TITLE: Morphogenetic Bone for Fracture Healing: A Review of the Clinical-Effectiveness and Guidelines

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CONTEXT AND POLICY ISSUES:

Bone morphogenetic proteins (BMPs) are a group of about twenty proteins that are expressed during bone healing, and play an important role in new bone formation. BMPs induce the formation of new bone through multiple pathways. BMPs act as signaling agents and promote the migration of bone-forming cells (osteoblasts) into an area where bone needs to be repaired. As well, they bind to the surface of mesenchymal cells (undifferentiated cells that have the potential to develop into a number of different cells), which causes them to differentiate into osteoblasts. BMPs also help in the production of bone matrix and in vascularization.

Injured bone does not always heal as expected or within the anticipated time frame. Delayed union occurs when a fractured bone does not heal as quickly as it should, which occurs in 16% to 60% of fractures. If healing has not occurred within six months, it is termed a nonunion, which occurs in 4% to 10% of fractures. In these situations, a bone graft may be used as treatment to induce bone growth and healing. The gold standard for bone graft is autogenous iliac crest bone graft (AICBG) as it is histocompatible and non-immunogenic. However, there are some drawbacks of AICBG in that the amount of AICBG available is limited, particularly in patients who have had previous bone grafts. As well, complications at the site of bone harvesting are common. BMPs are an alternative to AICBG and there are two products currently available in Canada: recombinant human Bone Morphogenetic Protein-2 (rhBMP-2), which is marketed as the INFUSE bone graft, and recombinant human Bone Morphogenetic Protein-7 (rhBMP-7), which is marketed as the OP-1 (osteogenic protein-1) bone graft. rhBMP-2 and rhBMP-7 must be applied locally and retained at the site in order to be effective in producing new bone. To achieve this, carrier devices or matrices are used. For rhBMP-2 an absorbable collagen sponge is used, while rhBMP-7 uses a bovine collagen carrier in granular form.

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rhBMP-2 and rhBMP-7 are alternatives to AICBG in nonunion of the long-bones and may overcome some of the disadvantages of AICBG. Evidence of the clinical-effectiveness of BMPs and current guidelines about their use can help in inform policy decisions about these products and define their place in treatment. This report will review and summarize the relevant literature about the use of rhBMP-2 and rhBMP-7 for nonunion of fractures.

RESEARCH QUESTIONS:

1. What is the clinical-effectiveness of bone morphogenetic proteins for fracture healing?

2. What guidelines exist for the best use of bone morphogenetic proteins for fracture healing?

METHODS:

A limited literature search was conducted on key health technology assessment resources, including PubMed, The Cochrane Library (Issue 2, 2009), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international health technology agencies, and a focused Internet search. The search was limited to English language articles published between 2004 and June, 2009. Filters were applied to limit the retrieval to health technology assessments (HTAs), systematic reviews, meta-analyses, randomized controlled trials (RCTs), controlled clinical trials, and guidelines.

HTIS reports are organized so that the higher quality evidence is presented first. Therefore, HTA reports, systematic reviews, and meta-analyses are presented first. These are followed by RCTs, controlled clinical trials, and evidence-based guidelines.

SUMMARY OF FINDINGS:

From the literature search three relevant systematic reviews, one relevant meta-analysis, and one relevant RCT were identified in which the clinical effectiveness of BMPs was assessed in fracture healing. No relevant controlled clinical trials or guidelines were identified.

