MINIREVIEWS

524 Radiation exposure and reduction in the operating room: Perspectives and future directions in spine surgery
Narain AS, Hiji FY, Yom KH, Kudaravalli KT, Haws BE, Singh K

531 Use of recombinant human bone morphogenetic protein-2 in spine surgery
Lykissas M, Gkiatas I

ORIGINAL ARTICLE

Basic Study

536 Possibilities for arthroscopic treatment of the ageing sternoclavicular joint
Rathcke M, Tranum-Jensen J, Krosgaard MR

Retrospective Study

545 Epidemiology of open fractures in sport: One centre's 15-year retrospective study
Wood AM, Robertson GAJ, MacLeod K, Porter A, Court-Brown CM

553 Acetabular revisions using porous tantalum components: A retrospective study with 5-10 years follow-up
Evola FR, Costarella L, Evola G, Barchitta M, Agodi A, Sessa G

561 Non-ossifying fibromas: Case series, including in uncommon upper extremity sites
Sakamoto A, Arai R, Okamoto T, Matsuda S

Observational Study

567 Distal radius volar rim plate: Technical and radiographic considerations
Spiteri M, Roberts D, Ng W, Matthews J, Power D

SYSTEMATIC REVIEWS

574 Return to sport following tibial plateau fractures: A systematic review
Robertson GAJ, Wong SJ, Wood AM

588 Systematic review on the use of autologous matrix-induced chondrogenesis for the repair of articular cartilage defects in patients
Shaikh N, Seah MKT, Khan WS

CASE REPORT

602 Painless swollen calf muscles of a 75-year-old patient caused by bilateral venous malformations
Piekaar RSM, Zwitser EW, Hedeman Joosten PPA, Jansen JA
ABOUT COVER

Editorial Board Member of World Journal of Orthopedics, Michalis Zenios, BM BCH, MSc, Senior Lecturer, Paediatric Orthopaedics, University of Nicosia, Limassol 3025, Cyprus

AIM AND SCOPE

World Journal of Orthopedics (World J Orthop, WJO) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJO covers topics concerning arthroscopy, evidence-based medicine, epidemiology, nursing, sports medicine, therapy of bone and spinal diseases, bone trauma, osteoarthropathy, bone tumors and osteoporosis, minimally invasive therapy, diagnostic imaging. Priority publication will be given to articles concerning diagnosis and treatment of orthopedic diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

We encourage authors to submit their manuscripts to WJO. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great basic and clinical significance.

INDEXING/ABSTRACTING

World Journal of Orthopedics is now indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central and Scopus.

FLYLEAF

EDITORIAL BOARD

EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Orthopedics

ISSN
ISSN 2218-5836 (online)

LAUNCH DATE
November 18, 2010

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Quanjun (Trey) Cui, MD, Professor, Department of Orthopaedic Surgery, School of Medicine, University of Virginia, Charlottesville, VA 22908, United States
Bao-Gan Peng, MD, PhD, Professor, Department of Spinal Surgery, General Hospital of Armed Police Force, Beijing 100039, China

EDITORIAL BOARD MEMBERS
All editorial board members resources online at http://

EDITORIAL OFFICE
Xiu-Xia Song, Director
World Journal of Orthopedics
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLICATION DATE
July 18, 2017

COPYRIGHT
© 2017 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT
All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS
http://www.wjgnet.com/bpg/gerinfo/204

ONLINE SUBMISSION
http://www.f6publishing.com
Use of recombinant human bone morphogenetic protein-2 in spine surgery

Marios Lykissas, Ioannis Gkiatas

Marios Lykissas, Department of Spine Surgery, Metropolitan Hospital, 18547 Athens, Greece

Ioannis Gkiatas, Orthopaedic Department, University Hospital of Ioannina, 45500 Ioannina, Greece

Author contributions: Lykissas M performed the majority of the writing, collecting all the bibliography that was used; Gkiatas I performed writing as well as input in writing the paper and designed the outline.

