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# Fusion Rates of Lateral Lumbar Interbody Fusion Using Recombinant Human Bone Morphogenetic Protein-2

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## Abstract

**Study Design:** Retrospective observational case series.

**Objectives:** Lateral lumbar interbody fusion (LLIF) has been widely performed with recombinant human bone morphogenetic protein-2 (rhBMP-2), but the fusion rates using this graft alternative have not been well studied. We aimed to evaluate fusion rates in 1- and 2-level LLIF with rhBMP-2 and their relationship with fixation, as well as rates of BMP-related complications.

**Methods:** Institutional review board (IRB)–approved spine registry cohort of 93 patients who underwent LLIF with rhBMP-2 (71 one-level cases and 22 two-level cases). Minimum 1-year clinical follow-up and computed tomography (CT) scan for fusion assessment. Postoperative CT scans were used to evaluate the rate of fusion in all patients. Instrumentation and complications were collected from chart and imaging review.

**Results:** Average age was 65 years (67% female). For 1-level cases, 92% (65/71) had complete fusion and 8% (6/71) had either incomplete or indeterminate fusion. Three of the 6 patients who had incomplete or indeterminate fusion had bilateral pedicle screw instrumentation, 1 patient had unilateral posterior fixation, and 2 had no fixation. In 2-level cases, 86% (19/22) had complete fusion and 14% (3/22) had either incomplete or indeterminate fusion. The 3 patients who had incomplete or indeterminate fusion did not have fixation.

**Conclusion:** Interbody fusion rates with rhBMP-2 via LLIF was 92% in 1-level cases and 86% in 2-level cases, indicating that rhBMP-2 may be used as a viable graft alternative to allograft options for LLIF. Higher rates of pseudarthrosis occurred when not using fixation.

## Keywords

lateral lumbar interbody fusion, rhBMP-2, fusion rates, instrumentation

## Introduction

A new alternative to the traditional transperitoneal or retroperitoneal approach for performing an anterior lumbar interbody fusion (ALIF) is the lateral lumbar interbody fusion (LLIF). This technique is performed via a less-invasive retroperitoneal approach, which can be completed in a less morbid manner in the mid and upper lumbar spine. The LLIF procedure preserves the anterior and posterior longitudinal ligaments and does not require mobilization of the great vessels, which is commonplace above the fifth lumbar vertebra when utilizing a traditional ALIF approach. The exposure allows for a more thorough disc space preparation than with transforaminal lumbar interbody fusion (TLIF).

Compared with TLIF and posterior lumbar interbody fusion (PLIF), LLIF does not require direct entry into the spinal canal or neuroforamen or the retraction of nerve roots. The risk of postoperative epidural fibrosis/adhesions and iatrogenic nerve root injury from direct intraoperative manipulation is minimized with the LLIF technique.[1,2] A substantially larger

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interbody cage is placed during LLIF when compared with the cages placed in TLIF/PLIF. This results in greater cage–end plate contact for the LLIF compared with TLIF/PLIF. These larger cages may provide superior initial stability, less risk of cage subsidence, and a potentially more favorable biomechanical environment when derived from previous biomechanical studies of interbody cage technology. A cage with a larger footprint also allows for a greater volume of bone graft material, which may further enhance fusion.[3-6] The use of alternative graft materials can supply the necessary volume more efficiently and less morbidly than harvesting autograft. Alternative graft material reduces the risk of donor site pain and complications associated with autogenous harvesting. A wide variety of these graft materials are available.

One of the commonly employed biologic grafting materials deployed after LLIF is recombinant human bone morphogenetic protein-2 (rhBMP-2). rhBMP-2 has osteoinductive growth factors that stimulate pluripotential cells to migrate into the area and form bone and has been shown to result in high fusion rates after ALIF.[7,8]

Although rhBMP-2 has been widely utilized in LLIF, the fusion rates have not been well studied for this application. A small group of patients was evaluated by Malham et al[9] in this regard, but a larger scale evaluation is warranted. rhBMP-2 has its own unique group of complications that include retrograde ejaculation, osteolysis, seroma formation, postoperative radiculitis, ectopic bone formation, and soft-tissue swelling.[10-13]

The primary objective of this study was to evaluate fusion rates in 1- and 2-level LLIF when using rhBMP-2. Secondarily, we aimed to evaluate the impact of fixation on fusion rates and the rate of BMP-related complications.