Health technology assessments

In 2007, Garrison et al. produced a HTA report with the objective of assessing the clinical-effectiveness and cost-effectiveness of BMPs in the non-healing of fractures and spinal fusion, relative to the current standards of care. For clinical-effectiveness, there was no restriction on study design as long as the study assessed BMPs for either fracture or spinal fusion. Healing rate, fusion rate, number of secondary interventions, adverse events, and quality of life were the outcomes of interest for clinical-effectiveness. A total of 53 clinical studies were included, 27 of which were in fracture healing (treatment of acute fracture or nonunion). Nine of the included studies for fracture healing were RCTs. The remaining studies were case series and case reports. Eight of the RCTs involved patients with tibial nonunions and one involved patients with scaphoid nonunions. The BMPs used in the nine RCTs were described as follows: rhBMP-7 (n=2), BMP-7 (n=4), rhBMP-2 (n=2) and BMP (n=1). One of the nine RCTs was carried out in multiple countries, which included Canada. In terms of quality, all studies were rated as low to moderate by the HTA authors.
Based on radiographic results, the HTA found that the union rate for nonunion of tibial fractures did not differ between patients who received intramedullary nailing with BMP or autogenous bone graft (OR = 0.82; 95% CI 0.25 to 2.64; p = 0.74) during surgery. In healing of acute tibial fracture, the union rate was higher in patients treated with BMPs (OR=1.65; 95% CI 1.12 to 2.45; p=0.01). For nonunion of fractures, the use of BMPs did not have a statistically significant effect (OR = 0.89; 95% CI 1.35 to 2.28; p = 0.81) on the number of secondary interventions required in one study. For acute tibial fractures, the need for secondary interventions was significantly reduced in patients treated with BMPs (OR=1.58; 95% CI 1.01 to 2.46; p=0.04). Data were not pooled for other endpoints such as time to healing, operating time, blood loss, and length of stay. Instead, a narrative analysis was performed and results for acute tibial fractures and nonunions were presented together. Time to healing, operating times, and lengths of stay were described as comparable for patients treated with BMPs and autogenous bone graft, whereas blood loss was lower in patients treated with BMPs. The authors stated that a lack of data impeded the ability to assess whether treatment with BMPs affected pain, the ability to weight bear, and the time at which patients could fully weight bear. For scaphoid nonunion, bridging of bone was greater in patients treated with BMPs after four weeks relative to autogenous bone graft, but the difference was not statistically significant at nine months post-surgery. At 24 months, all patients had good functional results, regardless of treatment. The authors concluded that the use of BMPs may eliminate the need for autogenous bone grafting, thus avoiding the costs and complications related to harvesting autograft. They further concluded that BMPs are more effective than the conventional intervention alone for successful union of acute tibial fractures, but that there was no evidence that BMPs are more or less effective than conventional treatment for tibial fracture nonunion. The authors of the report expressed concern there were differences in the baseline characteristics of patients in the treatment and control groups in a number of the included RCTs and that these characteristics could potentially affect healing and bias the results. Further, the included RCTs were of low to moderate quality according to the quality assessment performed by the authors of the HTA report and the length of follow-up in some studies may have been insufficient to assess some outcomes. Generalizability of the results may be limited by the fact that only one study included a Canadian site. As well, given that the analysis combined results for rhBMP-2 or rhBMP-7, it is not clear if the results are generalizable to either rhBMP-2 or rhBMP-7 alone.

In 2005, the ECRI Institute published an HTA report that evaluated rhBMP-7 for healing nonunion of tibial fractures. The purpose of the report was to determine if the OP-1 implant (rhBMP-7) resulted in better health-systems-related, radiographic, and patient-oriented outcomes than those of bone autografting in the treatment of nonunion of tibial fractures, and how the complication rates of the two techniques compared. An additional objective of the report was to assess the morbidity associated with bone harvesting. Studies were included if they were published as full reports in the English language, concurrently compared the OP-1 implant with autograft bone for the treatment of nonunion fractures of the tibia, had at least 10 patients in the treatment and control groups, reported health systems-related, bone bridging, or patient-oriented outcomes, scored greater than 2.5 on ECRI’s quality checklist, reported data from tibial nonunion fractures separately (if studies included more than one fracture type), and reported data from the OP-1 implant (if patients were treated with different morphogenetic proteins). Case reports, abstracts, letters, and foreign-language articles were excluded. For morbidity associated with bone harvesting, there was no restriction on study design, as long as the study reported on the occurrence of bone-harvest-site morbidities in at least 50 patients.

