Perioperative complications with rhBMP-2 in transforaminal lumbar interbody fusion

Kirk Owens · Steven D. Glassman ·
Jennifer M. Howard · Mladen Djurasovic ·
Jonathan L. Witten · Leah Y. Carreon

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Abstract Bone morphogenetic protein (BMP) is commonly used as an ICBG substitute for transforaminal lumbar interbody spine fusion (TLIF). However, multiple recent reports have raised concerns regarding a substantial incidence of perioperative radiculopathy. Also, given the serious complications reported with anterior cervical BMP use, risks related to swelling and edema with TLIF need to be clarified. As TLIF related complications with rhBMP-2 have generally been reported in small series or isolated cases, without a clear denominator, actual complication rates are largely unknown. The purpose this study is to characterize perioperative complications and complication rates in a large consecutive series of TLIF procedures with rhBMP-2. We reviewed inpatient and outpatient medical records for a consecutive series of 204 patients [113 females, 91 males, mean age 49.3 (22–79) years] who underwent TLIF using rhBMP-2 between 2003 and 2007. Complications observed within a 3-month perioperative interval were categorized as to etiology and severity. Wound problems were delineated as wound infection, hematoma/seroma or persistent drainage/superficial dehiscence. Neurologic deficits and radicul-

opathies were analyzed to determine the presence of a clear etiology (screw misplacement) and identify any potential relationship to rhBMP-2 usage. Complications were observed in 47 of 204 patients (21.6%) during the 3-month perioperative period. Major complications occurred in 13 patients (6.4%) and minor complications in 34 patients (16.7%). New or more severe postoperative neurologic complaints were noted in 13 patients (6.4%), 6 of whom required additional surgery. These cases included one malpositioned pedicle screw and one epidural hematoma. In four patients (2.0%), localized seroma/hematoma in the area of the foramen caused neural compression, and required revision. In one additional patient, vertebral osteolysis caused foraminal narrowing and radiculopathy, but resolved without further surgery. Persistent radiculopathy without clear etiology on imaging studies was seen in six patients. Wound related problems were seen in six patients (2.9%), distributed as wound infection (3), hematoma/seroma (1) and persistent drainage/dehiscence (2). Overall, this study demonstrates a modest complication rate for TLIF using rhBMP-2. While perioperative complications which appeared specific to BMP usage were noted, they occurred infrequently. It will be necessary to weigh this incidence of complications against the complication rate associated with ICBG harvest and any differential benefit in obtaining a solid arthrodesis.

K. Owens · S. D. Glassman · M. Djurasovic
Department of Orthopaedic Surgery,
University of Louisville School of Medicine,
210 East Gray Street, Suite 1003,
Louisville, KY 40202, USA

J. M. Howard · J. L. Witten
University of Louisville School of Medicine,
500 South Preston Street,
Louisville, KY 40202, USA

S. D. Glassman · M. Djurasovic · L. Y. Carreon (✉)
Norton Leatherman Spine Center,
210 East Gray Street, Suite 900,
Louisville, KY 40202, USA
e-mail: leah.carreon@nortonhealthcare.org

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Introduction

In 1982, Harms and Rollinger [1] introduced a modification to the posterior lumbar interbody fusion (PLIF) technique

that has come to be termed transforaminal lumbar interbody fusion (TLIF). TLIF has since gained popularity due to the need for significantly less nerve root retraction which was associated with a high complication rate for PLIF [2–5].

Since its approval by the Food and Drug Administration (FDA) in 2002, rhBMP-2 (INFUSE, Medtronic, Memphis, Tennessee) has had a significant impact on spinal surgery. Despite being approved only for anterior interbody fusion with an LT cage (Medtronic, Memphis, Tennessee), rhBMP-2 has been used largely in an “off-label” manner [6]. Several studies have demonstrated the successful use of rhBMP-2 in TLIF and posterolateral fusion [7–11]. However, recent reports of a high complication rate in anterior cervical fusion [12–14] have raised concerns regarding the use of rhBMP-2 for any application.

Complications have been reported in up to 35% of cases with the use of rhBMP-2 in TLIF [7, 15, 18, 19]. These complications include CSF leak, hematoma, pedicle screw malposition, neurologic deficit and radiculitis. Unfortunately, most of the existing studies on TLIF have been limited, in that they have reported complications as isolated cases or small case series. It is important to examine these complications in consecutive patients in order to establish a clear denominator especially due to the increasing use of rhBMP-2 in TLIF. Therefore, the purpose of this study was to review a large consecutive series of patients undergoing TLIF with rhBMP-2 in order to characterize the perioperative complications associated with the procedure, and those complications related specifically to rhBMP-2 use.