## Methods

An institutional review board–approved spine registry was used to identify 93 patients who underwent LLIF via a retroperitoneal approach utilizing rhBMP-2 (71 one-level cases and 22 two-level cases). The average age was 65 years, and 67% were female. Inclusion criteria included 1-year clinical follow-up and a computed tomography (CT) scan for evaluation of fusion. Surgical indications for LLIF included spondylolisthesis (grade 1 or 2), foraminal stenosis, adjacent segment disease, disc herniation, degenerative disc disease, central and lateral recess stenosis, history of prior interbody fusion, and history of pseudarthrosis. All patients were treated with LLIF fusion using standard techniques described by Rodgers et al.[5] Patients were analyzed according to the use of 1-level fusion versus 2-level fusion and with respect to the use of spinal fixation.

The primary surgeons routinely ordered CT scans at either the 1- or 2-year postoperative time points for evaluation of fusion. Patients were excluded if they had less than 1-year follow-up, no postoperative CT scan, coronal curves greater than 30° as assessed using Cobb methodology, or more than 2-level interbody fusion. Fusion categories were defined as (1) complete fusion, (2) incomplete/progressing fusion, or (3) indeterminate as described by Brantigan-Steffee-Fraser classification (see Table 1).[14] The use and type of fixation in both 1- and 2-level cases were established via radiographic and chart review. Complications potentially related to BMP utilization were determined through retrospective inpatient and outpatient chart review. These included infection, neurologic deficit, radiculitis, osteolysis, seromas, and ectopic bone formation.

rhBMP-2 was combined with a calcium triphosphate-type bone graft extender on a routine basis to additively fill the interbody cages. CT scans were used for evaluation for osteolysis and ectopic bone formation.

## Results

Postoperative CT scans were used to evaluate the rate of fusion in all 93 patients. The median postoperative time to obtain the CT scans was 19 months for 1-level and 20 months for 2-level cases. The most common levels treated were L4-L5 (61%) in 1-level cases and L3-L5 (59%) in 2-level cases.

In the 2-level group, 91.5% (65 of 71) had complete fusion and 8.5% (6 of 71) had either incomplete or indeterminate fusion. Of these 6 cases, 3 patients had bilateral pedicle fixation, 1 had unilateral pedicle fixation, and 2 had no fixation. In the 2-level group, 86% (19 of 22) had complete fusion and 14% (3 of 22) had either incomplete or indeterminate fusion. In all of the 3 cases of incomplete fusion within the 2-level group, one level fused completely while the other did not (indeterminate in all 3 cases). Nineteen cases (86%) successfully fused at both levels, which represents an overall fusion rate by level of 93% (41 of 44 total levels fused). Fusion rate by level within the combined cohorts (1- and 2-level fusions group combined) was 92% (106 of 115).

Bilateral posterior fixation was utilized in 58.2% (67 of 115) of levels in this series, while unilateral posterior fixation (12.2%; 14 of 115) and lateral plate fixation (4.3%; 5 of 115) were used less frequently. Stand-alone LLIF was employed in 25.2% of the fusion levels in the series (29 of 115). When evaluating the likelihood of fusion relative to fixation type, patients who had any fixation were 4.3 times more likely to be successfully fused compared with patients who had stand-alone LLIF (95% confidence interval = 1.1-17.2). Patients with any fixation had a fusion rate of 95.3% (82 of 86), while patients with stand-alone LLIF had a fusion rate of 82.8% (24 of 29; $P = .044$).

