

The Utility and Effectiveness of Bone Morphogenetic Protein in Foot and Ankle Surgery

John M. Schuberth, DPM,¹ Lawrence A. DiDomenico, DPM,² and Robert W. Mendicino, DPM³

A review of the use of bone morphogenetic protein in 38 cases in 35 patients at high risk for bone healing complications following foot and ankle surgery was performed. Multiple relevant variables were analyzed with respect to the incidence of healing, including age; diabetes mellitus; Charcot neuroarthropathy; prior infection; type of procedure; and the use of femoral head allograft, electrical bone stimulation, and external fixation. The overall incidence of successful healing was 84.21%. A statistically significant decrease in the incidence of bone healing was observed if the patient was 50 years of age or older (P = .03), and all 16 patients younger than 50 years healed their index operation. If 60 years of age was the benchmark, a statistically significant decrease in the rate of healing was observed (P = .02). Logistic regression showed that a 10-year increase in age almost doubled the risk of not healing (odds ratio = 2.613). Furthermore, 4 (66.66%) of the 6 patients who did not heal had diabetes mellitus and were older than 60 years. This combination of risk factors was associated with a statistically significant decrease in the likelihood of bone healing (P < .01). Of the 10 cases to exhibit postoperative drainage, only 50% of these successfully healed, whereas 96% of the remaining 28 cases successfully healed (P = .0026). The results of this study demonstrate the utility of bone morphogenetic proteins in foot and ankle surgical patients at high risk for bone healing complications. Level of Clinical Evidence: 2 (The Journal of Foot & Ankle Surgery 48(3):309–314, 2009)

Key Words: arthrodesis, bone morphogenetic protein, Charcot neuroarthropathy, fracture, nonunion, tibial osteotomy

Although most fractures and bony surgical corrections of the lower extremity heal uneventfully, delayed unions and nonunions remain a challenge for both the surgeon and patient. In the past, improved union rates and outcomes have been attributed to increased mechanical stability afforded by the advances of fixation devices, including external fixation (1). Moreover, the increased utility of operative intervention for complex limb salvage in entities like Charcot neuroarthropathy has resulted in an awareness of the complexities of bone consolidation, despite the availability and use of improved fixation constructs (2). More recently,

appreciation for the capacity of biologic modulation of the healing process has led to the proliferation of a class of substances known as orthobiologic agents, which are thought to increase the likelihood and rate of bone healing (3–11). Such products include demineralized bone matrix, platelet gels, cancellous allograft, calcium phosphates, calcium sulfates, bone marrow aspirates, bone morphogenetic proteins, and others. Regardless of the substance, the concentration of nascent bone morphogenic substances in autogenous graft, platelet gels, and demineralized bone matrix is limited and may not be capable of producing the desired effect of differentiation of tissue into bone (3, 12). The direct application of clinically significant concentrations of potent substances that can induce bony union can be appealing to both the patient and surgeon. In particular, the ability of such substances to influence tissue differentiation that promotes bone formation is also desirable.

Bone morphogenetic proteins (BMPs) were first described by Marshall Urist (13) when he observed de novo bone formation in rabbits after implantation of decalcified bone in soft tissue pouches. To date, more than 20 BMPs have been discovered and 7 of them have demonstrated a prominent role in bone formation (3, 4, 14, 15). These proteins are members of the transforming growth factor-beta superfamily that are involved in the cascade of cellular events that contribute to tissue formation and regeneration, including stem-cell commitment, differentiation, and proliferation (14).

Address correspondence to John M. Schuberth, DPM, Chief, Foot and Ankle Surgery, Kaiser Foundation Hospital, Department of Orthopaedic Surgery, French Campus, 450 6th Avenue, San Francisco, CA 94118. E-mail: Jmfoot@aol.com

¹Chief, Foot and Ankle Surgery, Kaiser Foundation Hospital, Department of Orthopaedic Surgery, San Francisco, CA.

