Clinical Spine Surgery: Invited article

The use of bone morphogenetic protein in the intervertebral disc space in minimally invasive transforaminal lumbar interbody fusion: 10-year experience in 688 patients

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Source of Funding: None

Conflicts of Interest: J.P. Mobasser is a consultant and receives royalties from Medtronic. He also receives royalties from Innomed, Inc.; A. Vaccaro is affiliated with the *Clinical Spine Surgery* journal.

ABSTRACT

STUDY DESIGN: Retrospective Cohort

OBJECTIVE To characterize one surgeon's experience over a 10-year period using rhBMP-2 in the disc space for minimally invasive transforaminal lumbar interbody fusion (MIS TLIF).

SUMMARY OF BACKGROUND DATA: MIS TLIF has been utilized as a technique for decreasing patients' immediate post-operative pain, decreasing blood loss, and shortened hospital stays. Effectiveness and complications of rhBMP-2's use in the disc space is limited due to its off-label status.

METHODS: Retrospective analysis of consecutive MIS TLIFs performed by senior author between 2004-2014. rhBMP-2 was used in the disc space in all cases. Patients were stratified based on the dose of rhBMP-2 utilized. Patients had 9-12 month CT scan to evaluate for bony fusion and continued follow-up for 18 months.

RESULTS: A total of 688 patients underwent a MIS TLIF. A medium kit of rhBMP-2 was utilized in 97 patients, and small kit was used in 591 patients. Fusion rate was 97.9% and this was not different between the two groups with 96/97 patients fusing in the medium kit group and 577/591 patients fusing in the small kit group. Five patients taken back to the operating room for symptomatic pseudoarthrosis, four re-operated for bony hyperostosis, and ten radiographic pseudoarthroses that did not require re-operation. A statistically significant

difference in the rate of foraminal hyperostosis was found when using a medium sized kit of rhBMP-2 was 4.12% (4/97 patients), compared to a small kit (0/591 patients, p = 0.0004)

CONCLUSIONS: Utilization of rhBMP-2 in an MIS TLIF leads to high fusion rate (97.9%), with an acceptable complication profile. The development of foraminal hyperostosis is a rare complication that only affected 0.6% of patients, and appears to be a dose related complication, as this complication was eliminated when a lower dose of rhBMP-2 was utilized.

KEY WORDS: TLIF; lumbar fusion; minimally invasive; Bone morphogenic protein; neuronavigation; O-arm

EVIDENCE: Level 4

Introduction

Minimally invasive spine (MIS) techniques have gained widespread popularity and acceptance in the recent years due to minimizing soft tissue dissection, shorter hospital stays, and shorter recovery period.[1-11] Achieving interbody fusion has been challenging for some surgeons, partially due to the paucity of bony surfaces that are exposed and decorticated. When performing interbody fusion through a minimally invasive approach, that degree of difficulty is even higher. Achieving successful interbody fusion can be challenging and as a result, biologic agents are often considered to augment fusions.

Recombinant bone morphogenetic protein-2 (rhBMP-2) has been demonstrated to lead to high levels of fusions, however, its use has decreased significantly in recent years in large part due to the identification of under-reported complications in the initial industry sponsored studies.[12–14] Over the past decade, there has been concern with the use of rhBMP-2 leading to seroma formation, osteolysis, bony hyperostosis and even possibly cancer.[15,16] While the risk of cancer has not been definitely proven or refuted, there is little doubt that the other complications can occur; however, the prevalence of these complications is unclear, and may be dependent on the dose and the surgical technique in which rhBMP-2 is utilized. With regards to its use in an MIS TLIF, a potentially concerning complication is the development of hyperostosis leading to recurrent foraminal stenosis. There have been several reports of bony hyperostosis requiring re-operation after an MIS TLIF utilizing rhBMP-2, but these reports are deficient in incidence, dosing, and technique in relation to the use of rhBMP-2.[17,18] The purpose of this study is two-fold. First, is to determine the fusion rates as well as the rate of rhBMP-2 associated complications in a large series of patients who underwent an MIS TLIF utilizing rhBMP-

2. The second purpose is to determine if the dose of rhBMP-2 affects the fusion and complication rate.

Materials and Methods

Study Design

Institutional review board approval was obtained for this study, and study was performed without financial assistance. We performed a retrospective analysis of 688 consecutive patients undergoing a 1 and 2 level TLIF procedure from January 2004 to January 2014. The chart was then mined for patients undergoing minimally invasive vs open procedures. All patients had demographic information recorded including, age, gender, BMI, smoking status, diabetic status, and bone density performed and these are listed in Table 1. All patients were followed for a minimum of 18 months with standard post operative imaging with at least 1 CT scan to assess for screw position and fusion at 9–12 months after surgery. Complications including seroma formation, infection and osteolysis requiring reoperation were also investigated. It should be noted that technique was changed from the conventional fluoroscopic technique to the fully navigated technique in 2006. This change in technique was purely for percutaneous placement of intrumentation and did not change fusion techniques.