Conflict-of-interest statement: There is no conflict of interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Invited manuscript

INTRODUCTION

During the last 10 years, the use of bone morphogenetic proteins (BMPs) has become very popular in orthopaedic surgery. BMPs are osteoinductive factors which are capable of inhibiting chondrocyte differentiation independently and they are recognized...
as important regulators of growth, differentiation, and morphogenesis during embryology\cite{1,2}. They are members of the superfamily of transforming growth factor-β (TGF-β) and play an important role in the development and regeneration of various tissues including bone, cartilage, and tendons\cite{3,4}. Urist\cite{5} in 1965 described first these factors with the term “bone autoinduction principle”. During the last two decades BMPs gradually gained popularity in bone healing and especially in spinal fusion enhancement. BMPs are released by platelets and osteogenitor cells and their main role is to stimulate cellular proliferation, angiogenesis, osteoblast differentiation, and direct bone matrix formation\cite{6}. More than 20 different types of BMPs have been identified since Urist\cite{5} described their properties and all of them have significant osteogenic properties. From all types of BMPs, BMP-2 has been found to be the most osteoinductive and its efficacy to generate an osseous fusion mass has been well established in several preclinical spine models\cite{7}.

In spine surgery, autogenous bone grafting is often used to stimulate fusion. Due to the insufficiency of traditional techniques of bone grafting in long spinal fusions or spinal fusions in adverse metabolic conditions, bone graft substitutes, such as recombinant human bone morphogenetic protein-2 (rhBMP-2), have been introduced in the clinical practice\cite{8}.

**INDICATIONS**

RhBMP-2 in spinal surgery was first studied clinically in anterior lumbar interbody fusion (ALIF) and was compared with iliac crest bone graft\cite{9}. The fusion rate of rhBMP-2 group was 94.5% whereas the fusion rate in the group where iliac crest bone graft was used was 88.7%. More studies supporting the effectiveness of rhBMP-2 in spine fusion followed, which resulted in the approval of rhBMP-2 by the United States Food and Drug Administration (FDA) for single-level ALIF within specific threaded cages in skeletally mature patients. In a meta-analysis in 2014 the authors report that rhBMP-2 in lumbar spine fusion can increase the fusion rate\cite{10}, while reduce the reoperation rate and operating time. It does not increase the complication rate, the amount of blood loss, and the hospital stay.

**OFF-LABEL USE**

Although rhBMP-2 has been approved by the FDA for a single narrow method of spinal fusion, over the last 10 years, numerous articles on BMP-2 have documented its use for a far wider range of spinal applications. Since its approval, rhBMP-2 has gained popularity as an effective bone-graft substitute as it obviates the need for autologous bone graft harvesting and eliminates associated complications and donor site morbidity\cite{11,12}. Many surgeons, began the off-label use of the product in all spinal regions\cite{13-17}, after which new complications associated with the use of rhBMP-2 emerged, including among others severe soft-tissue swelling following anterior cervical disectomy and fusion, heterotopic bone formation, and vertebral body osteolysis in the thoracic and lumbar spine\cite{18-20}. Ong et a\cite{21} reported that the 85% of all surgeries in which rhBMP-2 was used were for “off-label” applications. These off-label indications included posterior lumbar interbody fusion, transforaminal lumbar interbody fusion, posterior lumbar fusion, anterior cervical disectomy and fusion (ACDF), and more recently, lateral lumbar interbody fusion\cite{22}.

Rihn et a\cite{23}, in 2009 published their study about the use of rhBMP-2 in single-level transforaminal lumbar interbody fusion. They showed high rate of fusion and improvement of symptoms. Nevertheless, its use was associated with complications that raise concern including a high rate of postoperative radiculitis. One year later, Oliveira et a\cite{24} presented their results using rhBMP-2 in standalone lateral lumbar interbody fusion. Following a 24-mo follow-up, the authors concluded that single level disc degenerative disease can be successfully treated with standalone lateral lumbar interbody fusion using rhBMP-2 providing except of pain relief significant cost reduction. Complications included cage subsidence, heterotopic bone formation, persistent stenosis, and adjacent level degeneration.

According to a current retrospective cohort study\cite{25}, during the last years a decrease in the off-label use of BMP-2 in spinal fusions and particularly in cervical spine fusions was noticed. The authors noted that although there was a tendency of decreased odds from 2009 to 2012, a higher resource utilization and odds for complications remained in patients in whom BMP-2 was used.