²Adjunct Professor, Ohio College of Podiatric Medicine, Cleveland, OH; Section Chief of Podiatric Medicine & Surgery, St. Elizabeth Medical Center, Youngstown, OH; Director, Reconstructive Rearfoot & Ankle Surgical Fellowship, Ankle and Foot Care Centers / Ohio College of Podiatric Medicine, Cleveland, OH.

³Chief, Division of Foot and Ankle Surgery, Western Pennsylvania Hospital, Pittsburgh, PA.

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Recently, several studies have been published describing the use of bone morphogenetic protein in the management of fractures and nonunions of long bones, with promising results (4–6, 8, 16). The various applications described include trauma management, spinal surgery, osteonecrosis, and repair of segmental defects (6, 8–10, 14, 16). The use of BMP in the foot and ankle has been reported only infrequently (7, 17). As such, the indications for the application of BMP in the foot and ankle have yet to be rigorously defined. The purpose of this study was to relate our collective experience with the use of a specific form of BMP in foot and ankle surgery patients at a high risk for failure to heal bone, and to establish more finite guidelines for the use of BMP in the foot and ankle. To this end, we undertook a retrospective cohort study to calculate the incidence of bone healing in this group of patients, and we analyzed the influence of a number of independent variables in an effort to explain the outcomes.

Patients and Methods

A retrospective analysis of patients who received BMP (OP-1, Stryker Biotech Hopkinton, MA) as an adjunct to reconstructive foot and ankle surgery was undertaken. The patients that comprised the cohort came from the clinical practices of the 3 authors of this article during the 3-year period from April 2004 through April 2007. The data were abstracted from the medical records independently by each of the respective authors and assimilated in a database. To be included in the investigation, patients needed only to have been treated with the use of BMP. The decision to use BMP was based on the individual surgeon's concern for the likelihood of complicated bone healing, as determined by a history of previous nonunion, infection, or diabetes with or without neuroarthropathy, as well as the surgeon's experience. As such, the cohort was considered to be a population at risk for failure of bony union. Demographic information included the patient's age, gender, past medical history, number and type of previous surgery, the type of fixation, whether or not electrical bone growth stimulation was used, the type of bone graft used, and the type of biologic enhancers and carriers used with the BMP. Bony union at the site of BMP administration was the outcome of interest, and this end point was determined by a combination of unequivocal radiographic evidence of bony consolidation and a lack of pain at the site of the index operation in those patients without a sensory neuropathy. In addition, the time to union, the period of non-weight bearing, and type of post-operative immobilization were also recorded. Complications such as wound dehiscence or drainage were also noted. Nonunion was determined if there was persistent radiographic lucency at the surgical site and/or palpable or visible motion across the surgical site. An Investigational Review Board exemption was obtained at every author's institution.

TABLE 1 Results of bone healing in high-risk patients using bone morphogenetic protein in foot and ankle surgery, by surgeon (N = 38 cases in 35 patients)

Variable	Surgeon			Total	Successful Union
	A	B	C		
Forefoot surgery	0	3	1	4	4
Ankle fusion	3	0	8	11	10
Tibiotalocalcaneal fusion	0	1	4	5	3
Distal tibial osteotomy	4	0	4	8	8
Diabetes mellitus without Charcot neuroarthropathy	1	0	8	9	6
Diabetes mellitus with Charcot neuroarthropathy	2	3	5	10	9
Nonunion	6	6	13	25	22
Prior infection	2	2	2	6	4
External fixation	6	3	12	21	17
Femoral head allograft	1	1	4	6	4
Iliac crest or tibial autograft	1	0	1	2	2
Bone growth stimulation	3	8	16	27	22

A biostatistician analyzed the data; Fisher's exact test and logistic regression were used to determine if any statistically significant associations existed between the independent variables and the outcome of interest.

