BMP-7 Versus BMP-2 for the Treatment of Long Bone Nonunion

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The authors compared the results of treating nonunion with either bone morphogenetic protein (BMP)-7 or BMP-2. Between 2001 and 2009, 214 limb segments were treated for nonunion with either BMP-7 or BMP-2 at the authors’ institution. Sixty-three subjects received 76 units of BMP-7. Radiographic healing occurred in 70% of limb segments at an average of 30 weeks after surgery, and 75% of limb segments were weight bearing at an average of 23 weeks after surgery. In 15.8%, persistent nonunion necessitated additional surgery. Average follow-up was 32 months.

One hundred twelve subjects received 138 units of BMP-2. Radiographic healing occurred in 93% of limb segments at an average of 19 weeks after surgery, and 88% were weight bearing at an average of 15 weeks after surgery. In 6.25%, persistent nonunion necessitated additional surgery. Average follow-up was 17 months.

Several significant differences were observed. Patients in both BMP-7 and BMP-2 groups were able to fully weight bear at an average of 23 and 15 weeks, respectively (P<.001). Further, both BMP-7 and BMP-2 groups healed at an average of 30 and 19 weeks, respectively (P<.001). Additionally, healing occurred in more limb segments in the BMP-2 group (93%) than in the BMP-7 group (70%) (P<.001). No difference in the complication rate was seen between groups. Patients who received BMP-2 for the treatment of nonunion had a higher rate of radiographic healing, achieved radiographic healing more quickly, and were able to bear weight sooner than those who underwent treatment with BMP-7. [Orthopedics. 2014; 37(12):e1049-e1057.]

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In the United States, approximately 5% to 10% of fractures result in nonunion or delayed healing. Nonunion leads to a considerable economic burden, results in a large expenditure of healthcare dollars, and reduces the patient’s ability to be a contributing member of the workforce. Song et al compared the medical costs of tibial fractures in patients who healed normally and those who experienced nonunion and estimated that the annual incremental medical cost associated with fracture nonunion was $20,364 (P<.001).

Nonunion occurs most commonly in the tibia, but it also occurs in other long bones, such as the fibula, humerus, and femur. Many factors contribute to the development of nonunion, including nutritional or smoking status, diabetes, infection, inadequate fixation, vitamin D or calcium deficiency, the degree of initial bone defect and soft tissue destruction, and the use of steroids or nonsteroidal anti-inflammatory drugs (NSAIDs).

Because of the complex nature of nonunion, it is difficult to compare the modalities of effective treatment. The 2 governing principles in the treatment of nonunion are (1) achieving adequate stability with fixation and (2) improving bone biology. To improve bone biology, the surgeon should debride the bone ends until reaching clean, healthy, bleeding bone. The surgeon should also promote proper signaling with the use of bone morphogenetic protein (BMP) and create scaffolding for bone ingrowth with autograft or allograft. Autograft has been the gold standard for supplementing bone biology. It contains BMPs and the scaffolding needed for bone ingrowth.

Growth factors that are part of the transforming growth factor beta family, BMPs play a critical role during many processes, such as embryogenesis and skeletal formation. Kloen et al documented the relationship between BMPs and BMP inhibitors in bone callus and compared it with nonunion sites. The expression of BMP inhibitors was comparable between nonunions and fracture callus, but BMP expression was notably lower in the cartilaginous component of nonunions compared with fracture callus.

Several technologic advances in the isolation and production of 2 BMPs (BMP-2 and BMP-7) made it possible to augment the nonunion site and increase the local signals needed to initiate the cascade of bone healing. Both BMP-2 and BMP-7 have been shown to induce ectopic bone formation.

Several clinical studies showed the efficacy of BMP-7 alone in supplementing bone union compared with only autologous iliac crest bone graft. Jones et al reported the efficacy of using BMP-2 plus allograft compared with autograft alone for open tibial shaft fractures. Swiontkowski et al also showed the efficacy of BMP-2 compared with fixation alone in treating open tibial shaft fractures. In the current study, the BMP-2 group had statistically significantly fewer secondary bone grafting procedures as well as a lower rate of infection.