Methods

We reviewed medical records in a consecutive series of 204 patients who underwent TLIF using rhBMP-2 between 2003 and 2006. Demographic data included age, gender, smoking history, comorbidities, and diagnosis. Surgical data included operative time, estimated blood loss, fusion levels, rhBMP-2 kit size as well as any other bone graft extenders. Perioperative data consisted of number of days in the ICU or TCU, overall hospital length of stay, and discharge disposition.

Complications within a 3-month perioperative period were categorized as to their etiology and severity. Major complications were defined as those which were potentially life threatening, required reoperation in the perioperative period or left some permanent injury. Minor complications were those events which required additional intervention but did not significantly alter the course of treatment. Medical complications were attributed to the surgical procedure if they occurred during the 3-month perioperative period, whereas complications potentially related to rhBMP-2 were included regardless of the time frame.

Wound related problems were classified as wound infection, hematoma/seroma, or superficial dehiscence/suture reaction. Wound infections were defined by the need for surgical debridement and subsequent antibiotic treatment, regardless of culture results. Fluid collections which were clinically evident, but resolved without treatment, or underwent drainage with negative cultures and no antibiotic treatment were characterized as hematoma/seroma. Superficial wound drainage was the description applied to cases of suture reaction or superficial dehiscence which was managed as an outpatient with local care and went onto adequate wound healing, with or without oral antibiotic coverage.

Neurologic deficits and radiculopathies were analyzed to determine the presence of a clear etiology and identify any potential relationship to the use of rhBMP-2. Particular attention was paid to the development of new, contralateral, or more severe leg pain postoperatively. Postoperative imaging was reviewed and any indication of heterotopic fluid collection or bone formation was sought.

All patients underwent open single or two-level TLIF by one of our institution's six surgeons. A standard posterior midline approach was made with subperiosteal dissection. After placement of pedicle screws, a unilateral facetectomy was performed. The side of the transforaminal approach was selected based on the patients more symptomatic leg pain. The annulus was then incised and the disk removed. rhBMP-2 combined with local autograft, iliac crest bone graft and/or various bone graft extenders were placed in the interbody space along with a polyetheretherketone (PEEK) cage. In the majority of cases where one large or one small sponge was used, the rhBMP-2 soaked ACS was divided into three. One-third of the sponge was placed in the disc space, and one-third was placed in either lateral gutters. Thus, in the majority of patients (95.6%) the dose of rhBMP-2 in the interspace was 4 mg, but ranged from 1.4 to 6 mg. Placing rhBMP-2 posteriorly in the disc space was avoided. Rods were then contoured in lordosis and placed into position. Bone graft with or without extender and rhBMP-2 were placed in the lateral gutters. The wound was closed in layers in standard fashion over a drain.

Results

The study cohort of 204 patients (Table 1) included 91 men and 113 women with a mean age of 49.3 years (range 22–79). The mean follow-up was 29.8 ± 9.0 months. Indication for surgery included spondylolisthesis (27%), instability (5.4%), stenosis (10.8%), scoliosis (2.9%), disc pathology (26%), non-union (1.5%), adjacent level degeneration (8.3%) and post-discectomy instability (18.1%). Eighty-three patients (40.7%) were smokers.

One hundred sixty-three (79.9%) underwent single-level fusions and 41 (20.1%) two-level fusions. The mean operative time was 278 min (range 132–568) with a mean estimated blood loss of 692.8 cc (range 60–3,000). A large INFUSE kit was used in 195 (95.6%) cases. Two cases (1%) used a single small kit, 6 (2.9%) used two large kits, and 1 (0.5%) used three large kits. Iliac crest bone graft was taken in 45 (22.1%) patients and local bone graft was used in 174 (85.3%). Various other bone graft extenders used consisted of allograft (24%), mastergraft ceramic (10.3%), and demineralized bone matrix (33.8%).

Complications were observed in 47 of 204 cases (21.6%) with 13 (6.4%) major and 34 (16.7%) minor complications. Major surgical complications were pneumonia (1), vascular injury (1), neurologic complications (7), wound infection (3), and wound hematoma/seroma (1) (Table 2, 3).