Results

The results of the investigation are depicted in Tables 1 and 2. Thirty-five patients in 38 cases received OP-1 as a component of their surgical procedure. The time of follow-up ranged from 4 to 37 months with a mean of 9.7 months. The incidence of successful bone union was 32 (84.21%) of the 38 index procedures and union occurred at an average of 14.25 weeks (range 8–30 weeks) following BMP implantation. In the 6 nonunion cases, 2 occurred in 1 patient with 2 different attempts at tibiotalocalcaneal fusion. This patient also had diabetes mellitus, a prior infection, and a previous nonunion at the time of the index procedure. Of the other 4 patients who resulted in a nonunion, 1 had diabetes without Charcot neuroarthropathy, 1 had Charcot neuroarthropathy, 1 underwent ankle fusion, and 2 received femoral head allograft.

The patients included in this investigation had undergone a total of 80 initial surgical procedures. All but 1 of the 35 patients had at least 1 prior surgical procedure on the affected extremity (range 1–6). However in 11 of the remaining 34 patients, these prior procedures were performed for reasons other than bony consolidation of the index site. These procedures were primarily debridements or open reductions of fractures (6 patients), total ankle replacements (3 patients), or bony

TABLE 2 Number of cases and successful unions in high-risk patients using bone morphogenetic protein in foot and ankle surgery, by surgeon (N = 38 cases in 35 patients)

Variable	Surgeon			Total
	A	B	C	
Separate cases by surgeon	7	9	22	38
Successful unions by surgeon	7	7	18	32
Proportion of cases that healed successfully, %*	100.00	77.78	81.82	84.21

*The incidence of bone healing did not vary to a statistically significant degree ($P < .05$) based on the surgeon of record

stabilization of adjacent joints (2 patients). Of the 35 patients, 10 had 2 prior surgical procedures at the index site that were intended to provide bony consolidation, making the index procedure the third attempt at union. Twenty-three patients (65.71%) had existing postsurgical nonunions as the primary indication for the use of BMP. Twelve (34.29%) patients had operations that were at high risk for nonunion and included 5 with Charcot neuroarthropathy, 3 with a failed total ankle with interposition of a large femoral head allograft, 2 patients with high-energy open distal tibial fractures, and 1 patient with bilateral talar body extrusions that required femoral head allografts. Five (14.29%) patients were active smokers at the time of the index procedure. The carrier used for delivery of the BMP was autologous blood or platelet gel in 36 cases, and a synthetic collagen was used in the remaining 2 cases.

Analysis of the individual patient characteristics taken separately and compared with the rate of healing revealed the following:

Forefoot Procedures

There were 4 patients who had BMP implanted in the forefoot region. Although each of these patients healed their operations, the incidence of healing was not statistically significantly different compared with the incidence of healing in those patients who underwent midfoot, hindfoot, ankle, and distal tibial procedures (82%; $P = 1.000$).

Ankle (Tibiotalar) Fusion

Ankle fusions represented 29% of the surgical procedures ($n = 11$ fusions in 10 patients). There was 1 nonunion after ankle fusion, compared with 5 nonunions (25 patients) in the rest of the population, and this difference was not statistically significant ($P = .65$). One patient with diabetes failed to unite the ankle fusion after the use of BMP on 2 separate occasions, and that patient had 2 prior attempts at fusion without the use of BMP (4 attempts overall). Three patients with diabetes and Charcot neuroarthropathy had an average of 2 attempts at ankle fusion (2 each) before the index procedure. Two of these

3 cases went on to heal after the third fusion operation. Further, these 3 patients had an average of 5 prior surgical procedures on the ankle before inclusion in this investigation.

Tibiotalocalcaneal Fusions

Three (60%) of the 5 patients with tibiotalocalcaneal fusions healed, and this difference was not statistically significantly different ($P = .16$) in comparison with the rate of fusion for the remainder of the cohort.

Distal Tibial Osteotomies

Healing occurred in all 8 patients with distal tibial osteotomies, and this difference was not statistically significant ($P = .31$) in comparison with the remainder of the cohort. Three of these 8 patients were diabetic, and none had more than 1 prior operation in an attempt to achieve union.

