

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

5,800

Open access books available

142,000

International authors and editors

180M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Application of Bone Morphogenetic Protein in Spinal Fusion Surgery

Siavash Beiranvand and Farshad Hasanzadeh-Kiabi

Abstract

Lumbar and cervical fusions are one of the most common types of spine surgeries performed globally with approximated 450,000 spinal fusion surgeries performed annually. (give reference) Bone Morphogenetic Proteins (BMPs) are secreted cytokines with several functions, within the TGF- β superfamily. BMP act as a disulfide-linked homo- or heterodimers and have been recognized as strong and effective regulators of important biological processes like formation and repair of osteocytes and chondrocytes, cell proliferation during embryonic development. Recombinant human bone morphogenetic protein 2 (rhBMP-2) is a very effective osteogenic growth factor that has been demonstrated to be effective in different types of spinal fusions and reduces the reliance on the use autologous iliac crest bone graft. In recent years there have been limitations regarding the use of rhBMP-2 because of issues like high costs, benefits, and safety issues about rhBMP-2. In this review, a comprehensive overview about the application of rhBMP-2 in spinal fusion surgery is given.

Keywords: Recombinant Bone Morphogenetic Proteins, Spinal fusion surgery, TGF- β , cytokines

1. Introduction

The use of osteobiologics to improve the outcome of spinal fusion has contributed to an increase in spinal fusion surgical procedures worldwide [1]. There are many different types of bone graft fusion materials currently on the market, however there is still a need for a cost effective biological material to achieve a successful permanent arthrodesis [2]. Presently iliac crest autograft, used for spinal fusion surgeries, is desirable as it possess osteo-biological properties with reduced risk of diseases transmission and graft rejection [3]. However, according to some studies, autograft has been linked to longer surgery time, few donor site availability [4], and chronic donor site pain [5, 6]. These limitations and disadvantages have led to novel therapeutic bone graft options for spinal fusion surgery [5, 7], like BMPs.

Marshall Urist was the first to describe BMP in 1965. It belongs to the transforming growth factor- β family. There are various types of BMP molecules that exist, however few of them have been associated with osteoblast differentiation and bone development [7]. Recombinant rhBMP-2 is the market available form of

BMP-2 FDA approved for anterior lumbar interbody fusion (ALIF) [8]. There have been several clinical studies on the anterior lumbar interbody fusions and all have reported effective fusion rates, reduced operative time, reduced blood loss, and reduced hospital duration with the administration of rhBMP-2 when compared to iliac crest bone graft (ICBG) [9]. However, there have been conflicting reports as to whether rhBMP-2 is efficient in spinal fusion. A well-done study was performed by Papakostidis et al., who investigated the benefits of rhBMP-2 in promoting posterolateral fusion. They concluded in their report that rhBMP-2 significantly increases rates of fusion, reduced hospital stay with the administration of BMP-2, compared to autologous iliac crest bone graft [10]. Lee et al. also confirmed the efficacy of the administration of rhBMP-2 in elderly patients undergoing posterolateral lumbar fusion at a single operative level [11]. Similarly, researchers like Meisel and colleagues also reported a 95–100% successful arthrodesis with use of BMP-2 when performing posterior lumbar interbody fusion [12]. However, recent systematic reviews question the efficacy and use of BMP-2 over iliac crest bone graft as noted in the Yale University Open Data base (YODA) Project and FDA reports. Including 13 randomized-controlled and 31 cohort studies, the study reported that for spinal fusion, rhBMP and iliac crest bone graft have similar efficacy. However, incidence of adverse event might be greater in anterior lumbar-body fusion and anterior cervical spine fusion. Furthermore, rhBMP can increase 24-month cancer risk [8]. These reports concluded that there were no substantial clear benefits of the administration of BMP-2 in spine fusion over autologous bone graft, and in fact there were more complications linked with BMP-2 use [13] (**Figure 1**).



Figure 1. Lateral radiograph of the cervical spine demonstrating massive soft-tissue swelling (arrows) following anterior cervical discectomy and fusion surgery using rhBMP-2. Image was culled from.

2. Types of BMPs

There are about 20 different BMPs, however only BMP-2 is presently FDA approved for human spinal surgery [14, 15]. In addition, BMP-7 has been investigated for human use but is not FDA approved.

