Posterior Lumbar Revision Surgery using Rhbmp-2 As a Salvage Solution in the Management of Pseudarthrosis-Three Case Study and Review of the Literature

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Abstract

Background: Pseudarthrosis after posterior lumbar interbody fusion (PLIF) surgery is a failure of lumbar fusion, where no solid osseous consolidation is obtained between two vertebrae within 1 year after surgery. It is a highly described topic in spine surgery, as it is performed in large numbers all over the world. Pseudarthrosis can be responsible for chronic intractable low-back pain, instrumentation failure and radiculopathy. Recombinant human bone morphogenetic protein 2 (rhBMP-2), or Dibotetermin alfa, is a bone morphogenetic protein (BMP), which stimulates local bone formation.

Case presentation: 3 patients presented with instability, radiculopathy, and intractable low back pain. They underwent prior posterior lumbar interbody fusion surgery, in a different medical center, because of degenerative disease of the spine. Radiological imaging was performed, confirming the diagnosis of lumbar pseudarthrosis.

Methods: A single-center retrospective case series study was performed to collect data concerning the use of rhBMP-2 (InductOs - Medtronic, MA, USA) in revision surgery to manage symptomatic pseudarthrosis after previous posterior lumbar interbody fusion surgery.

Conclusions: The data collected in this study confirms successful interbody fusion and pain reduction after revision surgery. A correct dosing of rhBMP-2 and its application in spine surgery, more specific in a posterior approach, is safe. A literature review shows no evidence for additional carcinogenic effects because of BMP exposure in spine surgery.

Keywords: Degenerative; Pseudarthrosis; Revision surgery; rhBMP-2; Spine surgery

Abbreviations: PLIF: Posterior Lumbar Interbody Fusion; rhBMP-2: Recombinant Human Bone Morphogenetic Protein 2; BMP: Bone Morphogenetic Protein; CT-scan: Computed Tomography scan; TGF-b: Transforming Growth Factor Beta; Tc-99m: Technetium-99, A Product of Molybdenum-99; MA: Massachusetts; USA: United States of America; NRS: Numerical Rating Scale; CI: Confidence Interval; ALIF: Anterior Lumbar Interbody Fusion

Introduction

Pseudarthrosis after previous lumbar interbody fusion surgery for lumbar degenerative disease is a highly described topic in spine surgery, as it is performed in large numbers all over the world. Pseudarthrosis after posterior interbody fusion surgery is a failure of lumbar fusion, where no solid osseous consolidation is obtained between two vertebrae within 1 year after surgery [1,2]. Pseudarthrosis can occur with or without the presence of symptoms [3,4]. Pseudarthrosis can be responsible for chronic intractable low-back pain, instrumentation failure and radiculopathy [3,4]. It can occur multiple years after spinal surgery, even when osseous consolidation was noted on radiological findings postoperatively [12]. The rates of pseudarthrosis after spinal interbody fusion surgery ranges from 3 to 35% and depends on multiple factors (e.g. surgical technique, approach, multiple segment surgery, age, smoking, comorbidity…) [1,3-10]. The rate of pseudarthrosis increases as more risk factors are present [1,4].
There are no international accepted criteria or guidelines defining the “diagnosis” of pseudarthrosis. In 1993, Brantigan and Steffee defined a classification tool to assess radiographic bony fusion after spinal surgery (Table 1) [5,11].

The detection of pseudarthrosis can be objectified by radiological imaging. A Computed Tomography scan (CT scan) permits the detection of osseous consolidation at the fusion site, the presence of traction spurs and possible material failure analysis [5,12]. Dynamic flexion-extension radiography may be used to detect segmental spine instability. Planar bone scintigraphy can provide information about the rate of activity of osteoblasts [2,3]. A high osteoblastic activity correlates with spinal micromotion or segmental instability, which is seen in pseudarthrosis [3,4]. When assessing fusion status, bone scintigraphy has a relatively low sensitivity and has a moderate positive predictive value [3,4]. Therefore, this technique is not routinely used as a standalone diagnostic tool. It’s recommended to perform a surgical revision, once pseudarthrosis in symptomatic patients is diagnosed [3,4,8,13].

