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Review Article

Contemporary concepts in spine care—the use of bone morphogenetic protein in spine fusion

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Abstract

BACKGROUND CONTEXT: Because pseudarthrosis remains a clinically significant complication after spinal arthrodesis, the role of recombinant bone morphogenetic proteins (BMPs) is continually evaluated in spine surgery.

PURPOSE: This article reviews the important literature in clinical research involving the use of BMPs in the augmentation of spinal fusion.

STUDY DESIGN/SETTING: Review article.

METHODS: A literature search was performed via MEDLINE through PubMed with the dates January 1960 to July 2007 using the keywords "bone morphogenetic protein, BMP, spinal arthrodesis, and/or bone healing." Pertinent preclinical and clinical publications were chosen based on relevance and quality for inclusion in this study.

RESULTS: Publications focused on the historical context and potential clinical applications using BMP were selected to delineate the risks, benefits, and current indications for the augmentation of spinal arthrodesis.

CONCLUSIONS: Although multiple commercially available recombinant BMPs have demonstrated clinical success in interbody and posterolateral fusions, the associated costs preclude its routine use in spinal arthrodesis. The spine surgeon must assess each patient individually based on age, bone quality, diagnosis, comorbidities, and risks of nonunion to determine the cost effectiveness of the use of BMP to augment spinal fusion.

Keywords: BMP; Bone morphogenetic protein; Spine fusion; Spine arthrodesis

Introduction

Despite advances in the technologies and instrumentation of spine surgery, pseudarthrosis still occurs in 10% to 15% of all patients [1–4]. Furthermore, approximately 500,000 autogenous bone grafting procedures are performed annually, of which nearly 50% are used for spinal fusion [5]. Because the procurement of autologous bone graft is fraught with significant morbidity and postoperative pain [6–13], the study of bone graft substitutes in spine surgery has expanded to include recombinant growth factors, cell-based therapies, and the use of gene transfer strategies to enhance bone formation and improve fusion rates.

The significant rates of pseudarthroses and reports of operative morbidity from the harvest of autograft can limit the success rates of primary spine fusion in certain patients. In addition, the stringent biological environment created from revision procedures presents a more complicated array of problems and unpredictable outcomes after further surgical intervention. Dense fibrous tissue, intervertebral disc, and muscle cells commonly encountered during revision procedures have been found to inhibit host bone repair [14]. Because the success rates of fusion in this poor osteoinductive environment are relatively low, recent studies have been directed toward the development of new biologic substitutes to improve outcomes in both primary and revision procedures. For this reason, interest in bone graft substitutes and enhancers for the supplementation of spine surgery is on the rise.

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Recombinant growth factors such as the bone morphogenetic proteins (BMPs) have been an important recent development in the armamentarium to enhance spinal arthrodesis rates. The significant osteoinductive potential of recombinant growth factors coupled with the avoidance of complications associated with bone graft harvest have encouraged the research into optimizing the clinical use of these powerful proteins. Although BMPs have a number of potential applications in spine surgery, this article will concentrate on the recent advances in the induction of spinal fusion.

Historical context and background

The discovery of BMPs by Urist in 1965 [15] has led to a diverse area of research dedicated to the identification and characterization of osteoinductive growth factors. Members of the Transforming Growth Factor (TGF)-ß superfamily, BMPs have been proposed for a number of applications in orthopedic surgery [16]. Although a total of 14 different BMPs have been reported [17], much of the recent study in the literature has focused on BMP-2, -6, -7, -9, and -14 (MP-52).

Recombinant BMP-2 (rhBMP-2) and BMP-7 (or osteogenic protein-1, rhOP-1) have been evaluated in numerous preclinical models, and successful healing in long bone defects has been reported [16,18–20]. Similar findings have been demonstrated in spinal arthrodesis models in animals [21–24]. US Food and Drug Administration (FDA) approval was recently granted for the use of rhBMP-2 to enhance anterior spinal fusion [25] and rhOP-1 to supplement posterior spine fusions [26]. In other orthopedic applications, human clinical trials evaluating the efficacy of rhBMP to treat open tibia fractures, distraction osteogenesis, and osteonecrosis of the hip are underway [27].