**ADVANTAGES**

One of the main advantages of the use of rhBMP-2 in spinal fusion is the elimination of adverse events that have been associated with iliac crest bone graft harvesting despite the improvement of bone-harvesting techniques. These complications include pain, hematoma formation, sacral fracture, and infection\cite{8}.

In spine surgery, the rhBMP-2 fusion rate is usually compared with the iliac crest bone graft fusion rate. In the first prospective randomized controlled trial in 2000 Boden et a\cite{26} supported that arthrodesis occurred more reliably in patients treated with rhBMP-2 filled cages than in controls treated with autogenous bone graft. In general, the fusion rate with the use of rhBMP-2 ranges from 94.5% to 100%, whereas with the use of iliac crest bone graft the fusion rate ranges from 88.7% to 100%. The main complaint in the group of patients treated with iliac crest bone graft was the pain at the donor site. It was also suggested that there is more blood loss with the use of iliac crest bone graft, as well as more operating time. Moreover, in some specific cases, such as in women with osteoporosis, it was speculated that the osteoinductive ability of
rhBMP-2 was more efficient when compared to iliac crest bone graft.\(^{10,17}\)

In 2009, Dawson et al.\(^{27}\) combined rhBMP-2 on an absorbable collagen sponge with a ceramic-granule bulking agent in patients undergoing single level posterolateral lumbar fusion. The group of patients who received this combination was compared with a control group of patients who were treated with autogenous iliac crest bone graft. The authors concluded that the combination of the absorbable collagen sponge soaked with rhBMP-2 and ceramic granules provided not only improved clinical results, but also higher radiographic fusion rates when compared to the control group of patients.

The cost should also be taken seriously into consideration. In 2008, Glassman et al.\(^{28}\) compared the perioperative costs for patients treated with rhBMP-2 or iliac crest bone graft. Surprisingly, the mean cost for the 3 mo perioperative period was $33860 in the rhBMP-2 group and $37227 in the iliac crest bone graft group. A decreased physician fee was also noticed in the rhBMP-2 group ($5082 and $5316, respectively).

Taking all these into consideration, someone can assume that there is no difference between the rhBMP-2 and the iliac crest bone graft in terms of obtaining a solid spinal fusion. Nevertheless, it seems that the rhBMP-2 can achieve an “easier” and faster fusion with no donor site morbidity.

COMPLICATIONS

The first studies presenting the results of rhBMP-2 in spine surgery, reported no adverse events directly related to BMP-2 usage.\(^{27}\) It has to be mentioned though that all these studies were industry supported.

More recently, authors started to present disadvantages for the use of BMPs especially in its off-label indications. Epstein\(^{29}\) in 2013 presented several complications associated with the off-label use of rhBMP-2 including heterotopic ossification, postoperative seroma/hematoma formation, increased infection rate, arachnoiditis, dysphagia following ACDF, retrograde ejaculation after ALIF, increased neurologic deficits, and cancer. Neurologic deficits following lateral lumbar interbody fusion with the supplementary use of rhBMP-2 were also recorded in another study where 919 treated levels were reviewed.\(^{30}\) Immediately after surgery, sensory and motor deficits were identified in 38% of the patients treated with rhBMP-2 and in 23.9% of the patients fused with cancellous allograft or iliac crest bone autograft. At the last follow-up, the percentage of sensory and motor deficits was decreased to 24.1% and 17.3%, respectively. A potential deleterious effect of rhBMP-2 on the lumbosacral plexus was suggested.\(^{32}\) Mitchell et al.\(^{31}\) in an experimental study in 2016, modeled the clinical use of BMP-2 for posterior lumbar fusion. They concluded that the implantation of rhBMP-2 on the lumbar spine may trigger neuroinflammatory responses in the dorsal root ganglia.

Certain cancer cell lines have been shown to have BMPs receptors and local administration of these growth factors has led to stimulation of cell growth of cancer lines in vitro.\(^{32}\) In a comparative study of 463 patients, Carragee et al.\(^{33}\) concluded that a high dose of 40 mg of rhBMP-2 in lumbar spinal arthrodesis is associated with an increased risk of new cancer. On the other hand, in a current study of Beachler et al.\(^{34}\) in a large population of elderly United States adults who underwent lumbar arthrodesis, rhBMP-2 was not associated with cancer risk or increased mortality.