Giamnoudis and Dinopoulos recognized the clinical implications and adverse economic effect of nonunions and recommended the proactive use of BMPs in difficult cases (eg, persistent nonunion, bone loss, infection, unavailable or insufficient autograft). Dahabreh et al showed a 47% decrease in the cost of nonunion treatment using BMP-7 compared with all previously unsuccessful procedures (P=.001).

However, no previously published clinical reports compared BMP-2 with BMP-7 in the treatment of long bone nonunions. The current study compares the results of the use of BMP-2 and BMP-7 at a single center to treat complex nonunions caused by trauma, limb lengthening, and failed arthrodesis.

**Materials and Methods**

This study was approved by the authors’ institutional review board. The authors conducted a retrospective, sequential, nonrandomized study. The medical records and radiographs of 231 patients who received either BMP-7 (OP-1, Olympus Biotech Corporation, Hopkinton, Massachusetts) or BMP-2 (INFUSE, Bone Graft, Medtronic Sofamor Danek USA, Inc, Memphis, Tennessee) between 2001 and 2009 to treat nonunion were reviewed. During the study period, OP-1 was owned by Stryker (Kalamazoo, Michigan).

Written consent for the use of BMP-7 was obtained because it was indicated for use only as a humanitarian device for recalcitrant nonunions. Before BMP-2 became commercially available, BMP-7 was the only BMP available for several years.

All patients who received BMP-2 were also informed of its off-label use for the treatment of long bone nonunion.

Of 231 patients, 56 were excluded from this study because medical charts or radiographs were unattainable. The study included 214 limb segments (175 patients).

Nonunions occurred in the tibia in 78 cases, in the humerus in 70 cases, and in the femur in 66 cases. One hundred seventy-six limb segments originally had a closed fracture, 29 had an open fracture, and this information was not available for 9 limb segments.

One hundred fifty-four bones had a segmental defect, with an average length of 1 cm (range, 0.1-10.5).

Three senior surgeons treated the nonunions with a similar 3-part strategy: stable fixation, establishment of healthy bone ends, and autograft with either BMP-2 or BMP-7. The amount of autograft was not standardized, but at least 35 mL bone graft was harvested from the autograft site because that is the minimum requirement for the senior author to harvest. The BMP-2 dose was always that of the largest sponge because all nonunions occurred in long bones.

Patient data collected included age, sex, medical comorbidities, weight-bearing status, size and type of defect, source of bone graft, use of alcohol or NSAIDs,
smoking status, duration of follow-up, healing status, and time to healing. Adverse events and secondary interventions after surgery were also noted. Persistent nonunion was defined as failure, and refracture through the grafting site was considered an adverse event.

Secondary interventions included inserting secondary bone graft (with or without BMP-7 or BMP-2 supplements), dynamizing the hardware to promote bone healing, and using an external bone growth stimulator.

Radiographic evaluation included visual inspection of cortices on anteroposterior and lateral view radiographs. Radiographic healing was defined as 3 intact cortices. Nonunion was defined as incomplete union of 2 or more of the 4 cortices, with no progressive healing for 3 months.

Clinical documentation of healing was defined as the ability to fully bear weight without pain.

Statistical Methods

The authors used SPSS version 17.0 software (SPSS, Inc, Chicago, Illinois), to collect and analyze all data. Descriptive statistics were used to calculate mean and range. Differences between groups were evaluated with chi-square and Student’s t test for equality of means. A difference of less than 0.05 was considered statistically significant. Multifactor regression analysis was performed to estimate relationships among variables.

RESULTS

Results With BMP-7

Thirty-three women and 30 men (76 limb segments), with an average age of 46 years (range, 11-85), received BMP-7 (Table 1).