2.1 Different applications of rhBMP-2 in spinal fusion

2.1.1 Anterior lumbar interbody fusion

Burkus and colleagues demonstrated that patients administered with recombinant rhBMP-2 inside a Lumbar Tapered Fusion Device (LT-CAGE) had statistically significant lower length of surgery, lower duration of hospitalization and higher fusion rates at 6 months, 1 year and 2 years, compared to patients administered with the conventional ICBG [16]. In another clinical study, Burkus and co-worker compared the administration effect of rhBMP-2 in ALIF with structural cortical allografts and the INTER FIX Threaded Fusion Device to ICBG [17]. They concluded that patients administered with rhBMP-2 exhibited better clinical and radiographic results, compared to ICBG patients [18]. Furthermore Burkus and colleagues reported that they recorded a superior and higher rates of radiographic fusion compared to the control group, in addition they demonstrated that rhBMP-2 resulted into an improved ODI outcomes, enhanced radiographic fusion rate, compared to the ICBG control group. **Table 1** shows a summary of different available clinical studies demonstrating the potency of rhBMP-2 in increasing fusion rates of various spine surgeries.

2.2 Posterolateral lumbar fusion

The efficacies of rhBMP-2 have been studied and reported over the past few years. Boden et al. in their prospective randomized multicenter clinical trials demonstrated that the administration of rhBMP-2 in posterolateral lumbar fusion (PLF) [19]. They compared the effect of rhBMP-2 in patients with suffering from degenerative disc disease following PLF [20]. The patients were divided into three groups: autograft with pedical screw fixation, rhBMP-2 with pedical screw fixation, and rhBMP-2 without pedical screw fixation [21]. They concluded that they

Anatomical location of rhBMP-2	Adverse events	% Of fusion	Reference
Posterolateral lumbar	None reported	100%	[18]
Anterior lumbar	None reported	94.5%	[13]
Posterolateral lumbar	None reported	95%	[19]
Posterolateral lumbar	None reported	96%	[20]
Posterolateral lumbar	None reported	88%	[21]
Anterior lumbar	There were reports of retrograde ejaculation	NA	[22]
Posterior cervical	There were evidences of large seroma with recurrence after surgery	NA	[23]
Posterior lumbar interbody	Osteolysis	83%	[24]
Posterior lumbar interbody	There were reports of increased incidence of radiculitis	96.5%	[25]
Posterior lumbar interbody	There were reports malignancy at 5 years	NA	[26]

Culled from [27].

Table 1.
 Showing the rates of fusion and adverse events associated with the application of rhBMP-2.

recorded a 100% fusion rate in the rhBMP-2 groups compared to the 40% fusion rate in the autograft group was 40.

Carreon and colleagues in their study, compared the application of autograft and higher dose rhBMP-2 in single-level of PLF case was carried out [22]. They concluded in their study that they recorded an 89% and 96% fusion rate in the autograft group and rhBMP- 2/CRM group respectively at 2 years follow-up. However they also recorded no similar clinical outcome measures between the two compared groups [23]. There have also been few smaller studies that reported related results of high fusion rates with the use of rhBMP-2 in PLF compared to ICBG [24].

2.3 Posterior lumbar interbody fusion

Haid and co-worker reported the efficiency of rhBMP-2 in posterior lumbar interbody fusion (PLIF), however there is a possibility for heterotopic bone formation. Haid and co-workers reported that they recorded 92.3% and 77.8% fusion rate with rhBMP-2 group and control group respectively, however there was an insignificant difference in clinical progress between the two compared groups [25]. They also reported via CT imaging that there was formation of ectopic bone around the PLIF [26].

2.4 Anterior cervical fusion

Baskin and colleague reported that there was a 100% fusion rate with the administration rhBMP-2 when compared with autograft [28]. Furthermore, they reported that the efficiency of rhBMP-2 was further improved when collagen sponges, PEEK cages, bioabsorbable spacers, and allograft rings were added to it [29]. However, the positive results have been marred by reports of the incidence of soft-tissue related complications including potentially life-threatening airway compromise from tissue swelling. Cole, Veeravagu [30] conducted a MarketScan database-based retrospective study regarding the use of rhBMP in anterior cervical discectomy and fusion procedure. The outcomes of the study indicated that the use of drug is associated with increased incidence of hematoma, seroma, dysphagia, and pulmonary complications. Low dose rhBMP is also not associated with reduced incidence of the postoperative complications [31]. The FDA has placed a black box warning on the use of rhBMP-2 in the anterior cervical spine indicating that the risk of use may outweigh the benefit and therefore, its use is not recommended in anterior cervical fusion.

