The use of rh-BMP2 in Standalone eXtreme Lateral Interbody Fusion (XLIF®): Clinical and Radiological Results After 24 Months Follow-up

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ABSTRACT

BACKGROUND CONTEXT: The eXtreme Lateral Interbody Fusion technique (XLIF®) is a safe and effective procedure for minimally invasive treatment of various spinal conditions. The XLIF allows for easier, less invasive true lateral access to the disc space. Lateral implantation also preserves the stabilizing ligaments, and the footprint of the device capitalizes on the biomechanical support of the ring apophysis, allowing its use without the need of additional supplementation. Due the emphasis on minimizing the invasiveness of the technique and for being considered as good as autograft, rh-BMP2 was used as bone graft to achieve fusion.

PURPOSE: The purpose of this paper is to show the clinical and radiographic results of a standalone lateral retroperitoneal minimal invasive approach for single level anterior spine fusion using rh-BMP2 as bone graft.

STUDY DESIGN/SETTING: A prospective, non-randomized, single center study.

METHODS: 15 patients underwent spinal fusion for single level DDD (L4-L5). None of the patients presented major osteoporosis condition or previous fusion surgery at L4-L5. Within the cases, 7 patients were male and 8 female, with a mean age of 45.7 (26-69 years). All patients completed two-year follow up. Radiological exams, such as X-ray and CT scans, neurological examination, and clinical outcome assessment using Oswestry Disability Index and VAS scores were performed at the preoperative and 1, 6 week, 3, 6, 12 and 24 months after surgery. The XLIF® procedure was done through the retroperitoneal space and through the psoas muscle to access the anterior spine, avoiding vascular lesions, and avoiding neural damages using nerve avoidance monitoring system (NeuroVision®). A partial discectomy was done and the end-plates were cleaned preserving the spinal ligaments, keeping the spine more stable than the traditional anterior surgery. A large peek cage was filled with synthetic bone graft containing rh-BMP2 (Infuse®) and inserted into the disc space. All procedures were standalone constructions without the need of supplementation.

RESULTS: The procedures were performed without major complications in an average 67.3 minutes and with less than 50cc blood loss. VAS and Oswestry scores statistically improved from preoperative to postoperative assessments. After surgery, was possible to observe 1 case (6.7%) of subsidence. Two patients had additional surgery (13.4%), one direct decompression due to congenital small pedicle screws and other due excessive bone formation that compressed the nerve root. All patients presented some source of bone formation 12 months after surgery, showing the efficacy of the standalone procedure.

CONCLUSIONS: Using the stand alone XLIF® procedure we were able to treat single level DDD in a minimal invasive way, targeting the disc space without the risks and morbidity associated with other fusion techniques. The technique provided pain relief and improvement in physical disability assessments. The study revealed that it is possible to treat DDD with standalone anterior spine fusion via lateral approach, which allowed rapid and efficient spine fusion with the use of a biological bone graft. The use of this technique improves patient's recovery and allows bone formation, reducing surgery costs due to a shorter hospital stay, less material implanted and the needless presence of an access surgeon.

FDA Device/Drug Status: XLIF®: Off-label for this indication; rh-BMP2: Off-label for this indication.

KEY WORDS: Fusion, rh-BMP2, XLIF
INTRODUCTION

Lumbar arthrodesis has been proven to be a safe and effective treatment for segmental spinal conditions such as degenerative conditions, instability, spondylolisthesis and other painful discogenic syndromes(1-6). Lumbar spinal procedures that do not interfere in the posterior muscles have significant advantages in comparison to posterior approaches to the lumbar spine(7). The XLIF technique is a less invasive alternative to achieve anterior lumbar spinal fusion, with the benefits of a minimally invasive procedure that include less tissue trauma during the surgical approach, less postoperative pain, shorter hospital stays, and faster return to activities of daily living(8). This technique can be used in a stand-alone construction, positioning the graft at an advantageous position within the intervertebral disc space, restoring the normal disc height, correcting the sagittal and coronal alignment, indirectly decompressing the neural structures, stabilizing the affected segment and facilitating the fusion process without the morbidity of other open surgery techniques.