There were 33 tibiae, 23 femora, and 20 humeri. Eighteen percent (11 of 62 patients) were smokers, 8% (5 of 62 patients) reported using alcohol regularly, 15% (9 of 62 patients) were diabetic, and 11% (7 of 62 patients) had a history of long-term NSAID use.

Fifty-one percent of the limb segments (39 of 76) had a previous infection at the site of the nonunion.

Seventy-six units of BMP-7 were used in each of 63 patients. Eighty-three percent (63 of 76 limb segments) received autograft and BMP-7, and 17% received BMP-7 only (3 limb segments) or allograft plus BMP-7 (10 limb segments).

Twenty-five percent of limb segments (19 of 76) were treated with an adjunctive external bone growth stimulator. Patients were encouraged to use a bone stimulator as soon as possible postoperatively as an adjuvant to bone healing. This is standard care for nonunion at the authors’ institution.

Seventy percent of limb segments (53 of 76) achieved radiographic healing at an average of 30 weeks (range, 7-92) after surgery (Figure 1 and Table 2). Routine postoperative follow-up with radiographic examination was performed at standard intervals of 6 weeks, 3 months, 6 months, 9 months, and 1 year, with additional radiographic examinations based on necessity and the nonunion healing.

Seventy-five percent of limb segments (57 of 76) were full weight bearing, with the average time to weight bearing being 23 weeks (range, 2-54) after surgery.

Twenty-one percent of limb segments (16 of 76) were non-weight bearing because of insufficient healing, and 3% (2 of 76 limb segments) were non-weight bearing for other reasons (eg, problems with the contralateral limb, obesity). Ten patients (15.8%) had persistent nonunion that necessitated additional surgery. Four percent of limb segments (3 of 76) had a complication requiring additional surgery (Table 2). Average follow-up was 32 months (range, 2-73).

Results With BMP-2

Forty-eight women and 64 men (138 limb segments), with an average age of...
37 years (range, 2-79), received BMP-2 (Table 1). There were 45 tibiae, 43 femora, and 50 humeri. Of the patients, 22% (24 of 111) were smokers, 6% (7 of 111) used alcohol regularly, 12% (13 of 111) were diabetic, and 14% (16 of 111) had a history of long-term NSAID use. Thirty-seven percent of limb segments (51 of 138) had a previous infection at the site of nonunion.

One hundred thirty-eight units of BMP-2 were used in each of 112 patients. Eighty-eight percent (121 of 138 limb segments) received autograft and BMP-2, and 12% received BMP-2 only (14 limb segments) or allograft plus BMP-2 (3 limb segments).

Twenty-nine percent of limb segments (40 of 138) were treated with an adjunctive external bone growth stimulator. Patients who had the bone stimulator were encouraged to use it as soon as they received it.

Radiographic healing occurred in 129 (93%) of 138 limb segments at an average of 19 weeks (range, 2-53) after surgery (Figure 2, Table 2). Eighty-eight percent of limb segments (122 of 138) were full weight bearing (clinically healed) at the completion of the study.

The average time to weight bearing was 15 weeks (range, 0-53) after surgery. Seven patients (6.25%) had persistent nonunion that necessitated additional surgery. Seven percent of limb segments (9 of 138) were non-weight bearing for other reasons (eg, problems with the contralateral limb, obesity).

In 4.3% (6 of 138 limb segments), a complication occurred and required additional surgery (Table 2). Average follow-up was 17 months (range, 3-56).

**Combined Results**

Primary treatment was internal fixation in 144 segments and external fixation in 64 segments. There was insufficient information on fixation for 6 segments.

Thirty-two subjects, across both groups, had more than 1 surgical procedure for bone grafting. Seven patients (7 limb segments) received both BMP-7 and BMP-2 in the same limb segment during different surgical procedures. These 7 patients underwent treatment with BMP-7 and did not heal. They underwent treatment with BMP-2 at an average of 22 months (range, 6-57) after the initial treatment with BMP-7. After treatment with BMP-2, all patients healed at an average of 18 weeks (range, 10-22).