Clinical research

The efficacy of rhBMPs has been evaluated in preclinical models of spine fusion. Recombinant BMP-2 has been shown to reproducibly heal the lumbar spine in rodents and nonhuman primates [18,24,28–36]. Furthermore, rhOP-1 has also demonstrated consistent bone healing properties in rodent and sheep models [36–40]. Results from these studies suggest that the use of rhBMP results in similar if not superior fusion rates with biomechanically stronger fusion masses when compared with autogenous bone graft [18,24,28–36].

The first clinical pilot study using BMP in an anterior interbody fusion cage reported high rates of radiographic fusion with more rapid improvement in clinical outcome [25]. In a larger multicenter trial in 46 patients who underwent anterior lumbar discectemy and interbody fusion with cortical allograft dowels, the combination of rhBMP-2 on an absorbable collagen sponge was directly compared with autogenous iliac crest bone graft (ICBG) [41]. At the 12- and 24-month follow-up, patients who received rhBMP-2 had superior rates of fusion and improved clinical outcome determined by self-reporting questionnaires when compared with autogenous ICBG [41]. Moreover, the same investigators reported greater new bone formation outside the interbody fusion device with the use of rhBMP-2 when compared with the use of autograft [41]. These studies have subsequently led to FDA approval for the use of rhBMP-2 for human subjects in anterior spinal fusion. Since then, additional studies have expanded the potential clinical uses of rhBMPs in the spine.

Vaccaro et al. [42] recently demonstrated the efficacy of rhOP-1 putty (3.5 mg rhOP-1 with 1 g Type I collagen) in the enhancement of posterolateral lumbar arthrodesis. In a randomized, prospective, multicenter study, a total of 36 patients with degenerative spondylolisthesis were treated with either rhOP-1 or autogenous ICBG in an uninstrumented posterolateral fusion after a decompressive laminectemy. At 1-year follow-up, 74% (14 of 19 patients) of the rhOP-1 and 60% (6 of 10 patients) in the autograft groups achieved a successful clinical and radiographic posterolateral arthrodesis (Fig. 1), which was not statistically significant [42]. These authors concluded that fusion rates

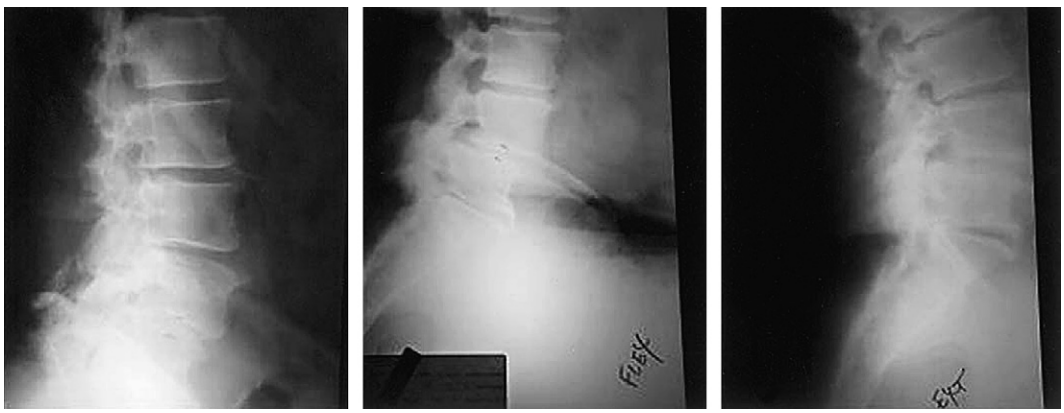

Fig. 1. Lateral neutral (Left), flexion (Center), and extension (Right) radiographs of a patient treated with recombinant osteogenic protein-1 and autograft in a posterolateral spinal arthrodesis without instrumentation demonstrating radiographic fusion 12 months after surgical implantation (reprinted with permission from Vaccaro et al. Eur Spine J 2003;12:495–500).

in the absence of internal fixation with the use of rhOP-1 putty was safe and yielded comparable results to that of ICBG.