The autologous bone is considered the best graft to achieve fusion because of its osteogenic, osteoinductive and osteoconductive properties in addition to no immunologic reaction and avoidance of infectious disease transmission. However, its use is limited and generates complications such as donor site pain and loss of sensation, besides the fact that the graft quality depends on the age and general condition of the patient(9). For these reasons, the development of new materials and techniques to substitute the use of auto grafts is necessary, but with results at least similar to the autologous bone graft. InFUSE™ Bone Graft (Medtronic Sofamor Danek, Memphis, TN) is a recombinant human bone morphogenetic osteoinductive growth factor that stimulates pluripotential cells to form bone and it is applied to an absorbable collagen sponge that replaces the need for autogenous bone grafts and eliminates the complications associated with iliac crest graft harvesting(10-13). The graft rh-BMP2 applied to an absorbable collagen sponge carrier has been shown to promote osteoinduction and fusion in the lumbar spine, enhancing rates of fusion, reducing surgical time and improving clinical outcomes(14,15).

Our report presents the two-year clinical and radiographic results of the use of InFUSE™ Bone Graft (rhBMP-2) with a collagen sponge carrier inside a peek cage in patients undergoing the eXtreme Lateral Interbody Fusion (XLIF) technique.

MATERIAL AND METHODS

Study Design. Prospective, nonrandomized, nonblinded study to evaluate the clinical and radiological results of the use of rh-BMP2 in patients that underwent single level XLIF.

Patient Selection Criteria. Patients with single-level lumbar degenerative disc disease at L4-L5 were included in the study. The diagnosis was based on the patient's history and symptoms, physical findings, functional deficits, and radiographic findings. All patients had the symptoms for a minimum of six months and had failed to respond to a conservative treatment regimen. The radiographic inclusion criteria did not require patients to have discography, although some were performed. Radiographic findings could be established on one or more studies: plain radiographs, magnetic resonance imaging, computed tomography (CT) scanning, or discography.

Patient Population. Fifteen patients at one single site had XLIF surgery between December 2006 and November 2007. All patients were between the ages of 26 and 69 years and had symptomatic degenerative disc disease at the L4–L5 level. All patients received In- FUSE™ Bone Graft, which is rhBMP-2 applied to an absorbable collagen sponge carrier, used in conjunction with a large PEEK implant. Data were collected before surgery, intraoperatively, and at 6 weeks and 3,6,12, and 24 months after surgery. Operative procedure details and adverse events were also recorded.

Surgical Technique. Under general anesthesia, the patients were placed in a true 90° right lateral decubitus position. The table was flexed to increase the distance between the iliac crest and the rib cage. After aseptic treatment of the skin, a k-wire and lateral fluoroscopic image were used to identify the lumbar disc’s mid-position and a mark was made on the patient’s lateral side, overlying the center of the affected disc space. Through this mark, a small incision was created for insertion of atraumatic tissue dilators and an expandable retractor, which were the working portal. A second mark was made posterior to this first mark to, with the index finger, sweep the peritoneum anteriorly and then to palpate down to the psoas muscle. Once the psoas muscle was identified, the index finger was swept up to the direct lateral target mark. A small incision was created for insertion of atraumatic tissue dilators and an expandable retractor, which were the working portal. A second mark was made posterior to this first mark to, with the index finger, sweep the peritoneum anteriorly and then to palpate down to the psoas muscle. Once the psoas muscle was identified, the index finger was swept up to the direct lateral target mark. An incision was made at this direct lateral location and an initial dilator (MaXcess System, NuVasive, Inc.) was introduced. The index finger was used to escort the dilator safely from the direct lateral
incision to the psoas muscle, protecting the intra-abdominal contents. The dilator was then placed over the surface of the psoas muscle, exactly over the disc space to be operated, as confirmed by AP and lateral fluoroscopy. The fibers of the psoas muscle were then gently separated with the initial dilator using blunt dissection and the NeuroVision JJB electromyographic (EMG) monitoring system (NuVasive, Inc.) to assess close proximity of the lumbar nerve roots to the advancing dilator. Subsequent dilators were introduced, gradually spreading the psoas muscle until the MaXcess retractor was inserted over the final dilator. The operative corridor was thus established and under direct vision a thorough discectomy was performed using standard instruments. Disc removal and release of the contralateral annulus using a Cobb dissector provided the opportunity to place a long implant that rested on both lateral margins of the epiphyseal ring, maximizing end plate support (Figure 1). Interbody distraction and implant placement in this anterior and bilateral epiphyseal position provided strong support for disc height restoration, sagittal and coronal plane imbalance correction, and indirect decompression of the neural structures. The rhBMP-2 was reconstituted using sterile water, and a single dose at a concentration of 1.5 mg/mL was administered. The concentration was the same in all patients. The exposure was copiously irrigated, and the retractor was removed slowly, so as to observe the psoas muscle rebounding and to confirm hemostasis. For both incision sites, the fascial layer was closed with 0 Vicryl and the subcutaneous layer was closed with 2.0 Vicryl sutures. A 4.0 monocryl was used for subcuticular closure. No drains were required.