A significant difference was observed between groups in relation to weight-bearing status, time to weight bearing, rate of radiographic healing, and time to radiographic healing. More limb segments were weight bearing in the BMP-2 group (88%) than in the BMP-7 group (75%) ($P < .001$). Patients in the BMP-7 and BMP-2 groups were able to fully weight bear at an average of 23 and 15 weeks, respectively ($P < .001$). More limb segments healed in the BMP-2 group (93%) than in the BMP-7 group (70%) ($P < .001$). Additionally, the BMP-2 group healed more quickly than the BMP-7 group, at an average of 19 and 30 weeks, respectively ($P < .001$). Although not statistically significant ($P = .09$), the complication rate in the BMP-2 group was lower (9%) than in the BMP-7 group (17%).

More limb segments in the BMP-7 group (51%; 39 limb segments) had previous infection than in the BMP-2 group (37%; 51 limb segments) ($P = .049$).

A statistical difference in healing time was found between patients who had a previous infection (average, 25 weeks) and those who were infection-free before surgical intervention (average, 19 weeks).
When the authors compared the healing rate between groups only in patients who had a previous infection, 46 of 51 infected limb segments in the BMP-2 group achieved radiographic healing compared with 29 of 39 infected limb segments in the BMP-7 group ($P<.05$).

A multifactor regression analysis was performed to detect possible influences on bone healing, including age ($P=.24$), previous infection ($P=.16$), and amount of follow-up ($P=.60$). No statistical significance was found.

The BMP-2 group also had improved time to radiographic union, with a mean of 21 weeks (range, 2-53) vs the BMP-7 group, with a mean of 30 weeks (range, 9-70) ($P<.05$). In addition, 46 of 51 infected limb segments in the BMP-2 group and 34 of 39 infected limb segments in the BMP-7 group achieved full weight bearing at the conclusion of the study ($P=.51$). The BMP-2 group had a mean of 16.2 weeks (range, 7-49) to full weight bearing vs 23.6 weeks (range, 9-85) in the BMP-7 group ($P<.05$).

To exclude the influence of the location of nonunion on the result, the authors performed a subgroup analysis between the different limb segments and found no effect of the location of nonunion on time to bone healing or weight bearing (Table 3).

**Discussion**

The current study is the first to compare the clinical efficacy of the 2 available BMPs, BMP-2 and BMP-7, in the treatment of long bone nonunions. The study groups were treated sequentially because initially the only BMP available was BMP-7. All initially enrolled patients with nonunion therefore received BMP-7.

The study assessed known bone-inhibiting factors in 2 populations and found no statistically significant differences between groups regarding NSAID use ($P=.564$), smoking status ($P=.545$), alcohol use ($P=.665$), or diabetes ($P=.598$) (Table 1).

Two differences were observed in the demographic characteristics of the 2 groups. The first was the average age of the BMP-2 group, 37 years (range, 2-79), which is statistically significantly younger than the BMP-7 group (average age, 46 years; range, 11-85) ($P=.007$). Because it could be a confounding factor for the final result, the authors searched the literature on the influence of age on bone healing. They found no article comparing the healing rate in patients in their 30s vs patients in their 40s. Fischgrund et al\(^{10}\) showed that bone healing with distraction osteogenesis occurs more rapidly in patients younger than 20 years compared with patients older than 20 years, and patients between 20 and 29 years have been shown to have significantly faster healing rates than patients 30 years and older. Robinson et al\(^{11}\) showed that the risk of nonunion was significantly increased by advancing age in both diaphyseal and lateral third fractures of the clavicle.