All MIS cases were performed by the senior author (JPM), a fellowship-trained spine surgeon who has been practicing since 2004. rhBMP-2 dosages, pseudoarthroses, hyperostosis requiring re-operation, all re-operations for any reason, seromas, spinal fluid leaks, dural tears, and hardware failures were recorded. Patients who had surgery prior to 2006 had a medium size kit, which consists of 8.4 mg of rhBMP-2 used at each level, and

patients after 2006 had a small kit containing 4.2 mg of rhBMP-2 used at each level. Besides the change in kit size, there were no other changes to the technique. Once all the data was collected, we compared the two groups and assested for any statistical difference using a T-test.

Description of the technique fully navigated technique:

This fully navigated TLIF is described using O-arm imaging, Sextant or Voyager percutaneous screw system, and METRx tubular retractor system (Medtronic; Memphis, TN). We position the patient on Jackson table with a chest pad and four post-hip pads.

The patient is then prepped and draped very wide and low making sure to drape in the iliac crest. The posterior superior iliac spine is palpated and the percutaneous pin is placed with the arrow on the pin facing towards the feet. The pin is driven into the posterior superior iliac spine in a medial to lateral trajectory allowing the reference arc to be placed facing the feet and leaning towards the midline of the sacrum. After the reference arc is placed, the O-arm image is obtained. Care should be taken not to bump the reference arc during acquisition of pictures or at any point thereafter.

Skin incision is planned based on navigation, and awl-tip navigated tap is used to tap the pedicles and measure the screw size based on the navigated image, and the plans are saved. The contralateral screws to the side of the TLIF are inserted, but the screw holes are only tapped on the ipsilateral side and plans are saved. These screws will be placed after the decompression and interbody work has been completed. The tubular retractor is then docked and the facet is removed using a combination of high-speed drill, kerrisons, or osteotomes, depending on the surgeon's preference. At our institution, we have favored

utilizing the drill and kerrisons for bone removal. The bone dust collector is utilized to capture the bone removed during drilling, and a funnel is packed with this bone in order to deliver it into the disc space.

Once the decompression has been completed, the disc space is prepped thoroughly making sure endplates are exposed. The small kit of rhBMP-2 sponges are wrapped around the harvested local autograft and passed through the annulotomy defect to the far side of the disc space. The rest of the harvested autograft is then packed into the disc space pushing the BMP sponges even further away from the annulotomy. The bone dust funnel is then inserted into the disc space, and the space is filled as much as possible. A peek cage full of bone is then inserted in the standard fashion placing it to the anterior margin of the intervertebral space. The procedure is finished with placing the ipsilateral screws and passing the rods down into the screw heads, followed by compression and set screw final tightening. Closure includes the fascial layer, followed by the subcutaneous tissues, and then the dermal layer.

Results

From the years of 2004–2014, 688 patients underwent an MIS TLIF. Ninety-seven patients have a medium kit of rhBMP-2 utilized and 591 patients having a small kit used. Additionally, 226 patients underwent 2 levels of fusion and 462 underwent a single level. Demographic data is listed in Tables 1 and 2, showing a good portion of these patients having barriers to surgery and especially fusion such as factors such as obesity, osteopenia, diabetes, and active smoking. Importantly there was no significant difference in the groups between patients undergoing a 1 and 2 level fusion, or those who underwent

a fusion utilizing a medium or a small kit of rhBMP-2.

The levels fused are listed in Table 3. Between the two groups, 914 levels were fused, and 3,204 screws were inserted. The majority of the levels as were fused at L4/5 and L5/S1 for both single and 2 level fusion, comprising 74% percent of all fusion levels.