Similarly, Boden et al. [43] reported the successful clinical use of rhBMP-2 in the healing of a posterolateral spine fusion in a comparison study involving 25 patients. Clinical improvement as defined by the mean Oswestry Disability Index score (6 weeks postoperatively) was greatest in the rhBMP-2-treatment-only group. Interestingly, the authors concluded that the use of a higher dose of recombinant growth factor in nonhuman primates (1.5–2.0 mg/mL) than in rodents (0.2–0.4 mg/mL), was required in healing a posterolateral spine fusion [43]. To date, it remains unclear why concentrations of BMP a million times greater than that found in the human body are required to successfully induce a spinal arthrodesis [44–46].

Follow-up studies using rhBMP-2 have confirmed its successful use in inducing a posterolateral spinal fusion diagnosed by computed tomography scan [47,48]. Glassman et al. [48] reported the use of a large INFUSE kit (Medtronic, Memphis, TN) (12 mg rhBMP-2, 1.5 mg/mL) in the posterolateral fusion bed as equivalent fusion success to ICBG. The authors concluded that INFUSE can effectively substitute for ICBG for both one- and two-level posterolateral instrumented fusions. Dimar et al. published 2-year radiographic results from an FDA investigational device exemption study comparing ICBG and rhBMP-2 combined with a compression resistant matrix (CRM) carrier for single posterolateral fusions. The authors demonstrated that patients in the BMP/CRM group experienced significantly higher fusion rates yet had less surgical time and blood loss than the ICBG group [47].

Reports in preclinical models have also indicated that modifications in the carrier can enhance the efficacy and local delivery of BMP [49,50]. Previous research has shown the requirement of relatively high doses of BMP-2 when used with a Type I collagen sponge in animal models [22,51]. Commercially available INFUSE bone graft also currently uses an absorbable collagen sponge scaffold. One study has reported the advantages of carrier modifications involving the addition of fast-resorbing biphasic calcium phosphate granules or allograft chips [49]. These alterations have been shown to add significant compression resistance and increase local confinement of recombinant growth factor. Using these carrier modifications, the amount of rhBMP-2 required to heal a nonhuman primate spine model was decreased significantly (3 mg/side vs. up to 32 mg/side with plain collagen sponge). Recently, combined carriers consisting of bovine collagen and tricalcium/hydroxyapatite (CRM) have been used to deliver BMPs to the region of interest [47].

The importance of associated carriers with BMP was elucidated when Barnes et al. [52] reported the results of rhBMP-2 delivered on an absorbable collagen sponge wrapped around a bulking agent consisting of biphasic calcium phosphate and collagen in a posterolateral fusion model in rhesus monkeys. Results from this and other studies suggest that the required dosage of rhBMP-2 for spinal arthrodesis can be reduced by optimizing the delivery of growth factor by combining the strengths of different carriers [49]. Conversely, carriers such as fibrin glue have been shown to inhibit bone formation induced from rhBMP and may provide protection from heterotopic ossification and diffusion of protein to undesirable adjacent areas [53].

Because the treatment of spinal pseudarthrosis is fraught with relatively poor outcomes and potential complications, the interest in the utilization of rhBMP for these clinical challenges is on the rise. With the use of different preclinical pseudarthrosis models, recombinant growth factors may eventually prove to be a more appropriate bone graft option than other existing choices including ICBG. With the use of a nicotine-exposed rabbit lumbar pseudarthrosis model, Osteogenic Protein (OP)-1 was found to increase the expression of crucial genes in bone repair such as angiogenin, vascular endothelial growth factor, and BMPs [54]. In fact, these authors concluded that application of a single BMP in relatively high concentrations to a biologically stringent environment can induce angiogenic and osteogenic gene expression greater than that seen with autologous graft. A separate pseudarthrosis rabbit model exposed to preoperative radiation was used to demonstrate the superiority of rhBMP-2 to ICBG in producing a greater rate of fusion [55]. These studies are valuable in establishing the clinical and practical advantages in the use of recombinant growth factors for challenging biological environments. Not only can a more reliable osteoinductive stimulus be delivered to a fusion bed devoid of vascular supply and osteoinductivity, but the significant morbidities of autograft harvest can also be avoided.

