinductive properties that assist with forming bone [6,10]. It is also well known that the harvest of the iliac crest can have long lasting morbidity. Dimitriou et al. conducted a review of 81 studies including 6,449 patients and found a greater than 19% morbidity associated with donor site pain, numbness, seroma and infection being the most commonly reported [3]. Kim et al. reported 16.5% patients had persistent numbness or pain at the donor site at 12 months post-operatively [4]. Alternatives such as ceramics and rhBMP-2 have been used to obviate the need for crest harvest but complications (osteolysis, ectopic bone formation) and pseudarthroses have been noted with these alternatives [11]. The purpose of this current study was to retrospectively review patients receiving an allogeneic growth factor (OsteoAMP), with or without supplemental BMA, and compare them to rhBMP-2, with and without OsteoAMP.

As reported in the current study, fusions were found to increase at each subsequent time point, reaching fusion rates above 98% at 24 months for both OsetoAMP allogeneic growth factor groups. In the subgroup of the growth factor with BMA, the fusion rate was 96.6% at 18 months which was similar to fusion rates previously reported by Roh et al of 98.9% when using the allogeneic morphogenetic protein for lumbar interbody fusion [9]. The increased fusion rates at early and mid-time points with the OsteoAMP groups may be potentially explained due to the unique process to better preserve naturally occurring angiogenic, mitogenic and osteoinductive growth factors (BMP-2, BMP-7, TGF-β1, VEGF, ANG-1, etc.) important in bone formation [5-7]. It is also unclear how dosage and preparation of the rhBMP-2 may affect rates of spinal fusion.

Authors have also reported that non-unions may occur in 10%-20% of patients for single level fusions when using autograft [12-17]. The use of rhBMP-2 has improved these fusion rates but also comes with potential complications as previously mentioned (osteolysis, seroma, etc.). When examining the fusion rates in the rhBMP-2 sub-groups, specifically at 12 months and 24 months, these values appear lower than the fusion rates previously reported to be above 88% by 24 months [18] for single level instrumented posterolateral fusions. It is possible the underlying clinical presentation and co-morbidities may be different across studies and sub-groups. It is also difficult to make direct comparisons of rhBMP-2 fusion rates as the dosage of rhBMP-2 per patient and/or level may different between/among groups due to the indications/morbidities mentioned above and the type of surgery. The elected dosage level for single level fusions can be quite large and likely affect fusion rates [19]. In addition, the variation of carrier type and rhBMP-2 dosage also likely affects fusion rates. An independent review of the use of rh-BMP2 in two dosage forms (4mg vs 40mg) (Infuse vs AMPLIFY, Medtronic, Memphis, TN) reported a higher cancer risk with increased dosages of rh-BMP2 and the authors felt that the physiologic response to the rh-BMP2 (ie: fusion, cancer risk, etc.) were dose dependent [20]. Further prospective studies are required to further examine these differences with greater focus on tracking the clinical presentations and co-morbidities while ensuring to measure dosage for the patient/level being treated.

There are limitations to the current study. This is a retrospective review of standing radiographs and CTs for confirm fusion when available. The number of patients in each group vary in sample size but a mid term power analysis from the 12 month data found greater than 90% power when comparing the OsteoAMP with BMA group to the other three groups. In addition, the reporting of clinical outcomes (relief of pain via VAS, restoration of function via ODI, patient satisfaction, etc) was not available in all patients at all-time points. Prospective studies should be initiated to capture these data points as the radiographic success, with additional outcomes data and increased patient sample sizes, may make OsteoAMP a compelling alternative to the osteobiologics used widely for posterior spinal fusions.

## Conflict of interest

Authors HA, 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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