The mechanism of rhBMP-2 action that may have led to complications described above has been investigated. Hsu et al.\(^{35}\) in an experimental study of posterolateral intertransverse lumbar spinal fusion demonstrated that the in vivo host response to rhBMP-2 may be associated with circulating proinflammatory and osteoclastic cytokines, such as tumor necrosis factor-α, macrophage inflammatory protein 1-alpha, and interleukin-1β. Additionally, angiogenesis was found to be stimulated through the induction of vascular endothelial growth factors secretion.\(^{36}\)

FURTHER RESEARCH

Increased use of rhBMP-2 in spine surgery has raised several controversial conflicts among investigators. During the last years a new promising project has been established, which aims to cope with the issue of unpublished or selectively published clinical evidence.\(^{37,38}\) The Yale University Open Data Access (YODA) project aims to serve patients and produce benefits for the companies that fund the vast majority of research in medical products. Lately two systematic reviews on rhBMP-2, which are based on patient-level data were shared through YODA. The agreement between the YODA team and Medtronic (rhBMP-2 company) included two parts. Firstly, two independent research groups were selected through a competitive process to evaluate the quality of the studies and synthesize evidence regarding the effectiveness and safety of rhBMP-2. Secondly, the YODA team made the data available to others for potential scientific questions. In this way all the clinical trial data for this product should have been made available in order to be used by other investigators for further analysis.

These two studies concluded in the same results after analyzing their data. Despite the higher fusion rate that was observed with the use of rhBMP-2, clinical results showed no significant differences between the use of iliac crest bone graft and rhBMP-2. The authors of both studies agreed that a clear safety risk is posed when rhBMP-2 is used in the anterior aspect of the cervical spine.\(^{39}\) As far as it concerns the carcinogenicity, one study showed significantly higher rate of cancer in patients who were treated with rhBMP-2, while the other presented statistically insignificant higher incidence of cancer in the rhBMP-2 group.
group. Both teams of investigators reached to the same conclusion: Despite the higher rate of cancer appearance, the overall absolute risk of carcinogenesis due to the use of rhBMP-2 for spinal fusion is generally low.\(^\text{40}\)

However, Carragee et al\(^\text{41}\) supported that despite access to Medtronic trial data, the YODA project will not be able to resolve many, if not most, fundamental safety and efficacy issues on various current uses because there are inadequate trials available.

**CONCLUSION**

RhBMP-2, due to its ability to stimulate bone formation, may offer an effective alternative method of fusion in spine surgery. The clinical outcomes and fusion rates are comparable with those of iliac crest bone graft. In some challenging situations though, rhBMP-2 may have even better results. Its cost is higher compared with the cost of other bone graft substitutes, but concerning the total cost for a patient who needs multiple surgeries to achieve a solid spinal fusion, it seems that rhBMP-2 may be proved cost effective. RhBMP-2 is very often used in spinal applications that have not been studied and/or approved by the FDA, where their results may be unpredictable. Long-term outcomes from randomized control trials are warranted to further clarify the appropriate dose, carrier, and indications of rhBMP-2.