During the 15-24 months these patients were followed, there were five patients taken back to the operating room for symptomatic pseudoarthrosis, four were re-operated for bony hyperostosis, and nine stable radiographic pseudoarthroses that did not require re-operation were found as shown in Table 4. There was no more than 1 level of hyperostosis or pseudarthrosis per patient. The stable pseudarthrosiss were both asymptomatic with regards to back and leg pain, and were radiographically stable without evidence of movement on flexion extension radiographs or evidence of hardware radiolucency on computed tomography scan. The diagnosis of stable pseudoarthroses is made due to the fact that there is a paucity of bridging bone within the disc space visible on CT scan without any sign of instability or hardware loosening.

The four patients re-operated for bony hyperostosis were patients done during the period between 2004 and 2007 where medium kits of rhBMP-2 were still being used in the disc space. The overall rate when using a medium sized kit of rhBMP-2 was 4.12% (4/97 patients), and this was significantly higher than the 0% (0/591 patients) rate of hyperostosis when a small kit was used ($p = 0.0004$). Importantly, even in the patients who did develop hyperostosis, no new deficits or symptomatic spinal fluid leaks were developed secondary to these re-operations. In the entire cohort, there were also no re-operations for seroma formation or osteolysis irrespective of the dose of rhBMP-2 utilized.

With regards to the fusion rate, a total of 914 levels were fused in 688 patients. Out

of the 914 levels fused, five levels required re-operation for non-union (0.7%), and there were 10 total levels of stable pseudoarthrosis that were found on routine CT scan. This is a 2.1% pseudoarthrosis rate with respect to patients and 1.6% pseudoarthrosis rate with respect to levels fused overall. When comparing patients who underwent surgery utilizing medium kit and a small kit of rhBMP-2, no difference was identified in the fusion rate of the levels [96/97 vs 577/591, p = 0.40 CI (-3.34 to 3.12), respectively]. The fusion rates are similar between the two groups but small kits did not cause any hyperostosis.

Discussion

This is one of the largest series of MIS TLIFs where rhBMP-2 was used universally used at every disc level to aid in fusion, and the study finds that the use of rhBMP-2 leads to a fusion rate of 98% with an acceptable complication rate. While there were no patients diagnosed with seroma or osteolysis, four patients were found to have foraminal hypersostosis. Importantly, this appears to be a dose related complication as the rate was significantly less (p = 0.0004) in patients who had a small kit of rhBMP-2 utilize.

The first point of discussion is the fusion rate. The percentage of smokers and patients with osteopenia in this series would suggest a higher rate of pseudoarthrosis than occurred. Even when taking into comparison the stable non-union patients, the rate of pseudoarthrosis was 2.1%, a number that is on par or exceeds most open TLIF series in the literature as is the reoperation rate of 0.7%.[1, 11, 19, 21] This finding is critical, because while the ability to adequately prepare the interbody space for a fusion has been demonstrated to be similar in open versus MIS techniques,[22] an open TLIF allows for both an interbody

fusion as well as a posterolateral fusion. The results of this study suggest that when rhBMP-2 is utilized in an MIS TLIF, the posterolateral fusion is not necessary. Several studies report open lumbar fusion techniques with rhBMP-2, citing pseudoarthrosis rates from 0.9%-3.5%. [23–25] There are fewer studies specifically looking at MIS technique, however Singh reports a pseudoarthrosis rate of 6.8%.[26] Another critically important finding in this study is that no difference was identified in the fusion rate between patients who had a medium or a small kit of rhBMP-2 utilized. Because there is an obvious difference in cost, and likely a dose dependent rate of complication, this finding demonstrates that at most, a small kit of rhBMP-2 is needed per level, and it is possible that an even smaller dose may be equally efficacious.

What is more controversial than the fusion rate, however, is the complication profile associated with use of rhBMP-2 in the disc space from the posterior approach. From the circulating case series,[18] it would seem that exuberant hyperostosis requiring reoperation is a common complication and should deter surgeons from its use. Although case reports are present in the literature, large series such as this one are limited, which makes quantifying the frequency of these complications difficult. In this series, 0.6% of patients needed a return to OR from complications related to bony overgrowth. Before and after the re-operations, there were no new neurologic deficits that were observed. When the numbers are broken down even further, 97 patients received medium kits of rhBMP-2 in their interspace and 591 received a small kit. Out of the 97 patients receiving the medium sized kit, 4 returned to the OR. Of the 591 consecutive patients receiving the small kit, there were no instances of bony overgrowth requiring re-operation. The results of this study were similar to those by Singh et al. [26] that reviewed 573 patients undergoing an MIS TLIF utilizing rhBMP-2. They reported

10 patients (1.75%) developed foraminal hyperostosis. Rihn reported a similar rate of bony hyperostosis of 2%.[27] Interestingly, in Singh's study, nine of the patients who developed formainal overgrowth had a small kit of rhBMP-2 used. So while the results of our study suggest that foraminal hyperostosis is a dose related complication, when comparing the current study results to the results of Singh, it is possible that this complication can also be affected by surgical technique.

