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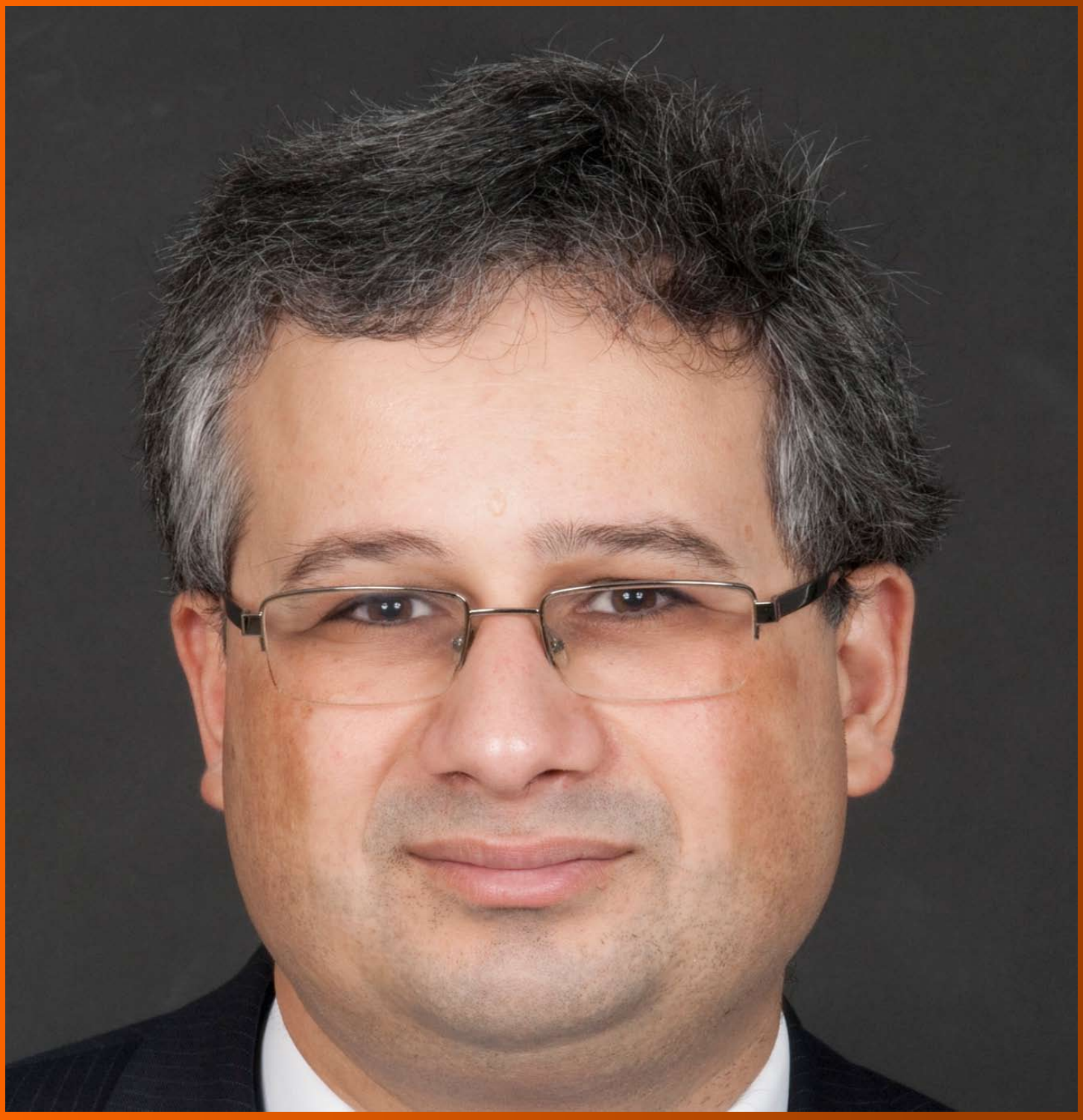

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MINIREVIEWS

Use of recombinant human bone morphogenetic protein-2 in spine surgery

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Abstract

Bone morphogenetic proteins are osteoinductive factors which have gained popularity in orthopaedic surgery and especially in spine surgery. The use of recombinant human bone morphogenetic protein-2 has been officially approved by the United States Food and Drug Administration only for single level anterior lumbar interbody fusion, nevertheless it is widely used by many surgeons with off-label indications. Despite advantages in bone formation, its use still remains a controversial issue and several complications have been described by authors who oppose their wide use.

Key words: Recombinant human bone morphogenetic protein-2; Spine; Fusion; Bone graft; Yale University Open Data project

Core tip: The use of recombinant human bone morphogenetic protein-2 is widely used in spine surgery not only in approved indications but also in off-label indications. Despite its ability to promote fusion there are many reported disadvantages. That's why the Yale University Open Data project aims to serve both the patients but also the companies which fund the vast majority of research in medical products.

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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[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[3,4]. Urist[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[6]. More than 20 different types of BMPs have been identified since Urist[7] 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[8].

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 grafts substitutes, such as recombinant human bone morphogenetic protein-2 (rhBMP-2), have been introduced in the clinical practice[9].

INDICATIONS

RhBMP-2 in spinal surgery was first studied clinically in anterior lumbar interbody fusion (ALIF) and was compared with iliac crest bone graft[10]. 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[11], while reduce the reoperation rate and operating time. Additionally, 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[12,13]. Many surgeons, began the off-label use of the product in all spinal regions[14-17], after which new complications associated with the use of rhBMP-2 emerged, including among others severe soft-tissue swelling following anterior cervical discectomy and fusion, heterotopic bone formation, and vertebral body osteolysis in the thoracic and lumbar spine[18-20]. Ong *et al*[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 infusion, transforaminal lumbar interbody infusion, posterior lumbar fusion, anterior cervical discectomy and fusion (ACDF), and more recently, lateral lumbar interbody fusion[22].

Rihn *et al*[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 al*[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[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[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 al*[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[7]. 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[22]. 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 interleukin1-β. 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[39].

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[8]. 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. 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[40].

However, Carragee *et al*[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.

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