2.5 Transforaminal lumbar interbody fusion

There have been studies to investigate the efficiency of rhBMP-2 on transforaminal lumbar interbody fusion (TLIF, **Figure 2**). Villavicencio et al., in their clinical study on 74 patients, underwent single and multiple-level TLIF administered with rhBMP-2 and combined with autograft [33]. They recorded that there was radiographic evidence of fusion in all 74 patients after 10 months [34]. Furthermore, they recorded few adverse events in the rhBMP-2 group noting two patients developed postoperative radiculitis. In another similar study by Rihn et al., 48 patients underwent single-level TLIF administered with rhBMP-2 [35]. They concluded radiographic fusion, improved clinical outcomes and satisfaction with surgical results in 95.8%, 83% and 84% of the patients, respectively. However, 27.1% of their patients had complications like transient postoperative radiculitis and symptomatic ectopic bone formation (**Table 2**).

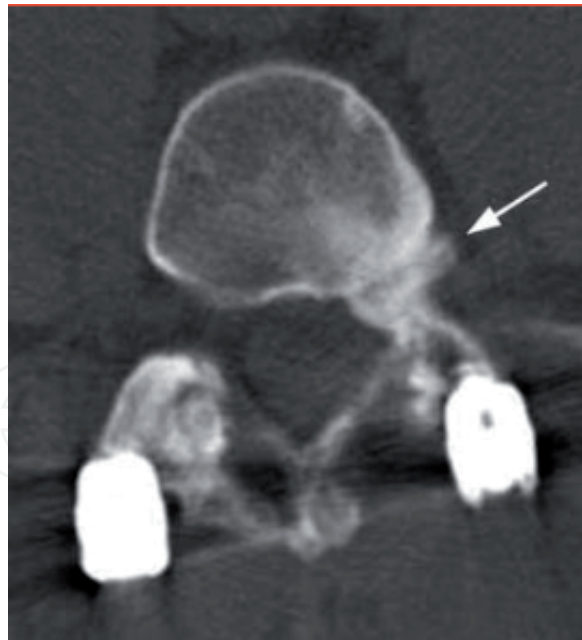


Figure 2.
 An axial CT scan of the lumbar spine demonstrating ectopic bone formation (arrow) in the left neural foramen impinging on the exiting nerve root in a patient who underwent a transforaminal lumbar interbody fusion with rhBMP-2. Culled from [32].

Type of fusion	Recommendations
Anterior Lumbar Interbody Fusion (ALIF)	There have been reports of insignificant difference between the administration of rhBMP-2 and ICBG. It is recommended that in the absence of an autograft procedure, rhBMP-2 administration can be opted for.
Posterolateral Fusion (PLF)	There have been reports of no significant difference between the administration of rhBMP-2 and ICBG. It is recommended that in the absence of an autograft procedure, rhBMP-2 administration can be opted for.
Posterior Interbody Lumbar Fusion (PLIF)	The use of rhBMP-2 has been linked with formation of ectopic bone resulting into neurological deficit, as such ICBG procedure is preferred.
Transforaminal Interbody Fusion (TLIF)	The use of rhBMP-2 has been linked with seroma formation and neurological deficits. Judicious administration of rhBMP-2 is advised

Culled from [36].

Table 2.
 Showing alternative therapies to the use of rhBMP-2.

3. Conclusion

The use of rhBMP-2 offers an alternative therapeutic option when iliac crest autograft is either unavailable or may result in severe side effects. There are various clinical studies investigating how the use of rhBMP-2 can be effective in achieving spinal fusion. However, though rhBMP-2 is effective at achieving spinal fusion patients need to be informed of the possible formation ectopic bone requiring additional surgery and seroma formation when performing transforaminal lumbar interbody fusion. There is a need for further study to minimize or lower the rates of complication linked with the application of rhBMP-2.

Conflict of interest

The authors deny any conflict of interest in any terms or by any means during the study.

Consent for publication

Informed consent was obtained from each participant.

Human and animal rights

No animals were used in this research. All human research procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013.