Diabetes without Charcot Neuroarthropathy

Diabetic patients without Charcot neuroarthropathy ($n = 9$) healed their index operation less often than did the remaining 26 patients (67% versus 90%), and this difference was not statistically significant ($P = .13$). More of the patients had diabetes with Charcot neuroarthropathy, but were classified separately as Charcot patients rather than diabetic patients. When diabetic patients with and without Charcot neuroarthropathy were compared with those without diabetes or Charcot, the incidence of healing was 80% and 89%, respectively, and this difference was not statistically significant ($P = .23$).

Diabetes with Charcot Neuroarthropathy

There were 10 cases performed on 10 patients with Charcot neuroarthropathy, representing 26% of the cohort. Nine of these cases went on to complete consolidation, and this rate did not statistically significantly differ from the healing rate in the remainder of the cases (28 cases in 25 patients) ($P = 1.00$). The patient with Charcot neuroarthropathy who did not heal had experienced a prior infection and multiple surgical debridements.

Nonunion

When procedures directed at a preexisting nonunion were taken into account ($n = 25$ nonunions in 23 patients), the rate of successful healing was 88% compared with a rate of 70% in the 13 procedures in 12 patients without an existing nonunion, and this difference was not statistically significant ($P = .39$). These 13 cases without a preexisting nonunion were those complicated by other conditions at the time of

the index procedure, and were considered to be at high risk for failure. These conditions included Charcot neuroarthropathy ($n = 6$), use of femoral head allografts with large interfaces ($n = 5$ in 4 patients), and diabetes without Charcot neuroarthropathy ($n = 2$).

Prior Infection

Four of the 6 (67%) patients who had prior bone infections at the site of the index operation healed, compared with 26 (81%) of the remaining 32 cases, and this difference was not statistically significant ($P = .23$). The 2 patients with prior infection who did not heal had persistent or recurrent osteomyelitis, whereas the other 4 had no residual infection and complete consolidation of the index site at the time of latest follow-up. However, 1 of these 4 patients developed osteomyelitis at a distant site and went on to below-the-knee amputation.

External Fixation

When external fixation was used to stabilize the extremity, the incidence of successful bone healing was 81%, compared with a rate of 88% when external fixation was not used, and this difference was not statistically significant ($P = .67$). Overall, the investigators felt that the cases requiring external fixation were less likely to heal, and for this reason they were stabilized with the external fixator.

Electrical Bone Growth Stimulation

Those patients who used electrical bone growth stimulation, either internal direct current or external pulsed electromagnetic field stimulation, displayed an incidence of healing of 81%, whereas those who did not undergo bone growth stimulation displayed an incidence of healing of 90%, and this difference was not statistically significant ($P = .39$).

Femoral Head Allografts

Femoral head allografts were used to fill large defects during reconstruction in 6 cases in 5 patients. Three of these cases (3 patients) involved failed total ankle arthroplasties, and another 2 cases (1 patient) were undertaken for the treatment of an absent talar body following bilateral traumatic extrusion. The remaining case (1 patient) involved an ankle fusion following a triple arthrodesis that resulted in a large tibiotalar defect. Four of these procedures went on to healing and complete consolidation. The 2 failures occurred after removal of ankle prostheses that had loosened, and 1 of these failed because of postoperative infection. Although one third of the cases in which femoral heads were used did not heal,

there was no significant difference in the heal rate compared with the rest of the study population (87%; $P = .23$).

Iliac Crest Autografts

Both cases in which iliac crest autograft was used to fill a defect or promote healing in addition to BMP went on to heal, and this incidence of healing was not statistically significantly different ($P = 1.00$) in comparison with the incidence of healing in the remainder of the cohort.