New or worsening perioperative neurologic complaints were noted in 13 patients (6.4%), 6 of whom needed additional surgery, including 1 malpositioned screw and 1

epidural hematoma. In 4 patients (2%), a seroma located in the area of the foramen caused neural compression, requiring revision (Fig. 1). In all these cases the radiculopathy were on the same side as and corresponded to the dermatomal distribution of the TLIF window. These patients started to complain of radiculopathy an average of 1.7 ± 1.9 months after surgery and their symptoms improved in an average of 4.0 ± 2.8 months after the evacuation of the seroma surrounding the nerve root. Of the seven patients who received more than a single large Infuse kit, only one patient presented with a postoperative radiculopathy and hematoma on the TLIF side that required an operative evacuation. In one patient, vertebral osteolysis, foraminal narrowing and radiculopathy resolved 6 months after surgery without further surgery or the need for revision.

Six patients (2.9%) had persistent radiculopathy without a clear etiology on imaging studies and required no additional surgery. The radiculopathy in these cases were on the same side as and corresponded to the dermatomal distribution of the TLIF window as well, with an average time of presentation of 1.7 ± 1.9 months after surgery. These patients were treated with oral steroids and Gabapentin (Pfizer, New York, NY) or Pregabalin (Pfizer, New York, NY, USA). The radiculopathy resolved in an average of 4.0 ± 2.8 months after the index surgery.

Wound related problems were seen in six patients (2.9%): three deep wound infections, one wound hematoma/seroma, and two dehiscences. Ileus (6), urinary tract infection (2) and other (18) minor complications were also observed.

Discussion

Circumferential lumbar fusion has been used to treat a number of spinal problems including degenerative disc

Table 1 Patient demographic and operative data

Age (years)	49.3, range (22–79)
Gender	91 M, 113 F
Diagnosis ^a	
Spondylolisthesis	55 (27.0)
Instability	11 (5.4)
Stenosis	22 (10.8)
Scoliosis	6 (2.9)
Disc pathology	53 (26.0)
Nonunion	3 (1.5)
Adjacent level degeneration	17 (8.3)
Post-discectomy instability	37 (18.1)
Smokers	83 (40.7)
Number of levels	
One level	163 (79.9)
Two level	41 (20.1)
Kit Size	
Large	195 (95.6)
Small	2 (1.0)
2 Large	6 (2.9)
3 Large	1 (0.5)
Extender/Filler	
Iliac crest bone graft	45 (22.1)
Local bone graft	174 (85.3)
Allograft	49 (24.0)
Mastergraft ceramic	21 (10.3)
Demineralized bone matrix	69 (33.8)
Operative time (min)	278, range (132–568)
Estimated blood loss (cc)	692.8, range (60–3,000)

^a Values are given as frequency (%)

Table 2 Summary of Complications

	Frequency (%)
Major complication	
Pneumonia	1 (0.5)
Vascular injury	1 (0.5)
Neurologic	7 (3.4)
Wound infection	3 (1.5)
Wound hematoma/seroma	1 (0.5)
Minor complication	
Radiculopathy–CT	6 (2.9)
Superficial wound dehiscence	2 (1.0)
Ileus	6 (2.9)
UTI	2 (1.0)
Other	18 (8.8)

Table 3 Specific complication rate in comparison to complication rate reported in literature

	Occurrence rate in the present study (%)	Occurrence rate with autograft literature (%)	Occurrence rate with rhBMP-2 literature (%)
Wound infection	1.5	1–6.1 [15, 18, 19, 28–30]	2.7–3.6 [7, 15, 19]
Hematoma/seroma	0.5	1–3 [18, 19, 30]	2.4–2.7 [7, 19]
Radiculopathy	6.4	2–7 [19, 28–31]	7–14 [7, 15, 18, 19, 32]

Fig. 1 35-year-old female with L5–S1 spondylolisthesis treated with transforaminal interbody fusion using a PEEK cage and rhBMP-2/ACS. 3 months after surgery, patient complained of increasing right leg pain. **a** Axial CT scan and **b** sagittal reconstruction at 3 months

demonstrates a cyst with a bony capsule in the disc space intruding into the L5–S1 neuroforamen. The patient required revision foraminotomy and cyst resection. Intraoperatively, the cystic structure was noted to be calcified and embedded in the disc space

disease, spondylolisthesis, and pseudarthrosis. It is associated with high rate of fusion and can provide a biomechanical advantage to a posterior-only fusion [20]. Methods for this 360 fusion have complications, however. Complication rates up to 77% have been reported with anteroposterior reconstruction for lumbar disc degeneration and instability [15–17] and up to 51% in PLIF [4]. Complications associated with TLIF have occurred at nearly half these rates [7, 15, 18, 19]. In addition, a financial analysis by Whitecloud [21] of TLIF versus anterior–posterior fusion found that TLIF had an average cost savings of approximately \$15,000 per admission. Therefore, TLIF provides an appealing and potentially cost-effective approach to circumferential lumbar fusion.