One study met the inclusion criteria. It was a RCT that enrolled a total of 122 patients with tibial nonunions for at least nine months with no evidence of progressive healing over the previous three months. Patients who did not require bone grafting or who had infections at the fracture
site were excluded. Shorter operating times, less blood loss, and shorter lengths of hospital stay were observed with the OP-1 implant compared to bone autografting, but differences were not statistically significant or clinically important. Differences in radiologic outcomes were not statistically significantly different, but according to the authors’ calculations the study had too few patients to adequately assess this outcome. The OP-1 implant was also found to be non-inferior relative to autografting for ability to weight bear nine months after surgery, pain on weight bearing nine months after surgery, and the mechanical complication rate. The rate of osteomyelitis was about seven times lower for patients who received the OP-1 implant than those who received autografts (p=0.002). Post-operative infection at the fracture site was also lower with the OP-1 implant compared to bone autografts. Eight studies met the inclusion criteria for assessing bone-harvest-site morbidities. These studies were part of a previously published systematic review. It was found that the major complication rate of bone harvesting (deep infections, nerve injuries, and deep hematomas) was 1% to 2% and that the rate of minor complications was 1% to 6%.

Overall, the authors concluded that very few outcomes favour OP-1 implantation over autogenous bone grafting, and therefore OP-1 could not be considered a replacement for autografting. However, the authors indicated that there was sufficient evidence to support the use of the OP-1 implant when prior attempts with bone autografting did not heal the tibial nonunion. When considering individual outcomes, the authors concluded that operative times and blood loss were reduced with the OP-1 implant. In terms of complications, it was concluded that OP-1 resulted in a lower rate of osteomyelitis and post-operative infection, but not in a lower rate of mechanical complications. The authors stated that no conclusions could be reached with regards to length of stay, radiologic outcomes, weight bearing, pain, and retreatment surgery rate. A major limitation to this report is that the findings were based on one RCT which included 122 patients. This could also affect the generalizability of the results.

In 2005, Ontario’s Medical Advisory Secretariat published an evidence-based review of the clinical efficacy of the OP-1 implant for long bone nonunion. Specific objectives were to summarize the safety and efficacy profiles of the OP-1 implant in the treatment nonunion and bone defects and to compare its clinical- and cost-effectiveness with the alternative technologies, in particular, autogenous bone graft. Studies that reported on the safety and effectiveness of OP-1 for the treatment of long bone nonunions and bone defects were included. Studies that compared the clinical outcomes of treatment with OP-1 in long bone nonunions and bone defects with other treatments were also included. There did not appear to be a restriction on study design, but studies were excluded if OP-1 was used for a different indication or the study focused on technical aspects of the OP-1 implant. Three relevant studies were identified; two were RCTs,8,9 and one of the RCTs assessed OP-1 in tibial nonunions8 (also included in the ECRI review and described previously). The other RCT assessed OP-1 in a collagen-based carrier compared to no treatment, collagen alone, or demineralized bone matrix (DBM) in bridging fibular defects made at the time of tibial osteotomy for deformity of the knee in 24 patients.9 The third study was an Ontario-based prospective pilot study that evaluated OP-1 compared to DBM or no treatment for recalcitrant long bone nonunions (tibia, humerus, femora, clavicle) in fifteen patients whose previous treatment had failed.10 This was a preliminary report in abstract form.

For fibular defects,9 radiological and DEXA (Dual Energy X-ray Absorptiometry) evaluation showed that bone failed to form in the group of patients who did not receive treatment (n=6). After 12 months, new bone formation with bridging occurred in four out of six patients in the DBM group, and 5 of the 6 patients in OP-1 group. The mean bone mineral density increases for the DBM and OP-1 groups were significantly greater than the group with no treatment (p =
0.001 and p=0.038, respectively). There was no difference in bone mineral density between the OP-1 and DBM groups. Results were not reported for the remaining six patients who were treated with collagen alone. The Ontario-based pilot study\textsuperscript{10} found that the long bone nonunion healed in 13 patients of the 15 patients (87\%) at a mean of 11 weeks postoperatively.

From the one RCT in tibial fracture nonunion,\textsuperscript{8} it was concluded that OP-1 was a reasonable alternative to autogenous bone grafting in the treatment of long bone nonunions. Limitations to this review include the lack of available evidence from which to base conclusions. As with the ECRI review, the findings were based on one RCT which could limit the generalizability of any conclusions. As well, it is not clear if the results would be generalizable to other long bones or if they would be specific to tibial fractures.

