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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. © 2008 Elsevier Inc. All rights reserved.

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

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reason, interest in bone graft substitutes and enhancers for the supplementation of spine surgery is on the rise.

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

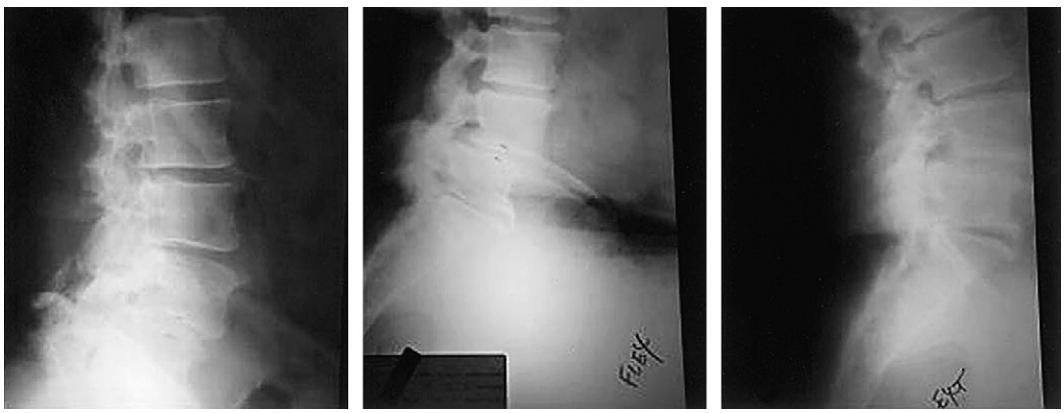

Fig. 1. Lateral neutral (Left), flexion (Center), and extension (Right) radiographs of a patient treated with recombinant osteogenic protein-1 and autograft in a posterolateral spinal arthrodesis without instrumentation demonstrating radiographic fusion 12 months after surgical implantation (reprinted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

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