**Clinical Outcome Measurements.** Clinical outcomes were collected using The Oswestry Disability Index (16) to measure the level of pain and disability associated with various activities, and Visual Analogue Scale to evaluate pain intensity for back and leg pain.

**Radiographic Outcome Measurements.** Radiographs and CT scans were used to evaluate fusion at 6, 12, and 24 months after surgery. Images were evaluated by one expert radiologist and two spinal surgeons. Fusion was defined as bridging bone connecting the adjacent vertebral bodies either through the implants or around the implants, less than 5° of angular motion, less than or equal to 3 mm of translation, and an absence of radiolucent lines around more than 50% of either of the implant surfaces. Stability and radiolucent lines were assessed on plain radiographs using anteroposterior, lateral, and flexion-extension views. Thin-slice (1 mm) CT scans with sagittal reconstructions were evaluated at 6, 12, and 24 months. The presence of continuous trabecular bone formation between the vertebral bodies was assessed using radiographs and CT scans. A fusion was considered successful only if all four criteria were achieved: 1) bridging trabecular bone connecting the two vertebral bodies either through the dowels or around the dowels as evaluated by thin-cut CT scans and radiographs; 2) no angular motion of 5° or more on dynamic plain radiographs; 3) no sagittal translation of more than 3 mm on dynamic plain radiographs; and 4) no radiolucencies that involved more than half of the interfaces between the dowels and the host vertebral end plates(17).

**Statistical Methods.** The data was analyzed using Student's t-test. P values less than 0.05 were considered statistically significant.

**RESULTS**

**Surgery:** All patients had surgery at L4-L5, as inclusion criteria. The mean operative time was 67.3 minutes (45 – 90 min) with an average blood loss less than 50cc and without occurrence of intra-operative adverse events. The average hospital stay was 24 hours (12 – 48 hours) (Table1).

**Outcomes assessment:** Patients showed statistical significant improvement in visual analogue scale at all

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
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<tbody>
<tr>
<td>Age</td>
<td>45.7 y/o (26 - 69)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>8</td>
</tr>
<tr>
<td>Male</td>
<td>7</td>
</tr>
<tr>
<td>Surgery time</td>
<td>67.3 min (45 - 90)</td>
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<tr>
<td>Hospital Discharge</td>
<td>24 h (12 - 48)</td>
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Table 1: Demographics (mean or absolute value, maximum and minimum)
postoperative visits, with an average improvement of 30% at their initial postoperative visit at one week after the procedure (Figure 2). The Oswestry Disability Index was used to assess pain its influence in daily activities. The mean scores showed statistical significant improvement 6 weeks after surgery and in all further follow up visits (Figure 3).

![Visual analogue scale for back pain showing statistical significant improvement one week after surgery and maintained in all further follow up intervals.](image1)

![Mean Oswestry Disability Index showing statistical significant improvement in all questionnaire sections 6 weeks after the procedure and maintained in all further follow up periods.](image2)

**Radiographic assessment:** At six months follow up, 11 patients (73.3%) had evidence of bone ingrowths, but only 3 (20%) were considered fused using the proposed fusion criteria (Figure 4). At nine months, only one patient (7%) did not have any signs of interbody fusion and 7 (47%) were considered to be fused. Twelve months after surgery, all patients (100%) showed evidence of bone formation, been considered fused 12 (80%) patients (Figure 5). At the final follow up at 24 months after surgery, all patients showed evidence of remaining fused, but three were considered as developing fusion (Figure 6).