rhBMP-2 has been reported to result in larger and more robust fusions when compared to autograft. Lower operative time and blood loss have been reported [10, 22, 23]. Consequently, its use has risen since FDA approval in 2002, but largely in an “off-label” manner [6]. Recent reports of complications with use of rhBMP-2 in anterior cervical fusions [12–14] and a subsequent FDA warning letter [24] regarding the use of cervical rhBMP-2 have fueled concerns over the use of rhBMP-2 in any application. Therefore, concern remains with the use of rhBMP-2 in TLIF.

In a study using rhBMP-2 in posterior lumbar interbody fusion (PLIF), Haid et al. [25] reported bone formation

outside the disc space and into the spinal canal or neuroforamen in nearly 75% of patients. Heterotopic bone was demonstrated in 20.8% in minimal access interbody fusion with rhBMP-2 in a study by Joseph et al. [26]. Conversely, Villavicencio et al. [7] in a series of 74 consecutive patients found no incidence of ectopic bone formation. In the FDA Investigational Device Exemption Study of anterior lumbar interbody fusions with rhBMP-2 and an LT cage [27], there were no reports of ectopic bone formation, implying that the intact annulus may posteriorly provide a barrier to the leaching of BMP into the spinal canal.

Various technical modifications have been described to try to minimize unwanted bone formation and the potential for neurologic sequelae. Villavicencio [7] placed the rhBMP-2 and autograft anterior to the structural allografts. More recently, Rihn et al. [19] noted a decreased rate of postoperative radiculitis following the use of a hydrogel sealant posterior to the interbody cage. Further studies are needed, however, to clarify if these technical modifications can reduce complications.

The specific cause of new neurologic complaints following TLIF remains unclear. Nerve root retraction and injury during cage insertion are possible. Theories exist attributing it to ectopic bone formation in the neuroforamen or a rhBMP-2-induced inflammatory reaction near the nerve root. The reported rates of postoperative radiculitis with TLIF using autograft have ranged from 2 to 7%

[19, 28–31]. In contrast, radiculitis occurs at a rate of 7–14% when rhBMP-2 has been used [7, 15, 18, 19, 32]. In our series, 13 patients (6.4%) presented postoperatively with new or worsened radiculopathy. Of that group, we believe that five patients (2.5%) demonstrated radiographic and clinical findings characteristic of rhBMP-2-induced compression in the area of the TLIF window. There was localized seroma in the foramen causing root compression on the same side as and corresponding to the dermatomal distribution of the TLIF window. The remaining 8 patients (4%) with radiculopathy without radiographic evidence are consistent with previously reported rates without the use of rhBMP-2.

Vertebral osteolysis has been well described after the use of rhBMP-2 in lumbar interbody fusion. Toth et al. [33] recently reported transient osteoclastic activity in sheep distal femora which was related to increasing dosage of rhBMP-2. Vaidya et al. [34] found an 82% rate of end plate resorption in evaluating rhBMP-2 with polyetheretherketone (PEEK) cages. Vertebral bone resorption was demonstrated on CT scan in 69% of cases in a study by McClellan et al. [35], but not all these patients were symptomatic. Lewandroski et al. [36] found only a 7% incidence in single-level TLIFs with rhBMP-2. Our study found only one patient (0.5%) who showed radiographic evidence of osteolysis as well as foraminal narrowing and radiculopathy. It is unclear whether this is specifically attributable to the rhBMP-2 alone, due to surgical technique resulting in endplate violation, or a combination of both. Deep wound infection or hematoma/seroma was seen in four patients (2%) which is similar to the reported deep infection rates between 2.5 and 3.6% [7, 15, 19].

The major limitation of this study was its retrospective design. We also did not have a contemporaneous control group to compare our results. There was also difficulty in characterizing postoperative radiculopathy in the absence of positive imaging. It is unclear whether this was a true surgical complication or persistence of the preoperative pathology.

In summary, this study of 204 patients demonstrates a modest complication rate for TLIF using rhBMP-2, with rhBMP-2-associated complications occurring infrequently. It will be necessary to weigh this incidence of complications against the complication rate associated with iliac crest bone graft harvest and any differential benefit in obtaining a solid arthrodesis.

Conflict of interest statement None.