Even when taking into account the re-operation for bony overgrowth, the re-operation rate for fusion related complications in this series was 1%, which most surgeons would argue is an acceptable number.[7,19, 21, 28] What's more, there were no re-operations secondary to seroma formation or osteolysis causing instability, suggesting that these phenomena may also be seen at doses higher than what was used or with a different technique. Kahn et al compared rhBMP-2 to autograft and found high rates of seroma and radiculitis, however he has also recommended using smaller doses to reduce the rate of radiculitis, which he reported to be 8.4% in his series. [29]

There are limitations to this study that are inherent to the retrospective nature of the study. Specifically, while this is one of the largest studies to date on the fusion rate and complications when rhBMP-2 is utilized for an MIS TLIF, the study is unable to report on health related quality of life outcome metrics. Additionally, these are the results of a single, high-volume academic surgeon, and thus is inherent to the biases of a study associated with one surgeon. Another potentially confounding factor is that the medium kit was used early in the surgeon's career when his surgical skills were still early in the learning curve, and this could affect the complication rate that we are attributing to the higher dose of rhBMP-2.

Utilization of rhBMP-2 in an MIS TLIF leads to high fusion rate (98.2%), with an acceptable complication profile. The development of extraforaminal hyperostosis is a rare complication that only affected 0.6% of patients, and appears to be a dose related complication, as this complication was eliminated when a lower dose of rhBMP-2 was utilized.

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Table 1: **Patient demographics organized by number of levels performed MIS (%)**

	Single Level (%)	Two Level (%)	P-Value for significant difference
Total Patients	462	226	
Male	183 (40)	98(42)	0.61
Female	276 (60)	128 (58)	0.61
Age in yr (range)	24-87	36-70	
Age in yr (mean)	57.7	54.3	0.71
BMI (range)	23.1-48.1	30.4-46.3	
BMI (mean)	40.2	37.1	0.43
Diabetes	93 (20)	54 (24)	0.23
Smoking	71 (15)	31 (14)	0.73
Osteopenia	79 (17)	26 (12)	0.09

MIS = minimally invasive spine.

Table 2:

Patient demographics organized by small and medium kit (%)

	Medium Kit (%)	Small Kit (%)	P-Value for significant difference
Total Patients	97	591	
Male	40 (41)	256 (43)	0.71
Female	57 (59)	337 (57)	0.71
Age in yr (range)	24-87	35-81	
Age in yr (mean)	56.8	57.8	0.85
BMI (range)	23.1-45.1	30.4-46.3	
BMI (mean)	37.7	38.8	0.84
Diabetes	24 (25)	147 (25)	1.00
Smoking	17 (18)	82 (14)	0.30
Osteopenia	17 (18)	81 (14)	0.30
Single Level	76	391	
Two Level	21	200	

Table 3: **Number of levels and anatomic levels fused**

	Single Level Open	Two Level Open
Total Levels fused	462	452
Total Screws	1848	1356
L1/2	0	0
L2/3	42	40
L3/4	81	75
L4/5	193	155
L5/1	146	182

Table 4: Levels of pseudoarthrosis and hyperostosis needing revision broken down by level

Number of levels	1 level	2 levels
Patients	462	226
Levels of pseudoarthrosis	1	4
Levels of hyperostosis	4	0
Medium kits used	84	13
Small kits used	378	213
Symptomatic Pseudoarthrosis levels (medium)	0	0
Hyperostosis levels (medium)	4	0
Symptomatic Pseudoarthrosis levels (small)	1	4
Hyperostosis levels (small)	0	0
Stable Pseudoarthrosis (medium)	0	1
Stable Pseudoarthrosis (small)	2	7
Fusion (medium)	84	12
Fusion (small)	375	202
Fusion % (medium)	100%	92.3%
Fusion % (small)	99.2%	94.8%