The second difference noted was infection history. The BMP-7 group had a higher percentage of infections (51% vs 37%) ($P=.049$). When the authors compared healing time in patients who had a previous infection, a statistically significant difference was found in healing time between patients who had a previous infection (25 weeks) and those who were infection-free before surgical intervention (19 weeks) ($P=.02$). In this difficult population of infected nonunions, the BMP-2 group still had significantly better radiographic healing rates than the BMP-7 group ($P<.05$). The BMP-2 group also had an improved time to radiographic union, with a mean of 21 weeks, compared with a mean of 30 weeks in the BMP-7 group ($P<.05$). Seven patients who were treated unsuccessfully with BMP-7 underwent further treatment with BMP-2, and all went on to heal.

Most patients who received BMP-7 underwent treatment during the early years of the study. The humanitarian use

**Table 2**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>BMP-7 (n=76)</th>
<th>BMP-2 (n=138)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiographic healing</td>
<td>70%</td>
<td>93%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Healing rate, mean (range), wk</td>
<td>30 (7-92)</td>
<td>19 (2-53)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Full weight bearing</td>
<td>75%</td>
<td>88%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Time to full weight bearing, mean (range), wk</td>
<td>23 (2-54)</td>
<td>15 (0-53)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Non-weight bearing: insufficient healing</td>
<td>21%</td>
<td>5%</td>
<td>N/A</td>
</tr>
<tr>
<td>Non-weight bearing: other reasons</td>
<td>3%</td>
<td>7%</td>
<td>N/A</td>
</tr>
<tr>
<td>Follow-up, mean (range), mo</td>
<td>32 (2-73)</td>
<td>17 (3-56)</td>
<td>N/A</td>
</tr>
<tr>
<td>Compartment syndrome</td>
<td>1/1%</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Superficial infection</td>
<td>0</td>
<td>2/1%</td>
<td>N/A</td>
</tr>
<tr>
<td>Deep infection</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Malalignment</td>
<td>1/1%</td>
<td>1/&lt;1%</td>
<td>N/A</td>
</tr>
<tr>
<td>Amputation</td>
<td>1/1%</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Broken hardware</td>
<td>0</td>
<td>1/&lt;1%</td>
<td>N/A</td>
</tr>
<tr>
<td>Regenerate collapse</td>
<td>0</td>
<td>1/&lt;1%</td>
<td>N/A</td>
</tr>
<tr>
<td>Fracture after removal</td>
<td>0</td>
<td>1/&lt;1%</td>
<td>N/A</td>
</tr>
<tr>
<td>Total complications</td>
<td>3/76 (4%)</td>
<td>6/138 (4.3%)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*Abbreviations: BMP, bone morphogenetic protein; N/A, not applicable.*
of BMP-7 occasionally made it difficult to use because some insurance companies were unwilling to cover its high cost. Also, as BMP-2 became readily available, it was easier to use because the handling characteristics of the protein delivery system allowed more of the protein to stay at the site of nonunion compared with the powder form of BMP-7. In addition, humanitarian device consent was not required with BMP-2, but was required with BMP-7. Because of this inherent bias, the more difficult nonunions inadvertently may have been placed in the initial BMP-7 category.

The 3 senior surgeons had a similar treatment strategy for nonunions that emphasized stable fixation, healthy bone ends, and autograft with either BMP-2 or BMP-7. In a minority of cases, BMP alone or BMP plus allograft was used.

Ninety-three percent of the limb segments in the BMP-2 group showed radiographic evidence of healing at an average of 19 weeks (range, 2-53). This was significantly ($P<.001$) better than the finding in the BMP-7 group, which had a radiographic healing rate of 70% at an average of 30 weeks (range, 7-92). This statistically significant difference also resulted in weight bearing at an average of 15 weeks in 88% of limb segments treated with BMP-2 compared with weight bearing at 23 weeks in 75% of limb segments treated with BMP-7. These differences in time to radiographic healing and time to weight bearing are even more important when lost time from work and wages are considered.