**REFERENCES**

1. Gkiztas I, Lykissas M, Kostas-Agnantis I, Koromilias A, Batis-tatou A, Beris A. Factors affecting bone growth. *Am J Orthop (Belle Mead NJ)* 2015; 44: 61-67 [PMID: 25658073]
2. Reddi AH. Bone morphogenic proteins: from basic science to clinical applications. *J Bone Joint Surg Am* 2001; 83-A Suppl 1: S1-S6 [PMID: 11263660 DOI: 10.2106/00004623-200100001-000 01]
3. Yamada M, Akeda K, Asamura K, Thinarj EJ, An HS, Uchida A, Masuda K. Effect of osteogenic protein-1 on the matrix metabolism of bovine tendon cells. *J Orthop Res* 2008; 26: 42-48 [PMID: 17676621 DOI: 10.1002/jor.20474]
4. Helm GA, Alden TD, Scheep JH, Kallmes D. Bone morphogenic proteins and bone morphogenetic protein gene therapy in neurological surgery: a review. *Neurosurgery 2000; 46: 1213-1222 [PMID: 10807254 DOI: 10.1093/neuros/46.5.1213-1222]
5. Urst MR. Bone: formation by autoinduction. 1965. *Clin Orthop Relat Res 2002; (395): 4-10 [PMID: 11937861 DOI: 10.1097/00003086-200200000-00002]
6. Valdes MA, Thakur NA, Namdari S, Chimbor DM, Palumbo M. Recombinant bone morphogenic protein-2 in orthopaedic surgery: a review. *Arch Orthop Trauma Surg 2009; 129: 1651-1657 [PMID: 19280204 DOI: 10.1007/s00204-009-0585-8]
7. Even J, Eskander M, Kang J. Bone morphogenetic protein in spine surgery: current and future uses. *J Am Acad Orthop Surg 2012; 20: 547-552 [PMID: 22941797 DOI: 10.5435/JAAOS-20-04-59]
8. Hsu WW. Recombinant Human Bone Morphogenetic Protein-2 in Spine Surgery. *JBJS Rev 2014; 2: pii: 01847447-201402060-00004 [PMID: 27500718 DOI: 10.2106/JBJS.RVW.M.00107]
9. Carragee EJ, Hurwitz EL, Weiner BK. A critical review of recombinant human bone morphogenetic protein-2 trials in spinal surgery: emerging safety concerns and lessons learned. *Spine 2011; 11: 471-491 [PMID: 21729796 DOI: 10.1016/j.spinee.2011.04.023]
10. Burkus JK, Gornet MF, Dickman CA, Zdeblick TA. Anterior lumbar interbody fusion using rhBMP-2 with tapered interbody cages. *J Spinal Disord Tech 2002; 15: 337-349 [PMID: 12394656 DOI: 10.1097/00002720-200209000-00002]
11. Zhang H, Wang F, Ding L, Zhang Z, Sun D, Feng X, An J, Zhu Y. A meta analysis of lumbar spinal fusion surgery using bone morphogenetic proteins and autologous iliac crest bone graft. *PLoS One* 2014; 9: e97049 [PMID: 24886911 DOI: 10.1371/journal.pone.0097049]
12. Mummaneni PV, Pan J, Haid RW, Rodts GE. 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. Invited submission from the Joint Section Meeting on Disorders of the Spine and Peripheral Nerves, March 2004. *J Neurosurg Spine* 2004; 1: 19-23 [PMID: 15291015 DOI: 10.3171/spine.2004.1.00109]
13. Villavicencio AT, Bumenskiene S, Nelsen EL, Bulsara KR, Favors M, Thramann J. Safety of transforaminal lumbar interbody fusion and intervertebral recombinant human bone morphogenetic protein-2. *J Neurosurg Spine 2005; 3: 436-443 [PMID: 16381205 DOI: 10.3171/spine.2005.3.6.0436]
14. Glassman SD, Carreon L, Durasovic M, Campbell MJ, Puno RM, Johnson JR, Dimar JR. Posterolateral lumbar spine fusion with INFUSE bone graft. *Spine J 2007; 7: 44-49 [PMID: 17197332 DOI: 10.1016/j.spinee.2006.06.381]
15. Glassman SD, Dimar JR, Burkus K, Hardackle JW, Pryor PW, Boden SD, Carreon LY. The efficacy of rhBMP-2 for posterolateral lumbar fusion in smokers. *Spine (Phila Pa 1976)* 2007; 32: 1693-1698 [PMID: 17621221 DOI: 10.1097/BRS.0b013e3180743660]
16. Boden SD, Kang J, Sandhu H, Heller JG. 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 (Phila Pa 1976)* 2002; 27: 2662-2673 [PMID: 12461392 DOI: 10.1097/00003696-200204110-00005]
17. Baskin DS, Ryan P, Sonntag V, Westmark R, Widmayer MA. 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 (Phila Pa 1976)* 2003; 28: 1219-124; discussion 1225 [PMID: 12811263 DOI: 10.1097/01.BRS.0000065486.22141.CA]
18. Shields LB, Raque GH, Glassman SD, Campbell M, Vitaz T, Harpring J, Shields CB. Adverse effects associated with high-dose recombinant human bone morphogenetic protein-2 use in anterior cervical spine fusion. *Spine (Phila Pa 1976)* 2006; 31: 542-547 [PMID: 16508549 DOI: 10.1097/01.BRS.0000201242.2750972]
19. Smucker JD, Rhee JM, Singh K, Yoon ST, Heller JG. Increased swelling complications associated with off-label usage of rhBMP-2 in the anterior cervical spine. *Spine (Phila Pa 1976)* 2006; 31: 2813-2819 [PMID: 17108835 DOI: 10.1097/01.BRS.0000245863.52371.e2]
20. Dmitriev AE, Castner S, Lehan RA, Ling GS, Symes AJ. Alterations in recovery from spinal cord injury in rats treated with recombinant human bone morphogenetic protein-2 for postlateral arthrodesis. *J Bone Joint Surg Am 2011; 93: 1488-1499 [PMID: 22204004 DOI: 10.2106/JBJS.L.00904]
21. Ong KL, Villarraga ML, Lau E, Carreon LY, Kurtz SM, Glassman SD. Off-label use of bone morphogenetic proteins in the United States using administrative data. *Spine (Phila Pa 1976)* 2011; 36: 1979-1980 [PMID: 21164768 DOI: 10.1097/BRS.0b013e31820613cc]
22. Lykissas MG, Aichmair A, Sama AA, Hughes AP, Lebl DR, Cammisa FP, Giroiri FP. Nerve injury and recovery after lateral lumbar interbody fusion with and without bone morphogenetic protein-2: a cohort-controlled study. *Spine J* 2014; 4: 217-224 [PMID: 242269858 DOI: 10.1016/j.spinee.2013.06.109]
23. Rihn JA, Makda J, Hong J, Patel R, Hilibrand AS, Anderson DG, Vaccaro AR, Albert TJ. The use of RhBMP-2 in single-level transforaminal lumbar interbody fusion: a clinical and radiographic analysis. *Eur Spine J* 2009; 18: 1629-1636 [PMID: 19475434 DOI: 10.1007/s00586-009-1046-1]
Oliveira L, Marchi L, Coutinho E, Abdala N, Pimenta L. The use of rh-bmp2 in standalone extreme lateral interbody fusion (Xliii®): clinical and radiological results after 24 months follow-up. World Spinal Column J 2010; 1: 19-25