Despite the overwhelming evidence in support of the routine use of rhBMPs in the enhancement of spinal arthrodesis, a number of studies have suggested potential complications with its clinical use. Smucker et al. [56] reported that 27.5% of a total of 69 patients who underwent anterior cervical spine fusions using rhBMP-2 had a clinical significant neck-swelling event compared with only 3.6% of patients in the non-rhBMP-2 group (Fig. 2). Other studies have confirmed the finding that the use of rhBMP-2 in the anterior cervical spine can be problematic [57,58]. Furthermore, the use of rhBMP-2 in transforaminal lumbar interbody fusion has been reported to lead to significant vertebral bone resorption in a total of 22 of 32 lumbar levels studied postoperatively with a computed tomography scan [59]. These authors concluded that rhBMP-2 was the direct cause of resorption, which led to graft subsidence and prevented solid radiographic union in a significant number of cases [59].

The continued research into the efficacy of rhBMPs in the augmentation of spinal arthrodesis offers promising results. Evidence from early clinical trials indicate that the use of rhBMPs results in fewer side effects, more rapid clinical improvement, and fusion rates that are as good

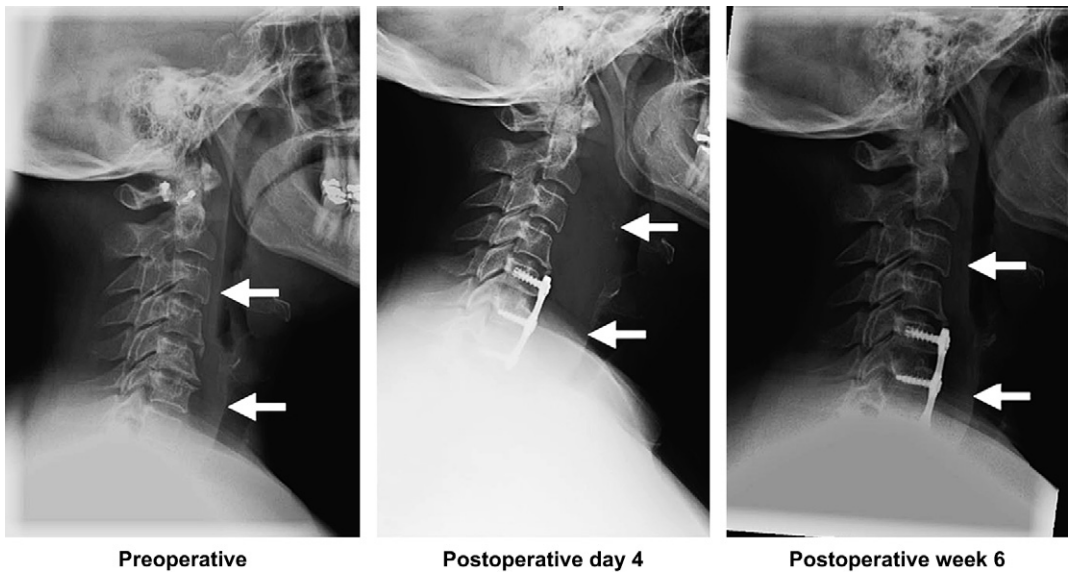

Fig. 2. Postoperative lateral cervical spine radiographs of a patient who underwent C5–7 anterior cervical discectomy and fusion with recombinant BMP-2, allograft, and plate. Arrows demonstrate marked severe anterior neck swelling and dysphagia on postoperative Day 4, which decreased to baseline by postoperative Week 6 (reprinted with permission from Smucker et al. Spine 2006;31(24): 2813–2819).

as, if not better than iliac crest autograft [25,39,41,43,47,60]. These studies have also shown that when used at an adequate dose with an appropriate carrier matrix, rhBMPs can be used for a wide range of spine problems with or without instrumentation for degenerative conditions, trauma, and even significant spinal deformity [61]. However, there remains great uncertainty with regard to the cost effectiveness of these recombinant growth factors, the potential burden on the health-care system from decades of recombinant protein use, and for which clinical indications they are most applicable. The identification of appropriate carriers for different clinical scenarios is even more essential to reduce both the dose and cost of recombinant proteins.