The current study provides clinical support to the basic science data collected by Cheng et al$^{32}$ on the osteogenic activity of the various BMPs in vitro. These authors found that BMP-2 was more effective than BMP-7 and had greater osteogenic activity at the stem cell level. However, BMP-7 was more effective once the cells had differentiated into osteoblastic precursors.

Another study by Pountos et al$^{33}$ evaluated the osteogenic differentiation of mesenchymal stem cells from osteoporotic bone and documented equal osteogenic response with BMP-2 and BMP-7. They...
found that BMP-7 was far more effective in inducing the osteoporotic mesenchymal stem cells to proliferate.

Fajardo et al\textsuperscript{14} showed that BMP-2 was inactivated in nonunion tissue by high levels of 2 matrix metalloproteinases (MMP-7 and MMP-12). Another report\textsuperscript{15} found that BMP production is low in experimental nonunion models.

These findings provide basic science support to the clinical successes attributed to BMPs in treating nonunions and may help to explain the effectiveness of BMP-2 in the treatment of long bone nonunions in the current study.

The authors resected the nonunion tissue and then inserted BMP-2, which flooded the area with this type of BMP and might have overcome the high levels of MMPs in the tissue. Much remains to be determined about the biology of nonunions, the specific actions of each BMP, and the point in the cascade of fracture healing at which each BMP is maximally effective.

More clinical reports have been published on BMP-7 than on BMP-2. Friedlaender et al\textsuperscript{21} reported an 81% (51 of 63 limb segments) rate of healing in tibial nonunions with BMP-7 and an intramedullary rod vs 85% (52 of 61 limb segments) with autograft and an intramedullary rod at a follow-up of 9 months ($P=.524$). In this prospective, randomized study, BMP-7 was as effective as autograft. The BMP-7 group had a significantly greater number of smokers and atrophic nonunions. Desmyter et al\textsuperscript{30} in a study of 62 cases, attributed a 79.6% healing rate for tibial nonunion to the addition of BMP-7. Vaccaro et al\textsuperscript{30} found BMP-7 safe and effective for noninstrumented posterolateral spinal fusions.

Many of these studies limited the study populations and the location of the fracture or nonunion.

Ronga et al\textsuperscript{37} reported 105 extremity and clavicle nonunions and found that treatment with BMP-7 plus osteoconductive agents was as effective as treatment with BMP-7 and autograft (85.7% union vs 86.0% union). Giannoudis et al\textsuperscript{38} reported a 100% healing rate in 45 long bone nonunions treated with BMP-7 and autograft, but did not consider compromised host status (eg, smoking, diabetes); therefore, this study did not account for the most difficult cases.

The current study was not a prospective randomized trial with all variables under control; however, the authors did account for compromised host factors, such as smoking and diabetes. The authors took the most challenging sampling of patients with different nonunion locations and multiple medical comorbidities and found a healing rate with BMP-7 of 70% in 76 cases. Therefore, these results are slightly less favorable than what is reported in the literature.

The efficacy of BMP-2 for accelerating bone healing in open tibial shaft fractures was shown by Jones et al\textsuperscript{24} as well as Swiontkowski et al.\textsuperscript{25} In the study by Jones et al\textsuperscript{24} 30 patients were enrolled and randomly assigned to receive BMP-2 and allograft or autograft alone for subacute tibial shaft fractures with diaphyseal defects of 1 to 7 cm. In the autograft group, 10 of 15 limbs healed, and in the BMP-2 and allograft group, 13 of 15 limbs healed.

In the study by Swiontkowski et al\textsuperscript{25} open tibial fractures treated with BMP-2 and intramedullary nailing vs intramedullary nailing alone had a statistically significant faster fracture healing rate as well as a reduced risk of nonunion. The BMP-2 group also had a statistically significant decrease in infection after open fracture compared with the control group. Based on these 2 articles\textsuperscript{24,25} using BMP-2 to treat open tibial fractures and segmental defects results in significantly improved patient outcomes.