Poeran J, Opperman M, Rasul R, Mazumdar M, Girard FP, Hughes AP, Memtsoudis SG, Vogioukas V. Change in Off-Label Use of Bone Morphogenetic Protein in Spine Surgery and Associations with Adverse Outcome. Global Spine J 2016; 6: 650-659 [PMID: 27781184 DOI: 10.1055/s-0036-1571284]

Boden SD, Zdeblick TA, Sandhu HS, Heim SE. The use of rhBMP-2 in interbody fusion cages. Definitive evidence of osteoinduction in humans: a preliminary report. Spine (Phila Pa 1976) 2000; 25: 376-381 [PMID: 10703113 DOI: 10.1097/00007632-200002010-00020]

Dawson E, Bae HW, Burkus JK, Stambough JL, Glassman SD. 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. J Bone Joint Surg Am 2009; 91: 1604-1613 [PMID: 19571082 DOI: 10.2106/JBJS.G.01157]

Glassman SD, Carreon LY, Campbell MJ, Johnson JR, Puno RM, Djurasovic M, Dhir MA. The perioperative cost of Infuse bone graft in posterolateral lumbar spine fusion. Spine J 2008; 8: 443-448 [PMID: 17526436 DOI: 10.1016/j.spinee.2007.03.004]

Epstein NE. Complications due to the use of BMP/INFUSE in spine surgery: The evidence continues to mount. Surg Neurol Int 2013; 4: S343-S352 [PMID: 23878769 DOI: 10.4103/2152-7806.114813]

Lykissas MG, Achimair A, Hughes AP, Sarna AA, Lebl DR, Tafer F, Du JY, Cammisa FP, Girard FP. Nerve injury after lateral lumbar interbody fusion: a review of 919 treated levels with identification of risk factors. Spine J 2014; 14: 749-758 [PMID: 24012428 DOI: 10.1016/j.spinee.2013.06.066]