References

- Harms J, Rollinger H (1982) A one-stage procedure in operative treatment of spondylolisthesis: dorsal traction-reposition and anterior fusion. *Z Orthop Ihre Grenzgeb* 120:343–347
- Molinari RW, Gerlinger T (2001) Functional outcomes of instrumented posterior lumbar interbody fusion in active-duty US servicemen: a comparison with nonoperative management. *Spine J* 1:215–224
- Fritzell P, Hagg O, Nordwall A, Swedish Lumbar Spine Study Group (2003) Complications in lumbar fusion surgery for chronic low back pain: comparison of three surgical techniques used in a prospective randomized study. *Eur Spine J* 12:178–189
- Okuyama K, Abe E, Suzuki T, Tamura Y, Chiba M, Sato K (1999) Posterior lumbar interbody fusion: a retrospective study of complications after facet joint excision and pedicle screw fixation in 148 cases. *Acta Orthop Scand* 70:329–334
- Barnes B, Rodts GE Jr, Haid RW Jr, Subach BR, McLaughlin MR (2002) Allograft implants for posterior lumbar interbody fusion: results comparing cylindrical dowels and impacted wedges. *Neurosurgery* 51:1191–1198
- Cahill KS, Chi JH, Day A, Claus EB (2008) Prevalence, complications and hospital charges associated with use of bone-morphogenetic proteins in spinal fusion procedures. *JAMA* 302:58–66
- Villavicencio AT, Burneikiene S, Nelson EL, Bulsara KR, Favros M, Thramann J (2005) Safety of transforaminal lumbar interbody fusion and intervertebral recombinant human bone morphogenetic protein-2. *J Neurosurg Spine* 3:436–443
- Boden SD, Zdeblick TA, Sandhu HS, Heim SE (2000) The use of rhBMP-2 in interbody fusion cages: definitive evidence of osteoinduction in humans: a preliminary report. *Spine (Phila Pa 1976)* 25:376–381
- Glassman SD, Carreon L, Djurasovic M, Campbell MJ, Puno RM, Johnson JR, Dimar JR (2007) Posterolateral lumbar spine fusion with infused bone graft. *Spine J* 7:44–49
- Singh K, Smucker JD, Gill S, Boden SD (2006) Use of recombinant human bone morphogenetic protein-2 as an adjunct in posterolateral lumbar spine fusion: a prospective CT-scan analysis at one and two years. *J Spinal Disord Tech* 19:416–423
- Alexander DJ, Abraham EP, Bailey SI, et al. (2005) A new rhBMP-2 formulation in posterolateral lumbar spine fusion; a prospective, randomized study. In: *Proceedings of the American Academy of Orthopaedic Surgeons Annual Meeting*, vol 6, p 532
- Smucker JD, Rhee JM, Singh K, Yoon ST, Heller JG (2006) Increased swelling complications associated with off-label usage of rhBMP-2 in the anterior cervical spine. *Spine* 31:2813–2819
- Shields LB, Raque GH, Glassman SD, Campbell M, Vitaz T, Harpring J, Shields CB (2006) Adverse effects associated with high-dose recombinant human bone morphogenetic protein-2 use in anterior cervical spine fusion. *Spine* 31:542–547
- Vaidya R, Carp J, Sethi A, Bartol S, Craig J, Les CM (2007) Complications of anterior cervical discectomy and fusion using recombinant human bone morphogenetic protein-2. *Eur Spine J* 16:1257–1265
- Villavicencio AT, Burneikiene S, Bulsara KR, Thramann JJ (2006) Perioperative complications in transforaminal lumbar interbody fusion versus anterior-posterior reconstruction for lumbar disc degeneration and instability. *J Spinal Disord Tech* 19:92–97
- Hee HT, Castro FP Jr, Majd ME, Holt RT, Myers L (2001) Anterior/posterior lumbar fusion versus transforaminal lumbar interbody fusion: analysis of complications and predictive factors. *J Spinal Disord* 14:533–540
- Gertzbein SD, Betz R, Clements D, Errico T, Hammerberg K, Robbins S, Shepherd E, Weber A, Kerina M, Albin J, Wolk D, Ensor K (1996) Semirigid instrumentation in the management of lumbar spinal conditions combined with circumferential fusion. A multicenter study. *Spine* 21:1918–1926
- Potter BK, Freedman BA, Verwiebe EG, Hall JM, Polly DW Jr, Kuklo TR (2005) Transforaminal lumbar interbody fusion:

- clinical and radiographic results and complications in 100 consecutive patients. *J Spinal Disord Tech* 18:337–346
19. Rihn JA, Patel R, Makda J, Hong J, Anderson DG, Vaccaro AR, Hilibrand AS, Albert TJ (2009) Complications associated with single level transforaminal lumbar interbody fusion. *Spine J* 9:623–629
  20. Duffield RC, Carson WL, Chen LY, Voth BI (1993) Longitudinal element size effect on load sharing, internal loads, and fatigue life of tri-level spinal implant constructs. *Spine* 18:1695–1703
  21. Whitecloud TS, Roesch WW, Ricciardi JE (2001) Transforaminal interbody fusion versus anterior–posterior interbody fusion of the lumbar spine: a financial analysis. *J Spinal Disord* 14:100–103
  22. Burkus KJ, Heim SE, Gornet MF, Zdeblick TA (2003) Is INFUSE bone graft superior to autograft bone? An integrated analysis of clinical trials using the LT-CAGE lumbar tapered fusion device. *J Spinal Disord Tech* 16:113–122
  23. Dimar JR, Glassman SD, Burkus KJ, Carreon LY (2006) Clinical outcomes and fusion success at 2 years of single-level instrumented posterolateral fusions with recombinant human bone morphogenetic protein-2/compression resistant matrix versus iliac crest bone graft. *Spine* 31:2534–2539
  24. FDA (2009) FDA public health notification: life-threatening complications associated with recombinant human bone morphogenetic protein in cervical spine fusion, issued: 1 July 2008. <http://www.fda.gov/cdrh/safety/070108-rhbm.html>. Accessed on-line 12 August 2009
  25. Haid RW Jr, Branch CL Jr, Alexander JT, Burkus JK (2004) Posterior lumbar interbody fusion using recombinant human bone morphogenetic protein type 2 with cylindrical interbody cages. *Spine J* 4:527–538
  26. Joseph V, Rampersaud YR (2007) Heterotopic bone formation with the use of rhBMP-2 in posterior minimal access interbody fusion. *Spine* 32:2885–2890
  27. Burkus JK, Gornet MF, Dickman CA, Zdeblick TA (2002) Anterior lumbar interbody fusion using rhBMP-2 with tapered interbody cages. *J Spinal Disord Tech* 15:337–349
  28. Chen Z, Zhao J, Liu A, Yuan J, Li Z (2009) Surgical treatment of recurrent lumbar disc herniation by transforaminal lumbar interbody fusion. *Int Orthop* 33:197–201
  29. Hackenberg L, Halm H, Bullman V, Vieth V, Schneider M, Liljenqvist U (2005) Transforaminal lumbar interbody fusion: a safe technique with satisfactory three to five year results. *Eur Spine J* 14:551–558
  30. Lauber S, Schulte TL, Liljenqvist U, Halm H, Hackenberg L (2006) Clinical and radiologic 2–4-year results of transforaminal lumbar interbody fusion in degenerative and isthmic spondylolisthesis grades 1 and 2. *Spine* 31:1693–1698
  31. Mummaneni PV, Pan J, Haid RW, Rodts GE (2004) Contribution of recombinant human bone morphogenetic protein-2 to the rapid creation of interbody fusion when used in transforaminal lumbar interbody fusion: a preliminary report. *J Neurosurg* 1:19–23
  32. Mindea SA, Shih P, Song JK (2009) Recombinant human bone morphogenetic protein-2-induced radiculitis in elective minimally invasive transforaminal lumbar interbody fusions. *Spine* 34:1480–1484
  33. Toth JM, Boden SD, Burkus JK, Badura JM, Peckham SM, McKay WF (2009) Short-term osteoclastic activity induced by locally high concentrations of recombinant human bone morphogenetic protein-2 in a cancellous bone environment. *Spine* 34:539–550
  34. Vaidya R, Sethi A, Bartol S, Jacobson M, Coe C, Craig JG (2008) Complications in the use of rhBMP-2 in PEEK cages for interbody spinal fusions. *J Spinal Disord Tech* 21:557–562
  35. McClellan JW, Mulconrey DS, Forbes RJ et al (2006) Vertebral bone resorption after transforaminal lumbar interbody fusion with bone morphogenetic protein (rhBMP-2). *J Spinal Disord Tech* 19:483–486
  36. Lewandrowski KU, Nanson C, Calderon R (2007) Vertebral osteolysis after posterior interbody lumbar fusion with recombinant human bone morphogenetic protein 2: a report of five cases. *Spine J* 7:609–614