Six complications potentially related to BMP occurred, including 4 cases of radiculitis and 2 cases of osteolysis. Among the 4 cases of radiculitis, 3 of the 4 improved within 2 years from the index surgery. The 2 cases of osteolysis occurred in 2 patients after 1-level surgery. In both cases of osteolysis, the rate of fusion at the time of CT assessment was graded as indeterminate. One case of osteolysis had no posterior fixation while the other had bilateral pedicle screw fixation. We did not observe any endplate fracture or violation in either case during the index surgery as reported on operative reports or via review of intraoperative reports or on postoperative

**Table 1.** Classification of Interbody Fusion Success: Brantigan, Steffee, and Fraser (BSF) Classification[a].

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|---|
| BSF-1: Radiographical pseudarthrosis is indicated by collapse of the construct, loss of the disk height, vertebral slip, broken screws, displacements of the carbon cage, or significant resorption of the bone graft, or lucency visible around the periphery of the graft or cage. |
| BSF-2: Radiographical locked pseudarthrosis is indicated by lucency visible in the middle of the cages with solid bone growing into the cage from each vertebral end plate. |
| BSF-3: Radiographic fusion: bone bridges at least half of the fusion area with at least the density originally achieved at surgery. Radiographical fusion through one cage (half of the fusion area) is considered to be mechanically solid fusion even if there is lucency on the opposite side. |

[a]Reproduced with permission from Fogel et al.[14]

radiographs. There were no cases of seroma formation, ectopic bone formation, or massive soft tissue swelling. Additionally, there were no infections, vascular injuries, bowel injuries, new postoperative neurologic deficits, or deaths.

## Discussion

Although autologous bone graft is considered the best option to achieve solid fusion, the morbidity associated with the donor site and the limited quantity of autologous bone available has led surgeons and researchers to develop other options. These other options include allografts, ceramics, mesenchymal stem cells, gene therapies, and growth factors, and various levels of evidence exist to support their use clinically.[15-21] Importantly, the use of such bone graft alternatives when performing LLIF has been commonplace given the large volume of graft needed, and the lack of local access to autogenous bone. Because of the historically strong evidence supporting BMP-2 in the anterior lumbar interbody environment, many surgeons began to utilize it for LLIF, as well.

BMP-2 has also been studied extensively in other areas within the lumbar spine and has demonstrated promising fusion rates in those other regions. Boden[16] found 100% fusion 6 months after surgery with rhBMP-2 compared with 67% of the control group using autologous iliac crest. Mroz et al[12] performed a literature review of 16 studies (1794 patients, 995 treated with rhBMP-2 and 799 without). Of 5 studies for PLIF or TLIF (301 patients), only 1 of the 4 studies for ALIF (279 patients) and 3 of the 7 studies for posterolateral lumbar fusion (272 patients) reported no significant improvement in fusion rates with rhBMP-2 compared with those without rhBMP-2 at the longest follow-up investigated. The average fusion rates at 24 months after surgery utilizing rhBMP-2 were 97.8% (316) for ALIF, 95.7% (141) for PLIF/TLIF, and 93.6% (422) for posterior lumbar fusion. Fusion rates without rhBMP-2 were 88.2% (228) for ALIF, 89.5% (86) for PLIF/TLIF, and 83.1% (372) for posterior lumbar fusion.

The use of BMP-2 in the LLIF environment has not been as well studied. Oliveira and colleagues[22] reported on a series of 15 patients undergoing 1-level stand-alone LLIF supplemented with rhBMP-2 for degenerative disc disease. All patients achieved solid fusion; however, 13% (2) required repeat surgery. One needed direct decompression because of small pedicles and insufficient indirect decompression. The second case developed heterotopic ossification in the foramen, for which a foraminotomy was subsequently performed. Malham et al[9] reported on the fusion rate after LLIF in 30 patients with rhBMP-2 and β-tricalcium phosphate granules. Fusion rates as assessed by CT progressed from 46% (12 of 26) at 6 months to 58% (15 of 26) at 9 months and 85% (22 of 26) at 12 months postoperatively. In patients with supplemental internal fixation, a 92% (12 of 13) fusion rate was observed, while without fixation only 77% (10 of 13) of patients exhibited complete fusion at 12 months.