Mitchell K, Shah JP, Dalgaard CL, Tsytisikova LV, Tipton AC, Dmitriev AE, Symes AJ. Bone morphogenetic protein-2-mediated pain and inflammation in a rat model of posterolateral arthrodesis. BMC Neurosci 2016; 17: 80 [PMID: 27905881 DOI: 10.1186/s12868-016-0314-3]

Feeley BT, Garnadt SC, Hsu WK, Liu N, Knene L, Robins P, Huard J, Lieberman J. Influence of BMPs on the formation of osteoblastic lesions in metastatic prostate cancer. J Bone Miner Res 2005; 20: 2189-2199 [PMID: 16294272 DOI: 10.1359/jbmr.050802]

Carragee EJ, Chu G, Rohatgi R, Hurwitz EL, Weiner BK, Yoon ST, Corner G, Kopjar B. Cancer risk after use of recombinant bone morphogenetic protein-2 for spinal arthrodesis. J Bone Joint Surg Am 2013; 95: 1537-1545 [PMID: 24005193 DOI: 10.2106/JBJS.L.01483]

Beachler DC, Yanik EL, Martin BL, Pfeiffer RM, Mirza SK, Deyo RA, Engels EA. Bone Morphogenetic Protein Use and Cancer Risk Among Patients Undergoing Lumbar Arthrodesis: A Case-Cohort Study Using the SEER-Medicare Database. J Bone Joint Surg Am 2016; 98: 1064-1072 [PMID: 27385679 DOI: 10.2106/JBJS.15.01106]

Hsu WK, Polavarapu M, Riaz R, Larson AC, Diegmueller JJ, Ghodasra JH, Hsu EL. Characterizing the host response to rhBMP-2 in a rat spinal arthrodesis model. Spine (Phila Pa 1976) 2017; 42: E691-E698 [PMID: 23429681 DOI: 10.1097/BRS.0000000000003977]

Deckers MM, van Bezoijen RL, van der Horst G, Hoogendam J, van Der Bent C, Pappapolous SE, Löwik CW. Bone morphogenetic proteins stimulate angiogenesis through osteoblast-derived vascular endothelial growth factor A. Endocrinology 2002; 143: 1545-1553 [PMID: 11897714 DOI: 10.1210/endo.143.4.8719]

Krumholz HM. Open science and data sharing in clinical research: basing informed decisions on the totality of the evidence. Circ Cardiovasc Qual Outcomes 2012; 5: 141-142 [PMID: 22438459 DOI: 10.1161/CIRCOUTCOMES.112.965848]

Ross JS, Lehman R, Gross CP. The importance of clinical trial data sharing: toward more open science. Circ Cardiovasc Qual Outcomes 2012; 5: 238-240 [PMID: 22438465 DOI: 10.1161/CIRCOUTCOMES.112.965798]

Krumholz HM, Ross JS, Gross CP, Emanuel EJ, Hodshon B, Ritchie JD, Low JB, Lehman R. A historic moment for open science: the Yale University Open Data Access project and meta-analysis. Ann Intern Med 2013; 158: 910-911 [PMID: 23779908 DOI: 10.7326/0003-4819-158-12-201306180-00009]

Fu R, Selph S, McDonagh M, Peterson K, Tiwari A, Chou R, Helfand M. Effectiveness and harms of recombinant human bone morphogenetic protein-2 in spine fusion: a systematic review and meta-analysis. Ann Intern Med 2013; 158: 890-902 [PMID: 23779906 DOI: 10.7326/0003-4819-158-12-201306180-00006]

Carragee EJ, Baker RM, Benzel EC, Bigos SJ, Cheng I, Corbin TP, Deyo RA, Hurwitz EL, Jarvik JG, Kang JD, Lurie JD, Mroz TE, Oner FC, Peul WC, Rainville J, Ratliff JK, Rihn JA, Rothman DJ, Schoene ML, Spengler DM, Weiner BK. A biological without guidelines: the YODA project and the future of bone morphogenetic protein-2 research. Spine J 2012; 12: 877-880 [PMID: 23199819 DOI: 10.1016/j.spinee.2012.11.002]

P- Reviewer: Alimehmeti RH, Kahlveci R, Lakhdar F
S- Editor: Kong JX L- Editor: A E- Editor: Wu HL