<table>
<thead>
<tr>
<th>Grade</th>
<th>Fusion result</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Obvious radiographic pseudarthrosis</td>
<td>Collapse of the construct, loss of disc height, vertebral slip, broken screws, displacement of the carbon cage, resorption of bone graft</td>
</tr>
<tr>
<td>2</td>
<td>Probable radiographic pseudarthrosis</td>
<td>Significant resorption of the bone graft, or a major lucency or gap visible in the fusion area (2mm or more around the entire periphery of the graft or cage)</td>
</tr>
<tr>
<td>3</td>
<td>Radiographic status uncertain</td>
<td>Uncertain non-union, bone graft visible in the fusion area at approximately the density originally achieved at surgery. A small lucency or gap may be visible involving just a portion of the fusion area with at least half of the graft area showing no lucency between the graft bone and vertebral bone.</td>
</tr>
<tr>
<td>4</td>
<td>Probable radiographic fusion</td>
<td>Bone bridges the entire fusion area with at least the density originally achieved at surgery. There should be no lucency between the donor bone and vertebral bone.</td>
</tr>
<tr>
<td>5</td>
<td>Radiographic fusion</td>
<td>The bone in the fusion area is radiographically more dense and more mature than originally achieved in surgery. Optimally, there is no interface between the donor bone and the vertebral bone; however, a sclerotic line between the graft and vertebral bone indicates fusion. Other signs of solid fusion include mature bony trabeculae bridging the fusion area, resorption of anterior vertebral traction spurs, anterior progression of the graft within the disc space, fusion of facet joints.</td>
</tr>
</tbody>
</table>

Table 1: Brantigan-Steffee classification tool [3].

Multiple recent studies describe the potential effects of using rhBMP-2 to stimulate local bone formation in spinal and/or revision surgery [9,14,15]. BMP is a bone morphogenetic protein, a growth factor, and is part of the transforming growth factor beta family (TGF-b) [14]. BMP (rhBMP-2) has the characteristic as a mainly local influencer in bone remodeling. BMP has multiple indications, but also some important pitfalls. When applying inappropriate doses of BMP-2, not only a local overreaction can occur, resulting in destructive osteolysis or locally compressing hyperostosis, but there are also potential systemic side effects [10,14]. There is limited evidence-based literature offering possible solutions in the management of pseudarthrosis after lumbar interbody fusion, nor are there general guidelines setting out a management approach once diagnosis of lumbar pseudarthrosis is made [10].

Methods

Design

A single-center retrospective case series study was performed to collect data regarding the use of rhBMP-2 (InductOs-Medtronic) in revision surgery to manage pseudarthrosis after posterior interbody lumbar fusion surgery. A set of questionnaires was developed to obtain information on different points in time about pain scores (numerical rating scale, NRS pain scale) for back and leg pain, mobility and painkiller intake. Informed consent was drafted for data analysis of these questionnaires.

rhBMP-2

The application of 4mg Dibotermin alfa (1.5mg/ml) is advised per spinal segment for European use (InductOs, manufacturer responsible for batch release: Medtronic BioPharma B.V., The Netherlands; manufacturer of the biological active substance: Wyeth BioPharma Division of Wyeth Pharmaceuticals LLC, Massachusetts, USA). Following the product characteristics, provided by Medtronic, the recommended dosage of dibotermin alfa is 4mg in the intervertebral space per spinal segment. It must be placed within the interbody fusion device, or in the anterior portion of the disc space.
Literature

Literature review shows one systematic review comparing the use of rhBMP-2 with the use of conventional bone grafts in revision surgery or described the use of rhBMP-2 in revision surgery after the diagnosis of pseudarthrosis was made [10].

To study the correlation between the use of BMP and developing cancer, literature review showed large retrospective studies with a combined cohort of over 600,000 patients, including a multivariate proportional hazards model and a relative risk comparison [16,17].

