Role of Recombinant Human Bone Morphogenetic Protein-2 on Hindfoot Arthrodesis

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KEYWORDS

• rhBMP-2 • Hindfoot • Arthrodesis • Fusion • Orthobiologics

KEY POINTS

- Despite improvements in fixation technique, hindfoot arthrodesis continues to be associated with modest nonunion rates.
- Of commercially available recombinant human bone morphogenetic proteins (rhBMPs), rhBMP-2 has the most osteogenic activity.
- The only study investigating the use of rhBMP-2 in hindfoot arthrodesis found a statistically significant increase in fusion rate compared with controls.
- rhBMP-2 is a valid treatment option for hindfoot arthrodesis.

INTRODUCTION

Despite advances in surgical technique, the treatment of hindfoot arthrodesis continues to be associated with complications, including delayed union, malunion, and nonunion.[1] Nonunion rates have been reported as high as 20% for triple arthrodesis.[2,3] Clain and Baxter[4] in 1994 demonstrated a nonunion rate of 6.25% for simultaneous calcaneocuboid and talonavicular fusions. Furthermore, the nonunion rates for isolated subtalar fusion, isolated talonavicular fusion and isolated calcaneocuboid fusion have been reported up to 16%,[5–11] 35%,[12–15] and 20%,[16] respectively.

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In addition, there can be many contributing factors associated with poor bone healing, including diabetes mellitus, smoking, immunosuppression, multiple surgeries, infection, rheumatoid arthritis, and pharmaceutical agents.[17–23] Chahal and colleagues[19] in 2006 reported that diabetic patients were 18.7 times more likely to develop malunion after isolated subtalar arthrodesis and Ishikawa and colleagues[20] in 2002 determined that smokers have a 2.7 times greater risk of developing a nonunion in hindfoot fusions compared with nonsmokers. In addition, the rate of union is significantly decreased by the failure of a previous subtalar arthrodesis.[5]

Improvements in fixation techniques and the use of bone grafts have been introduced to reduce nonunion rates. Autogenous bone graft has been beneficial in hindfoot arthrodesis enhancement owing to its intrinsic osteogenic and osteoinductive properties.[24] However, autogenous bone graft has potential limitations. The patient's age and size may restrict the quality and volume of autogenous bone graft obtainable. In addition, harvesting iliac crest bone can yield numerous minor complications, including acute and chronic donor site pain, gait disturbances, stress fractures, paraesthesias, and superficial infections, as well as major complications, including pelvic fracture, arterial injury, hernia, and peritoneal perforation.[25]

As an alternative to autologous iliac bone graft, adjuvant osteobiologics are being used in foot and ankle surgery. Osteobiologics are subcomponents of living cells that enhance the healing potential of bone via osteoinduction, osteoconduction, or osteogenesis. The osteobiologics used in foot and ankle surgery include platelet rich plasma, recombinant human platelet-derived growth factor, recombinant human bone morphogenetic proteins (rhBMPs) and bone marrow concentrate.[26] This paper investigates the role of rhBMPs, specifically rhBMP-2, in hindfoot arthrodesis.

BONE MORPHOGENETIC PROTEINS

Bone morphogenetic proteins (BMPs) were first reported in the literature by Urist in 1965[27] and more than 20 BMPs have been subsequently identified.[28] BMPs belong to the transforming growth factor superfamily and have chondroinductive and osteoinductive activity.[29] BMPs are composed of 2 major glycosylated subunits that are linked together by a disulfide bond. BMPs interact with 2 of 6 known surface receptors and initiate signal transduction via serine/threonine kinase receptors.[30,31] Activation of these intrinsic receptor serine/threonine kinases phosphorylates SMAD proteins that translocate into the nucleus leading to the expression of osteogenic-specific genes.[31,32] In addition, an alternate mechanism involves the mitogen-activated protein kinase pathway leading to the activation of p38.[31] Recent data suggest involvement of the RAS pathway and Erk kinase pathway, yet additional research into the regulation of these pathways and receptors are needed.[31,33,34] As with all signaling cascades, the BMP signaling pathway is highly regulated. Noggin, inhibin, and BMP-3 have been identified as BMP receptor antagonists[35,36] and additional proteins can block the action of the SMADs.[37] The availability of endogenous BMP is also regulated sclerostin, chordin, connective tissue growth factor (CTGF), follistatin, and gremlin regulate BMP availability.[36] Furthermore, BMP-2 has been determined to induce osteoblast differentiation of mesenchymal stem cells.[38]

BONE MORPHOGENETIC PROTEINS IN ANIMAL MODELS

BMPs play an important role locally at the fracture callus during bone healing. Bostrom and colleagues[39] in 1995 reported expression of BMP-2 and BMP-4 within the fracture callus after the fracture of rat femurs. Rabbit model studies have revealed that after administration, rhBMP-2 will stay locally at the fracture site for approximately