Discussion

Spinal arthrodesis is complicated by challenges including osteoporotic bone, a stringent biological environment and poor local vascularity. Bone graft substitutes are essential in obtaining consistent arthrodesis without the morbidity associated with autogenous graft. However, as a whole, available data vary widely regarding these substances and careful evaluation is necessary to identify the appropriate use of various bone graft agents. In making these critical decisions, surgeons must assess the host biologic environment and must ensure that four critical elements are present to promote bone repair: the presence of bioactive factors, responding cells, matrix, and an adequate vascular supply.

The body of evidence reporting the efficacy of rhBMP in clinical studies has grown considerably over the past 5 years. Since the first report of BMP-induced osteoinduction in a clinical trial [25], additional studies have reported the superiority of rhBMP-2 to the use of autogenous bone graft [25,39,41,43,47,60]. Moreover, patients treated with rhBMP-2 alone have been found to show more rapid and significant clinical improvement after spine fusion [43]. Reasons for this finding may be attributed to the subsequent shorter operative time and hospital stay [62]. Recent studies have shown that with adequate dosing of recombinant protein in patients without spinal instability, the use of rhBMP may decrease the need for instrumentation [42,63,64]. Furthermore, multiple investigators have demonstrated the osteoinductive versatility of rhBMP using multiple approaches. Recent evidence has reported the efficacy of rhBMP in posterolateral, interbody and transpedicular approaches in inducing radiographic and histologic spine fusion [39,41,43,59,60,64]. Future uses of rhBMP may lead to higher success rates in minimally invasive procedures and lessen surgical exposures and operative time.

However, despite excellent clinical results, many concerns still exist for the routine use of recombinant growth factors. Clinical studies that confirm the safety from the use of rhBMP-2 in humans [27,42] fall short in evaluating possible long-term effects. A number of complications have also been associated with its use in both the cervical and lumbar spine [56,57,59]. Furthermore, the cost of rhBMP currently precludes its routine use in spine arthrodesis, and further study will be necessary to delineate the clear indications in which BMPs should be used. At the current time, the administration of rhBMP to the surgical site requires a biological milieu that harbors responding cells and an adequate vascular supply to induce bone healing [65]. Stringent environments complicated by significant scar tissue in revision procedures, osteoporotic

bone stock, and multilevel constructs may require a more potent osteoinductive stimulus to provide a successful spine fusion.

Studies in our laboratory using a rat femoral defect and spinal arthrodesis model have indicated that a threshold level of BMP-2 production may be necessary to completely heal a large critical-sized defect [66–68]. The existence of a threshold level of BMP for osteogenic activity is an important finding because potential bone grafting strategies must provide an adequate osteoinductive signal not only of sufficient intensity but also of length to induce bone repair.

For these reasons, because of the exorbitant costs of the utilization of these recombinant proteins, its routine use is not recommended. However, individual patient characteristics that increase the risk of pseudarthrosis such as smoking, osteoporosis, multilevel and revision surgeries, and previous graft site harvest may justify the additional costs of BMPs as a bone graft substitute during surgery. Further studies delineating the indications of BMPs in spine surgery are warranted.

Future topics

The future of the use of bone graft substitutes to enhance spine arthrodesis remains bright. Apart from the proven efficacy of recombinant growth factors in inducing bone formation in the spine, new techniques are being developed to make the use of gene therapy systems more practical in delivering long-term BMPs in the spine [24,46,69,70]. Novel studies involving cell-based therapies may prove to offer a cost-effective option in bone repair using lower doses of rhBMP. Multiple avenues of research exist in the development of biologic substitutes for the enhancement of spine fusion. The continued laboratory and clinical characterization of spinal biologics will ultimately offer spine surgeons multiple options in the arena of spine fusion.

Conclusion with key points

- BMPs have demonstrated comparable fusion rates and clinical outcomes when compared with ICBG in both interbody and posterolateral fusions in prospective, randomized clinical studies.
- Continued research has focused on the optimization of a carrier for BMP to increase the delivery of protein to the region of interest.
- The utilization of BMPs has also been associated with unique complications such as local soft tissue edema and bone resorption.
- Because of the prohibitive cost of BMPs, its routine use in spine surgery is not necessarily recommended.
- Individual patient characteristics must be taken into account to justify its use to augment arthrodesis.
- New cell-based and gene therapies to increase the regional delivery of BMPs are under development to potentially offer a less expensive way to improve spine fusion rates.

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