Wound Dehiscence and Broken or Loosened Hardware

Three of the 4 cases where broken or loose hardware was observed in the postoperative period went on to consolidate, although the difference was not statistically significant in comparison with the incidence of healing in the remainder of the cohort ($P = 1.00$). However, when the wound exhibited drainage in the postoperative period ($n = 10$ cases in 10 patients), only 50% of these patients had bony union compared with an incidence of healing of 96% for the remainder of the cohort, and this difference was statistically significant ($P = .0026$).

Patient Age

When patient age at the time of surgery was analyzed in terms of healing, there was a statistically significant difference ($P = .03$) in the rate of consolidation if the patient was younger than 50 years of age ($n = 16$ patients, 100% healed), in comparison with those 50 years or older ($n = 19$ patients, 73% healed). If 60 years of age was the benchmark, similar results were obtained. In fact, 96% of the patients younger than 60 years healed, compared with 64% of those older than 60 years; and this difference was also statistically significant ($P = .02$). Among the 6 patients who did not heal, the mean average age was 65 years, compared with a mean age of 50 years for those patients who healed their index operation ($P < .01$). Logistic regression showed that a 10-year increase in patient age statistically significantly decreased the likelihood of healing (odds ratio = 2.613); in fact, as age increased by 10 years, the risk of not healing doubled. Furthermore, 4 of the 6 patients who did not heal also had diabetes, and were older than 60 years, and this incidence of healing was statistically significantly different ($P < .01$) in comparison with that in the remainder of the cohort.

Table 2 depicts the proportion of cases of successful bone healing by surgeon, and for the overall cohort. The incidence of bone healing was not statistically significantly different ($P > .05$) based on the surgeon of record.

Discussion

The discovery of bone morphogenetic proteins has provided a stimulus for advanced methods in foot and ankle surgery. In particular, these substances lend promise to the increase in success rates for difficult-to-heal bone conditions of the lower extremity. Unfortunately, randomized controlled trials that attempt to demonstrate unequivocal efficacy of BMPs in the lower extremity do not exist. Further, the morbid consequences of failure in limb salvage surgery make such trials difficult. Yet, extrapolation of data from other anatomic sites to the foot and ankle may be logical, but even the existing clinical trials have not yet determined whether or not each different clinical indication requires a specific recipe of bone-enhancing substances for success or if a single pathway for stimulating bone healing is sufficient. In addition, the ideal carrier for delivery of these proteins to the biologic substrate has yet to be determined. Although beyond the focus of this study, it is possible that the optimal characteristics of the carrier in foot and ankle surgery may be different for specific clinical situations and/or different from those for other anatomic sites. These questions remain foremost in determining the ultimate clinical utility of BMPs.

The results of this study expose the substantial difficulty in stratifying clinical efficacy of BMPs in foot and ankle surgery, primarily because of the multiple variables related to each case, including personal preferences of each surgeon. In essence, the use of orthobiologic substitutes in addition to BMP was arbitrary in this investigation, but based on a zeal for a positive patient outcome in this very difficult and high-risk patient population. Furthermore, it is difficult to understand the meaning of the observed overall success rate of 32 unions in 38 cases (84.21%) because a comparable benchmark does not exist.

There were 3 statistically significant correlations within this series. First, it appears that the age of the patient at the time of the index procedure had a profound predictive value for healing. The concept of increased risk of nonunion as age increases is not particularly surprising and may reflect an overall alteration in the biologic capacity to heal. The exact role of BMP specific to the various age groups is unknown and requires further study, yet surgeons can appropriately advise patients of healing potential in this regard. Second, it was also expected that increasing age and diabetes would negatively impact the union rate. Four of the 6 failures occurred in diabetic patients older than 60 years. Although the distribution of our patients with the known risk factor of diabetes mellitus was equitable with respect to age, this trend may be a consequence of the relatively small sample size in each group. However, this finding does reinforce empirical observations of our collective clinical experience in taking care of this high-risk population. Understanding the potential effect of diabetes on increasing age, or vice

versa, on healing can be powerful knowledge when advising patients of their prognosis. Third, the observation of a draining wound in the postoperative period had a distinctly negative effect on overall healing. Five of the 6 failures had drainage from the wound, but 1 patient with 2 separate draining wounds accounted for 2 separate failures. The effect of infection on the mechanism and efficacy of BMP is speculative, but existing evidence suggests that there is no interaction (17–20). The number of infected cases in this study was small ($n = 6$), but two thirds of the cases went on to heal.