Surgical technique

Multiple techniques were considered after a thorough literature study [1,9,14,18]. Due to body constitution in our population group, an anterior approach was not feasible [19]. Hence, a posterior approach during revision surgery was chosen. During the revision surgery procedure, we did a removal of the previous intervertebral cages, followed by an additional curettage of the disc space. New PLIF Peek cages were reinserted with rhBMP-2 within the cage. Dosing of the rhBMP-2 (InductOs, Diboterminalfa, MA, USA) was equally made in every case, using 1/3th of the total dose, being 4mg InductOs within the cage on each spinal segment. In addition, the loosened pedicle screws were replaced.

Case presentation

We describe a three patient study sample, who underwent prior posterior lumbar interbody fusion surgery, in a different medical center, because of degenerative disease of the spine (Table 2). The population group presented in our outpatient clinic with disabling low-back pain and leg pain. Two of these patients were male, one was female. The mean age in our population group was 50 years (55-40-56). Two patients smoked tobacco preoperatively. One quit smoking after our revision surgery, the other patient tried but didn’t succeed.

Radiological imaging using fine-cut Computed Tomography scan was performed, which showed halos and loosening of the pedicle screws. Moreover, an incomplete interbody fusion was described in all three patients on the L5/S1 spinal segment more than 1 year after their primary fusion surgery, classified as grade 1 by Brantigan-Steffee. Additionally, bone scintigraphy, using the tracer Tc-99m, was performed to locate high metabolic turnover. This confirmed high osteoblastic activity on the suspected spinal segments. These clinical and radiological findings resulted in the diagnosis of lumbar pseudarthrosis on the L5/S1 spinal segment (Table 2).

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>M</td>
<td>M</td>
</tr>
<tr>
<td>Age (y)</td>
<td>55</td>
<td>40</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>34.68</td>
<td>39.31</td>
</tr>
<tr>
<td>Initial operated spinal segments</td>
<td>3 (L3-S1)</td>
<td>1 (L5/S1)</td>
</tr>
<tr>
<td>Initial surgical technique</td>
<td>PLIF</td>
<td>PLIF</td>
</tr>
<tr>
<td>Pseudarthrosis spinal segment</td>
<td>L5/S1</td>
<td>L5/S1</td>
</tr>
<tr>
<td>Brantigan-Steffee degree (1-5)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Smoking preoperative (Y/N)</td>
<td>Y</td>
<td>N</td>
</tr>
</tbody>
</table>

Table 2: Study group characteristics before revision surgery was performed.

Results

A 2-year follow-up of the study group, resulted in a clinically significant reduction and relief in low-back pain (mean pain reduction: 26,8%) and leg pain (mean pain reduction: 86,9%), using the numerical rating scale (NRS pain-scale), as presented in Figure 1 and Table 3. Retrospectively, 2 years postoperative, all three patients confirmed they would do the revision surgery over again.

Figure 1: 2-year follow-up after revision surgery (NRS pain-scale assessment in time).
Radiological findings postoperatively, using fine-cut CT scans, showed a successful complete osseous consolidation in a 2-year follow-up in all three patients, scored as grade 5 by Brantigan-Steffee (Figures 2,3,4).

Figure 2: Preoperative CT-scan, showing no bone consolidation on the L5/S1 spinal segment (Brantigan-Steffee grade 1).

Figure 3: Preoperative bone scintigraphy, showing active inflammation, active tissue changes on the spinal segment (L5/S1) that was suspected and defined as pseudarthrosis.

Table 3: 2-year clinical follow-up (pain reduction, fusion degree, mobility and use of painkillers).

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain relief after 2 year (%)</td>
<td>Leg pain</td>
<td>75%</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Back pain</td>
<td>12.5%</td>
<td>25%</td>
</tr>
<tr>
<td>Brantigan-Steffee degree in a 2-y FU</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Active - mobile</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Painkillers after 2 year</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Type of painkillers</td>
<td>Opioids</td>
<td>Paracetamol</td>
<td>/</td>
</tr>
<tr>
<td>Reduction in painkillers</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Discussion

A review of the literature shows limited data concerning the use of BMP in revision surgery. One systematic review reported on the use of rhBMP-2 compared with the use of conventional bone grafts in revision surgery and described the use of rhBMP-2 in revision surgery after the diagnosis of pseudarthrosis was made [10]. An alternative surgical approach is the 360-degree fixation [19]. In some cases, revision surgery can be challenging because of local scar tissue. In these cases, the ALIF (anterior lumbar interbody fusion) technique can be a good alternative for the lower spinal segments (L4/L5 and L5/S1) to remove the present cages and replace them. When instability or material failure is reported preoperatively, performing this technique, it’s mandatory to do a revision of the posterior fixation elements in a posterior approach to ensure a stable 360-degree fixation.