**Adverse Events:** Two patients had additional surgery. In one case, the indirect decompression was not reached because of congenital small pedicles and a direct decompression was performed. One patient presented heterotopic bone formation due to excessive bone formation that led to foramen stenosis (Figure 7). A foraminotomy
was necessary do decompress the nerve. One patient had cage subsidence, but it did not influence the clinical and radiological outcomes, and the patient was considered to be fused 12 months after the procedure (Figure 8). An adjacent level degeneration was seen in one patient and an additional XLIF surgery was performed to treat the degeneration (Table 2).

**DISCUSSION**

Despite new strategies and techniques, the gold standard treatment for painful and unstable degenerative spinal conditions remains to be fusion. Although autologous bone graft is considered the best option to achieve solid fusion, the morbidity associated with donor site and its limited quantity available to use as a graft led surgeons and researchers to develop other options to improve bone formation, such as allografts, ceramics, mesenchymal stem cells, gene therapies and growth factors (18–23). Recombinant rhBMP-2 is the best studied of all the biological agents and has been shown to promote osteoinduction and increase rates of fusion in lumbar spine (24). Considered as good as iliac crest bone graft to achieve fusion, without the morbidity and pain regarding harvest of iliac crest autograft, the rhBMP-2 was the bone substitute utilized to stimulate bone in growth due the emphasis on minimizing the invasiveness of the fusion procedure in this prospective study (25).

The XLIF® technique is a modification of the retroperitoneal approach to the lumbar spine, published by Luiz Pimenta in 2001, who presented more than 100 lateral trans-psoas surgeries performed between 1998 and 2001 (26). In comparison to other techniques, the lateral approach has several advantages. First, there is no necessity of a general surgeon to perform the access because the manipulation of the peritoneum and great vessels is eliminated by approaching laterally. Second, due to direct visualization of the tissues, all dissection occurs without impairment of depth perception, as in laparoscopic approaches to the lumbar spine (27–28). Third, the far lateral approach avoids disturbance of the superior hypogastric nerve plexus and the incidence of retrograde ejaculation in XLIF procedure is null. Because the procedure is performed through a small incision and without the need of pedicle screws supplementation, the operative time and blood loss are much reduced, proven by the mean operative time of 67.3 minutes and an average blood loss less than 50cc in this present study. By an implantation of a larger implant that rests on both sides of the ring apophysis, the XLIF technique maximizes the endplate support and allows a standalone construction with a low incidence of severe cage subsidence. Restoring the disc height and providing stability by preserving the constraining ligaments, it is also possible to indirectly decompress the neural structures and correct the coronal, sagittal and spinopelvic balance.

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**Table 2:** Adverse events occurrence.

<table>
<thead>
<tr>
<th>event</th>
<th>case (rate)</th>
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<tbody>
<tr>
<td>Cage Subsidence</td>
<td>1 (6.6%)</td>
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<tr>
<td>Heterotopic Bone Forma</td>
<td>1 (6.6%)</td>
</tr>
<tr>
<td>ALD</td>
<td>1 (6.6%)</td>
</tr>
<tr>
<td>Persistent Stenosis</td>
<td>1 (6.6%)</td>
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The fusion rate in our series is similar to those found in other studies with rh-BMP2, showing that the bone formation apparently is uncompromised by the technique. Boden et al found 100% fusion 6 months after surgery in comparison to only 66.7% of the control group (autologous iliac crest). Cages were inserted via standard laparoscopic or open anterior surgical techniques(11). Using the same approach, Burkus et al found similar results in a more controlled trial. 100% of the investigational patients were fused after 12 months, while only 89.5% of the control group were considered fused at the same follow up period(17). Using the standalone posterior lumbar interbody fusion cage procedure (PLIF), R.W. Haid et al obtained 92.3% of fusion with the use of rh-BMP2. The investigational group presented a 35.3% rate of sagittal imbalance after surgery. The subsidence rate was not quantified, but its occurrence was recurrent(29). The subsidence rate in our series was very low in comparison to the literature. Only one subject (6.7%) presented subsidence, but it did not affect the clinical results and the patient was fused 12 months after surgery. The XLIF standalone technique is a safe and effective procedure to achieve fusion and indirect decompress the neural structures. This minimal invasive procedure allows through a single small incision the treatment of different degenerative conditions of the lumbar spine without the need of posterior supplementation, due to a larger implant footprint and keeping the ligaments and posterior musculature intact.

REFERENCES


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