Relatively high doses of BMP are required to produce a clinically important effect. This raises some concerns regarding the cost and benefit. There are several questions that must be explored before one can calculate the cost-benefit ratio, including the following: (1) Will the operation fail without the use of BMP? (2) Will the cost of 1 dose of BMP exceed the cost of subsequent care if the operation fails? (3) Should surgeons be responsible for the socioeconomic impact of new technology, particularly when the psychological cost of failure of the contemplated operation may be devastating to the patient? Although we do not attempt to speculate on the impact of these issues, the overwhelming majority of our patients had at least 1 previous operation. By the time of the index operation, many of the patients had already undergone 2 or more operations. In those cases where BMP was used in the initial operative session, it was overwhelmingly an operation with a high failure rate such as an ankle fusion in a metabolically active Charcot, ankle fusions with sclerotic bone in the distal tibia, or large interfaces that were bridged with femoral head allografts. BMP was also used when the immediate cost of failure would be an amputation (1).

Perhaps the relatively small surface areas in the foot and ankle may be an advantage in that carriers to expand the volume and deliver the BMP may not be necessary. In addition, the very low nonunion rate of most closed fractures of the foot and ankle may preclude the use of BMP in primary trauma cases. Although BMP was not used in the acute traumatic setting in this series, it can be argued that it would hasten bony consolidation in complex fractures of the calcaneus or distal tibia that would ultimately shorten the period of non-weight bearing (17).

Like most observational studies, we realize that this investigation was limited by a number of methodological shortcomings. Key limitations included the absence of consideration of some clinical variables that could reasonably influence bone healing, such as smoking status, to name one. We feel, however, that the independent variables that we did analyze were important and commonly associated with failure to heal in the lower extremity. Moreover, we did not analyze the statistical significance of the influence that the particular surgeon had on the outcome. Furthermore, we did not undertake a sensitivity analysis to attempt to

determine the influence of unmeasured potential confounding variables. In addition, the operating surgeons interpreted the results of the radiographs to determine the primary outcome, and this may have imparted some bias. Last, we did not take into consideration the influence that data linked by patient (a single patient accounting for more than 1 case) and data linked by surgeon (several patients treated by the same surgeon) had on our outcomes.

Based on our experience with bone healing in complicated lower extremity cases, and our understanding of the literature related to the use of BMPs, we believe that more clinical studies need to be performed to refine the indications for the use of BMPs in the foot and ankle. When the mechanism of action becomes better understood and the delivery system improves, BMPs will likely become a more powerful tool for surgeons to use in the treatment of difficult clinical cases. Although there are ethical issues that impede more controlled clinical studies, the need to sort out the variables and determine the best recipe of bone-producing substances is evident.

In summary, based on the results observed in this investigation, bone morphogenetic proteins were used in a wide variety of high-risk clinical situations in the foot and ankle. The incidence of successful bone healing was 84.21% and required a mean of 14.25 weeks (range 8–30) in this at-risk cohort of patients. Analysis of the influence of multiple independent variables on bone healing showed that the collective healing rate statistically significantly deteriorated in patients older than 50 years, and statistically significantly worsened in those older than 60 years. There was also a statistically significant decrease in healing in diabetic patients and those diabetic patients who were older than 60 years. Finally, among a group of patients already at risk for poor bone healing, the presence of a draining wound had a profound adverse impact on bony union. We believe that the results of this retrospective cohort study can be useful to foot and ankle surgeons treating patients at high risk for complicated bone healing, and the results can also be used in the development of future prospective investigations dealing with bone healing following foot and ankle surgery.

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