Bone morphogenetic proteins and spinal fusion

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Bone morphogenetic proteins (BMPs) have increasingly become a focus of research in the laboratory, with animal models, and in human clinical trials for the treatment of spinal disorders. Basic science research has elucidated the putative mechanism of action of BMPs, and the efficacy of BMPs in inducing bone formation has been evaluated in multiple animal models of anterior and posterior spinal fusion. Not only has BMP been shown to improve the quality and amount of bone formation when used as a supplement to autograft, it has also been shown to promote superior fusion in the absence of autograft, even in high-risk fusion models involving the use of nicotine or nonsteroidal antiinflammatory agents. Both completed and ongoing clinical trials have demonstrated the efficacy of recombinant BMP, leading to the first BMP product being approved for clinical use earlier this year.

Animal models and clinical trials have also been used to evaluate the safety of BMPs. Although few complications have been reported, BMPs can induce heterotopic bone formation, especially when placed adjacent to exposed neural elements. Potentially more serious, antibody formation has been seen in up to 38% of patients in some clinical trials. No clinical sequelae have been reported despite the development of antibodies against BMP, a naturally occurring human protein implicated in processes other than osteoinduction.

The future directions of biological manipulation of the osteoinduction process include further understanding of the interactions of the BMP subtypes, the interactions of BMP with its receptors, and exploring other molecules capable of osteoinduction.

**KEY WORDS** • bone morphogenetic protein • osteoinduction • spinal fusion

Bone morphogenetic proteins have dramatically changed the landscape of spinal surgery since their introduction nearly three decades ago. Initially described by Dr. Marshall Urist in 1965, the BMP family has generated an ever increasing flurry of scientific research, animal studies, and clinical trials during the past few decades. This year, the first recombinant BMP product approved by the FDA for use in spinal surgery was released, and several other BMP products are currently undergoing clinical trials for the treatment of spinal disorders.

With the advent of recombinant protein use in the field of spinal surgery, the surgeon must necessarily be familiar with the basic science behind the mechanisms of BMP, as well as with the wealth of data from animal and clinical studies supporting the judicious use of BMP. Although BMP promises an exciting new era for spinal surgery, the uninformed use of BMP—as with any rh protein used as a treatment tool—may result in clinical complications. It is not enough to know that BMP induces bone formation; the surgeon should understand how BMP promotes osteogenesis and in which situations it should and should not be used.

Toward this end, this paper reviews the historical background of the discovery and development of BMP as well as the known mechanisms of BMP-induced osteogenesis. Additionally, relevant animal studies are examined and the major clinical trials are discussed, as are the known possible adverse effects of BMP use.

**HISTORICAL BACKGROUND**

In 1965, Dr. Marshall R. Urist initially reported on the ability of demineralized bone matrix to induce in-growth of connective tissue and differentiation of cartilage and bone when implanted in extraskeletal locations in the rat. Urist ultimately extracted a glycoprotein from this demineralized bone matrix capable of osteoinduction: the first BMP. As defined by Urist, osteoinduction is the “process of recruitment of mesenchymal-type cells into cartilage and bone under the influence of a diffusible bone morphogenetic protein.” Since that initial report, nearly 30 BMPs have been identified, at least nine of which have proven osteoinductive effects.