# Bone Morphogenetic Protein. Is There Still a Role in Orthopedic Trauma in 2017?

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**KEYWORDS**

• Bone morphogenetic protein • Fracture • Trauma • Nonunion • Complications

**KEY POINTS**

- Recombinant bone morphogenetic protein-2 can be beneficial when treating open tibia fractures, specifically, Gustilo-Anderson type 3 injuries.
- Recombinant bone morphogenetic protein-7 can be beneficial when treating tibia shaft nonunions.
- Off-label use of bone morphogenetic protein is common despite limited evidence to support its use in these settings.
- Increasing reports of bone morphogenetic protein–related complications with off-label use are being described in the orthopedic trauma literature.
- The economic impact of BMP use in fracture care in the United States is unknown.

## INTRODUCTION

The discovery of bone morphogenetic proteins (BMP) by Urist[1] in 1965 was met with great optimism. The finding of an osteoinductive compound created the potential for manufacturing a growth factor that would assist with bone formation and healing. Over the years, numerous studies (both animal and human) showed the efficacy of BMP in enhancing bone growth.[2–5] Moreover, many of these studies have found ancillary benefits of BMP, such as decreasing infection rates and time to wound healing.[4] In 2001, the US Food and Drug Administration (FDA) gave marketing clearance for rhBMP-7 (OP-1; Stryker [Stryker Corporation, Kalamazoo, Michigan]) to be used for recalcitrant long bone nonunions. Subsequently, in 2004, rhBMP-2 (INFUSE; Medtronic [Medtronic, Fridley, Minnesota]) was approved for treatment of open tibia shaft fractures. Unfortunately, recent reports of complications have overshadowed these early promising results. Increased wound drainage, excessive bone growth, neuropathy, and even carcinogenesis have been presented as complications after use of BMP.[6–8] Additionally, concern over lack of mechanical strength and the high cost associated with BMP have been cited as shortcomings.[9] Many of the reports on complications occurred after use around the spine; however, there are also reports of complications associated with fracture care.[6,7,10]

Approximately 10 years ago BMP was seen as a miraculous adjuvant to assist with bone growth. However, in the face of an increasing number of complications and a lack of understanding its long-term effects, it is unclear what role BMP has in the current treatment of orthopedic trauma patients. This article reviews the current recommendations, trends, and associated complications of BMP use in fracture care.

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## HISTORY AND MECHANISM OF BONE MORPHOGENETIC PROTEIN

BMPs are a part of the transforming growth factor-β superfamily that is responsible for tissue repair and embryogenesis.[11,12] Twenty different BMPs have been discovered with many of them appearing to function in different ways. When acting together, these growth factors are able to provide a signal that causes mesenchymal stem cells to differentiate into osteoblasts, also known as *osteoinduction*. Specific proteins (BMP-2, -6, and -9) work early in the differentiation process, whereas most of the others, including BMP-7, help stimulate the final transition of preosteoblast to osteoblasts.[11]

Urist[1] is credited as being the founder of these growth factors after he implanted decalcified bone within rodent muscle and noticed subsequent bone growth. He defined this phenomenon as *osteoinduction*. In 1988, Johnson and colleagues[13] reported the first clinical outcomes of purified human BMP used to treat femoral nonunions. Eleven of the 12 femoral nonunions treated healed at an average of 4.7 months. Johnson performed additional clinical trials that continued to show promising results.[14,15] However, it became apparent early on that isolating large quantities of BMP from cadaveric bone was difficult and not a viable source for mass scale production.[12] Moreover, the specific dose of BMP required for efficacy was unknown, which led to use of recombinant gene technology to create specific BMPs that show evidence of osteoinduction alone.[12] Both rhBMP-2 (INFUSE) and rhBMP-7 (OP-1) are proteins that are now manufactured in mass quantities via recombinant technology. These proteins are currently the most widely used and most studied of the BMP family. Further studies followed that found that low doses of BMP resulted in minimal bone formation; however, higher doses of BMP can result in excessive bone formation and even bone resorption secondary to osteoclast activation.[11] Termaat and colleagues[11] explained that "The dose of BMP needed for clinical efficacy must overcome a threshold, and the dose-response curve becomes steeper as one progresses from rodent to nonhuman primate." The specific reason for this is still unclear. At this time, the current recommended doses of BMP-2 and BMP-7 are more than 1000 times greater than those of native concentrations.

## TREATMENT OF ACUTE FRACTURES

The treatment of open fractures is associated with high complications rates and poor functional outcomes. Loss of soft tissue and bone in these injuries may lead to delayed healing and nonunion. Much of the clinical research with BMP use in acute extremity injuries involves open fractures, specifically, open tibia fractures.

In 2002, the BMP-2 Evaluation in Surgery for Tibial Trauma (BESTT) trial was performed to determine the safety and efficacy of rhBMP-2 in the treatment of open tibia shaft fractures fixed with both reamed and unreamed intramedullary nails (IMN).[4] Four hundred fifty patients with open tibia shaft fractures were randomly divided into 3 groups:

1. The standard of care group (IMN plus soft tissue management)
2. The standard of care with 0.75 mg/mL of rhBMP-2
3. The standard of care with 1.50 mg/mL of rhBMP-2

The authors found that the group with 1.50 mg/mL of rhBMP-2 had significantly fewer reoperations, infections, wound complications, and hardware failures. Additionally, the group with the 1.50 mg/mL dose had faster healing times. At 1 year follow-up, the adverse events in the BMP group were similar to what was seen in a normal trauma setting. The authors stated that rhBMP-2 is a "novel adjunct" and advantageous when compared with the standard of care when treating long bone fractures. However, other investigators noted the disproportionate amount of patients in the control group that received unreamed IMN when compared with the study group.[16] The effect of reaming when treating tibia fractures with IMN has been well studied. The Study to Prospectively Evaluate Reamed Intramedullary Nails in Patients with Tibial Fractures (SPRINT) trial[17] found that the reaming is a strong confounding variable to consider in the BESTT trial results.

In 2006, Swiontkowski and colleagues[18] combined the data from the BESST trial with data from another prospective, randomized trial using the same methods. Patients from 2 subgroups were analyzed:

1. 131 patients with Gustilo-Anderson type 3A or 3B fractures
2. 113 patients treated with reamed IMN

This analysis found significant improvements in secondary procedures and infections in those from the first subgroup receiving rhBMP-2 at a concentration of 1.50 mg/mL. The second subgroup showed no difference between those that received rhBMP-2 and those that did not,