In contrast to these 2 prior reports, our study provides evaluation of a much larger series of patients treated with rhBMP-2 in LLIF and fusion assessment was completed universally via CT scan. Our results confirm a fusion rate of approximately 92% to 93%, which is commensurate with the results reported by Malham et al. We also found a lower fusion rate in patients treated without supplemental fixation, despite the use of BMP.

Other graft alternatives have been studied more substantially in LLIF. Berjano et al[23] performed a LLIF study that assessed fusion using CT scan. A total of 77 patients were included with a variety of diagnoses and fixation options. Using CT scans, a total of 87% (68) of the 78 operated levels were considered fused, 10% (8) operated levels were considered as stable, probably fused, and 3% (2) operated levels were diagnosed as pseudarthrosis. When stratified by type of graft material, complete fusion was obtained in only 75% of patients in which autograft was used compared with 89% of patients in which calcium triphosphate was used and 83% of patients in which a synthetic bone graft product was used.

Rodgers et al[24] reported on a prospective radiographic and CT assessment of fusions performed through the LLIF approach. Graft material used in the study was a combination of local autograft of vertebral body, demineralized bone matrix, cancellous allograft, and bone marrow aspirate. Sixty-six patients (88 operative levels) were examined 12 months after LLIF to determine the rate and quality of anterior lumbar fusion via CT. Ninety-seven percent (85 of 88) of levels and 97% (64 of 66) of patients achieved fusion. Patient satisfaction at 12 months after surgery was high, with 89.4% reportedly "satisfied or very satisfied" with their results. No revisions were necessary for pseudarthrosis.

Tohmeh et al[25] reported on 40 patients who were treated at 61 levels with LLIF and allograft cellular matrix (Osteocel Plus; NuVasive, Inc, San Diego, CA). They reported complete interbody fusion in 90% of LLIF levels using guided fluoroscopy or CT scans reviewed by a third party.

In our cohort, we found a 6.5% rate of probable BMP-related complications. These included osteolysis and seroma, which have been previously described in the BMP literature, as well as radiculitis. The local irritation of neural elements in the lumbar plexus by BMP elution from the intervertebral cage has

been theorized as a potential source of radiculitis, although this may simply be a result of the surgical approach. Given the potential for BMP to play a role in neurotoxicity, we chose to err on the side of including this symptomatic finding as related to the BMP in the absence of certainty.

In a review of 31 articles discussing complications following BMP use in spine surgery, Mroz et al[12] found a 44% rate of resorption/osteolysis, a 25% rate of graft subsidence, a 8% rate of ectopic bone growth, a 27% rate of cage migration, a 29% incidence of new-onset radiculitis, and a 29% inflammatory response to the collagen carrier.[12,26] In our study, we reported 2 cases of osteolysis and 4 cases of radiculitis, the majority of which (75%) improved by 2 years following surgery.

Limitations of our study include a lack of a control group to compare the rate of fusion of rhBMP-2 with other sources of allograft, but we had fusion rates that were comparable with those smaller studies using rhBMP-2 in LLIF. In addition, we were unable to determine if successful fusion completion had any specific correlation with clinical outcome measures. Another limitation of this study is the inability to compare rhBMP-2 dosages per level in an accurate manner with other studies (in which dosages were not disclosed/captured). As with other studies in the literature surrounding rhBMP-2 utilization, variation in complication and fusion rates may be proportional to the rhBMP-2 dose. Finally, although we had CT scans on all of our patients, which favors ideal fusion assessment, the retrospective nature of the study results in a less reliable mechanism for the capture of complication data.

This is one of the largest series reporting the rate of fusion and biologic-specific complications in LLIF with the use of rhBMP-2. In our study, we found successful interbody fusion using rhBMP-2 via LLIF in 92% of levels at 2 years. The fusion rate in this series is also similar to those found in other studies with rhBMP-2 applied through different surgical approaches.

## Declaration of Conflicting Interests

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