Several studies also documented the use of BMP-2 in the spine, noting superior fusion rates for lumbar fusion when comparing BMP-2 and bone marrow aspirate with allograft as an alternative to autograft.\textsuperscript{39} Rogozinski et al\textsuperscript{40} showed that BMP-2 is safe and effective in augmenting posterolateral lumbar spinal fusion when added to autograft. This study reported a healing rate of 100% in 16 patients.

Desai et al\textsuperscript{41} reported 9 recalcitrant tibial nonunions treated with BMP-2, intramedullary femoral autograft, and intramedullary nailing. These patients each had at least 4 previous nonunion surgical procedures. All 9 cases healed at an average of 27.6 weeks (range, 11-59).\textsuperscript{41} Bibbo et al\textsuperscript{42} published the results of 112 high-risk ankle and hindfoot fusions in 69 patients using BMP-2. In this study, 19% of patients had diabetes, 44% were smokers, and 68% had a history of high-energy trauma. Patients with infection were excluded. Of 112 fusion sites, 108 healed, for a healing rate of 96% at a mean of 11 weeks. This report showed the advantage of using BMP-2 to treat difficult foot and ankle arthrodeses.

The use of BMP-2 is approved by the US Food and Drug Administration for the treatment of open tibia fractures. It is

<table>
<thead>
<tr>
<th>Limb Segment</th>
<th>Average Time to Full Weight Bearing, wk (BMP-7/BMP-2)</th>
<th>Average Time to Full Bone Healing, wk (BMP-7/BMP-2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femur</td>
<td>21/18</td>
<td>34/20</td>
</tr>
<tr>
<td>Tibia</td>
<td>22/16</td>
<td>32/22</td>
</tr>
<tr>
<td>Humerus</td>
<td>31/13</td>
<td>27/18</td>
</tr>
</tbody>
</table>

Abbreviation: BMP, bone morphogenetic protein.
important to present the possible adverse effects of BMP. Woo et al. reported several adverse effects, including surgical site infection, heterotopic ossification, pseudarthrosis, and local inflammation, such as swelling and seroma formation. Almost 50% of these complications required additional surgery. Similar adverse events were reported in a study by Lyon et al. Tannoury and An reported adverse effects of BMP-2 in spine surgery, including antibody formation, nerve injury, heterotopic ossification, hematoma, and problems with wound healing. Special care is needed when using BMPs. These agents were approved for use in limited doses, but they are usually used at high doses and for other indications. Contact with neurovascular structures should be avoided. Caragee et al. found that a high dose of rhBMP-2 in spinal surgery was associated with an increased risk of new cancer.

The current study reports the largest series to date of long bone nonunions treated at a single center with BMP-2 and autograft in combination with viable bone ends and stable fixation. This study documents not only the safety of BMP-2 in long bone nonunions but also its effectiveness, especially when compared with BMP-7. The level of evidence for this study is III because it is not a prospective randomized, controlled study. It is difficult to conduct a prospective randomized, controlled study in such cases because of the many variables that contribute to nonunion. Many more studies, especially level I evidence-based clinical studies, need to be conducted so that orthopedic surgeons can critically evaluate the indications and clinical efficacy of BMPs for nonunion. More controlled comparison studies with BMP-2 and BMP-7 are also needed. Multicenter trials with careful control of every variable (eg, nonunion location, diabetes, smoking status) are necessary to allow further conclusions to be drawn. The safety of BMP-2 in children and pregnant women has yet to be determined.

**CONCLUSION**

The authors found that patients who received BMP-2 for the treatment of nonunion had a higher rate of healing, healed more rapidly, and were able to bear weight sooner than subjects who underwent treatment with BMP-7. The cost of administering BMP-2 to treat tibial nonunion ($5408) is negligible, considering the high annual incremental medical costs associated with tibial nonunion ($20,364).3

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