Availability of data and materials

All relevant data and materials are provided with in manuscript.

Contributors' statement page

Dr. Siavash Beiranvand: conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. Designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript. **Dr. Farshad hasanzadeh-kiabi:** Coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content.

Author details


Siavash Beiranvand¹ and Farshad Hasanzadeh-Kiabi^{2*}

¹ Department of Anesthesiology, Faculty of Medicine, Lorestan University of Medical Sciences, Khorramabad, Iran

² Department of Anesthesiology, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran

*Address all correspondence to: dr.f.hassanzadehkiabi@gmail.com

IntechOpen

© 2021 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

References

- [1] Resnick, D.K., *Evidence-based spine surgery*. Spine, 2007. **32**(11): p. S15-S19.
- [2] Carragee, E.J., E.L. Hurwitz, and B.K. Weiner, *A critical review of recombinant human bone morphogenetic protein-2 trials in spinal surgery: emerging safety concerns and lessons learned*. The spine journal, 2011. **11**(6): p. 471-491.
- [3] Mroz, T.E., et al., *Complications related to osteobiologics use in spine surgery: a systematic review*. Spine, 2010. **35**(9S): p. S86-S104.
- [4] Vahabi, S., et al., *Comparative study of 0.2% glyceryl trinitrate ointment for pain reduction after hemorrhoidectomy surgery*. The Surgery Journal, 2019. **5**(4): p. e192.
- [5] Vahabi, S., et al., *Comparison of the Effect of Different Dosages of Celecoxib on Reducing Pain after Cystocele and Rectocele Repair Surgery*. The Open Anesthesia Journal, 2020. **14**(1).
- [6] Vahabi, S., S. Beiranvand, and B. Radpay, *The Incidence of Vasovagal Response in Spinal Anesthesia during Surgery*.
- [7] Cheng, H., et al., *Osteogenic activity of the fourteen types of human bone morphogenetic proteins (BMPs)*. JBJS, 2003. **85**(8): p. 1544-1552.
- [8] Fu, R., et al., *Effectiveness and harms of recombinant human bone morphogenetic protein-2 in spine fusion: a systematic review and meta-analysis*. Annals of internal medicine, 2013. **158**(12): p. 890-902.
- [9] Burkus, J.K., H.S. Sandhu, and M.F. Gornet, *Influence of rhBMP-2 on the healing patterns associated with allograft interbody constructs in comparison with autograft*. Spine, 2006. **31**(7): p. 775-781.
- [10] Papakostidis, C., et al., *Efficacy of autologous iliac crest bone graft and bone morphogenetic proteins for posterolateral fusion of lumbar spine: a meta-analysis of the results*. Spine, 2008. **33**(19): p. E680-E692.
- [11] Lee, K.-B., et al., *The efficacy of rhBMP-2 versus autograft for posterolateral lumbar spine fusion in elderly patients*. European Spine Journal, 2010. **19**(6): p. 924-930.
- [12] Meisel, H.J., et al., *Posterior lumbar interbody fusion using rhBMP-2*. European Spine Journal, 2008. **17**(12): p. 1735-1744.
- [13] Simmonds, M.C., et al., *Safety and effectiveness of recombinant human bone morphogenetic protein-2 for spinal fusion: a meta-analysis of individual-participant data*. Annals of internal medicine, 2013. **158**(12): p. 877-889.
- [14] Dawson, E., et al., *Recombinant human bone morphogenetic protein-2 on an absorbable collagen sponge with an osteoconductive bulking agent in posterolateral arthrodesis with instrumentation: a prospective randomized trial*. JBJS, 2009. **91**(7): p. 1604-1613.
- [15] Moradkhani, M., et al., *Effects of Adjuvant Ketamine on Induction of Anesthesia for the Cesarean Section*. Current clinical pharmacology, 2020.
- [16] Burkus, J.K., et al., *Anterior lumbar interbody fusion using rhBMP-2 with tapered interbody cages*. Clinical Spine Surgery, 2002. **15**(5): p. 337-349.
- [17] Burkus, J.K., et al., *Use of rhBMP-2 in combination with structural cortical allografts: clinical and radiographic outcomes in anterior lumbar spinal surgery*. JBJS, 2005. **87**(6): p. 1205-1212.
- [18] Boakye, M., et al., *Anterior cervical discectomy and fusion involving a*

polyetheretherketone spacer and bone morphogenetic protein. Journal of Neurosurgery: Spine, 2005. **2**(5): p. 521-525.