Multiple potential side effects or complications are associated with the use of BMP [10,14,20-22]. Bone morphogenetic protein
has a potential in bone remodeling, resulting in potential local osteolytic effects or ectopic bone formation, especially when high doses are administered. A correct dosing is an important pitfall, that should be kept in mind when preparing for revision surgery [21,22]. Following the product characteristics of rhBMP-2 provided by Medtronic, a correct dosing (4mg per spinal segment) and an accurate administration was applied. No complications were objectified associated with BMP exposure on the operated spinal segments in our study group in a 2-year follow-up.

Furthermore, there were some concerns about the potential carcinogenic effects of rhBMP-2 used for spinal surgery [22-24]. Thawani et al. described a detailed analysis of in vitro effects of BMP on cancer cells [22]. Although it should be mentioned that there are only few cancer cells that actually respond to BMP. On the other hand, there is some evidence obtained by these in vitro studies that BMP has a potential inhibitory carcinogenic effect in certain cancers, which is now being studied [24].

Large retrospective studies were performed with a combined cohort of over 600,000 patients, including a multivariate proportional hazards model (hazard ratio: 0.99, 95% confidence interval: 0.95-1.02) and a relative risk comparison of developing cancer between a BMP group and a control group (0.938 with a 95% CI: 0.913 to 0.964) [16,17]. The conclusion of these large studies was that the use of rhBMP-2 was not associated with a rise in the risk of cancer, nor with a specific kind of cancer in a 2.9 year follow-up and a 4.7 year follow-up [16,17].

Taking into account the theoretical potential of tumor growth after BMP-exposure in primary and/or revision surgery, BMP is contraindicated when there is evidence of local cancer or in case of previous local cancer treatment [16,17,24,25].

Conclusion

Our case series describes successful lumbar interbody fusion after revision surgery, in a posterior approach, using rhBMP-2 (InductOs). All patients showed a complete solid bony fusion in a 2-year follow-up, scored as grade 5 by Brantigan-Steffee. No side effects or complications secondary to the use of rhBMP-2 were reported in our population group. The use of rhBMP-2 (InductOs) in spine surgery, more specific in a posterior approach, is safe.

A correct dosing of rhBMP-2 is primordial because of its potential in bone remodeling, resulting in potential locally osteolytic effects or ectopic bone formation. Literature review showed no association between the use of rhBMP-2 and an increase in the risk of cancer. The authors suggest that qualitative prospective studies with larger sample size and a longer follow-up are necessary, considering the worldwide use of BMP in spine surgery.

Declarations

Funding: No funding was received for this research.
Competing interests: The authors declare that they have no competing interest.
Ethical approval: For this type of study formal consent is not required.
Consent for publication: Informed consent was obtained from all individual participants included in the study.

Availability of data and material: All data generated or analysed during this study are included in this published article.

Authors’ contributions: All authors contributed to the study conception and design. Jeroen Cortier collected the data and follow-up questionnaires, provided by the treating neurosurgeon, Dimitri Vanhauwaert. Jeroen Cortier wrote the preliminary manuscript. Dimitri Vanhauwaert, Jeroen Van Lerbeirghe and Abdulhamid Cicek analyzed and interpreted the patient data regarding the postoperative clinical evolution. All authors (Jeroen Cortier, Abdulhamid Cicek, Sarah Hendrickx, Jeroen Van Lerbeirghe, Olivier Van Damme and Dimitri Vanhauwaert) read, commented, revised critically and ultimately approved the final manuscript.

References