[19] Dimar, J.R., et al., *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, 2006. **31**(22): p. 2534-2539.

[20] Dimar, J.R., et al., *Clinical and radiographic analysis of an optimized rhBMP-2 formulation as an autograft replacement in posterolateral lumbar spine arthrodesis.* JBJS, 2009. **91**(6): p. 1377-1386.

[21] Boden, S.D., et al., *Use of recombinant human bone morphogenetic protein-2 to achieve posterolateral lumbar spine fusion in humans: a prospective, randomized clinical pilot trial 2002 volvo award in clinical studies.* Spine, 2002. **27**(23): p. 2662-2673.

[22] Carragee, E.J., et al., *Retrograde ejaculation after anterior lumbar interbody fusion using rhBMP-2: a cohort controlled study.* The Spine Journal, 2011. **11**(6): p. 511-516.

[23] Glassman, S.D., et al., *RhBMP-2 versus iliac crest bone graft for lumbar spine fusion: a randomized, controlled trial in patients over sixty years of age.* Spine, 2008. **33**(26): p. 2843-2849.

[24] Hamilton, D.K., et al., *Use of recombinant human bone morphogenetic protein-2 as an adjunct for instrumented posterior arthrodesis in the occipital cervical region: An analysis of safety, efficacy, and dosing.* Journal of Craniovertebral Junction and Spine, 2010. **1**(2): p. 107.

[25] Haid Jr, R.W., et al., *Posterior lumbar interbody fusion using recombinant human bone morphogenetic protein type 2*

with cylindrical interbody cages. The Spine Journal, 2004. **4**(5): p. 527-538.

[26] Robin, B.N., et al., *Cytokine-mediated inflammatory reaction following posterior cervical decompression and fusion associated with recombinant human bone morphogenetic protein-2: a case study.* Spine, 2010. **35**(23): p. E1350-E1354.

[27] Even, J., M. Eskander, and J. Kang, *Bone morphogenetic protein in spine surgery: current and future uses.* JAAOS-Journal of the American Academy of Orthopaedic Surgeons, 2012. **20**(9): p. 547-552.

[28] Baskin, D.S., et al., *A prospective, randomized, controlled cervical fusion study using recombinant human bone morphogenetic protein-2 with the CORNERSTONE-SR™ allograft ring and the ATLANTIS™ anterior cervical plate.* Spine, 2003. **28**(12): p. 1219-1224.

[29] Helgeson, M.D., et al., *Adjacent vertebral body osteolysis with bone morphogenetic protein use in transforaminal lumbar interbody fusion.* The Spine Journal, 2011. **11**(6): p. 507-510.

[30] Cole, T., et al., *Usage of Recombinant Human Bone Morphogenetic Protein in Cervical Spine Procedures: Analysis of the MarketScan Longitudinal Database.* JBJS, 2014. **96**(17).

[31] Kukreja, S., et al., *Complications of Anterior Cervical Fusion using a Low-dose Recombinant Human Bone Morphogenetic Protein-2.* Korean Journal of Spine, 2015. **12**(2): p. 68-74.

[32] Rihn, J.A., et al., *The use of bone morphogenetic protein in lumbar spine surgery.* JBJS, 2008. **90**(9): p. 2014-2025.

[33] Humphreys, S.C., et al., *Comparison of posterior and transforaminal approaches to lumbar interbody fusion.* Spine, 2001. **26**(5): p. 567-571.

[34] Villavicencio, A.T., et al., *Safety of transforaminal lumbar interbody fusion and intervertebral recombinant human bone morphogenetic protein—2*. *Journal of Neurosurgery: Spine*, 2005. 3(6): p. 436-443.

[35] Rihn, J.A., et al., *The use of RhBMP-2 in single-level transforaminal lumbar interbody fusion: a clinical and radiographic analysis*. *European Spine Journal*, 2009. 18(11): p. 1629.

[36] Hustedt, J.W. and D.J. Blizzard, *The controversy surrounding bone morphogenetic proteins in the spine: a review of current research*. *The Yale journal of biology and medicine*, 2014. 87(4): p. 549.

IntechOpen