**Systematic reviews and meta-analyses**

In 2006, Swiontkowski et al.\textsuperscript{6} pooled results from two prospective RCTs with identical protocols in which rhBMP-2 was used to improve the healing of open tibial shaft fractures. One of the two studies took place in 59 trauma centres in 12 countries. The other study, the results of which were previously unpublished, took place exclusively in the United States. In the two studies, 510 patients with open tibial fractures were randomized to receive intramedullary nail fixation and routine soft-tissue management (the control treatment) or an absorbable collagen sponge impregnated with rhBMP-2 placed over the fracture at the time of definitive wound closure as well as the control treatment. Two different concentrations of rhBMP-2 were used in the original studies, but the authors of the meta-analysis chose only to include the group of patients who received rhBMP-2 at a concentration of 1.50 mg/mL (the FDA approved dosage) in the pooled analysis. Inclusion criteria for the original studies were not specified in the report, but patients who anticipated receiving planned bone-grafting as part of a staged treatment were excluded. The purpose of the pooled analysis was to perform two subgroup analyses. The first subgroup analysis included 131 of the 510 patients who had type-III open fractures, 65 of which were controls and 66 of which were treated with rhBMP-2. The second subgroup analysis included 113 of the 510 patients who underwent reamed intramedullary nailing (48 controls and 65 patients treated with rhBMP-2).

In patients with type-III open fractures, those patients treated with rhBMP-2 required fewer bone-grafting procedures (2\% compared to 20\% of controls; p = 0.0005), fewer invasive secondary interventions (9\% compared to 28\% of controls; p = 0.0065), and had a lower infection rate (21\% compared to 40\% of controls; p = 0.0234) than the control group. The average time to full weight-bearing was 95.1 days for the rhBMP-2 group and 126.6 days for the control group, but the p-value for this comparison was not reported. In patients who underwent reamed intramedullary nailing, differences between the control and the rhBMP-2 groups were not statistically significant for any outcome. The time to full weight-bearing was 83.8 days in the rhBMP-2 group compared to 80.4 days in the control group (p-value not reported). The authors concluded that the addition of rhBMP-2 to the treatment of type-III open tibial fractures can significantly reduce the frequency of bone-grafting procedures and other secondary interventions. One limitation to this meta-analysis was that it involved analyses of subgroups that were not specified a priori in the protocols of the original studies. Because of this, the authors felt that pooling the results of the two studies could lead to false positive results and that their results should be interpreted with caution. As well, this pooled analysis was based upon two studies, but it is not clear how these studies were identified. It is not known if other relevant published studies were available, but excluded. The authors stated that the use of reamed nailing differed across countries. Thus, it is not entirely clear of the results would be generalizable or relevant to the Canadian population.
Randomized controlled trials

In 2008, Ekrol et al. conducted an RCT to determine whether rhBMP-7 is an effective alternative to autogenous bone graft for healing symptomatic malunion after distal radial fractures. Thirty patients were randomly assigned to receive rhBMP-7 (n=14) or autogenous bone graft (n=16) harvested from the ipsilateral iliac crest. Surgery was performed by the senior author of the paper an average of 44 weeks after the original injury. Two different surgical techniques were used in the study because some patients experienced complications at the osteotomy site with the initial surgical technique. The first 10 patients (six in the autogenous bone graft group and four in the rhBMP-7 group) underwent non-bridging external fixation and the remaining patients (10 in each group) underwent internal fixation with pi-plate. Clinical, functional, and radiographical outcomes were assessed at regularly intervals up to 52 weeks post-surgery and were analyzed according to the surgical technique used. Outcomes included pain (evaluated using a 10 cm visual analogue scale), range of movement, grip strength, ability to perform normal activities of daily living (ADLs), and radiographic healing.

The study population consisted of 25 females and 5 males with a mean age of 60 years (range: 25 to 81). For the patients who had non-bridging external fixation, differences in radiological outcomes did not differ between groups, with the exception of healing time, which was 7 weeks on average (range: 4 to 12 weeks) for autogenous bone graft compared to 13 weeks (range 8 to 18 weeks) for the rhBMP-7 group (p=0.05). There were no differences in functional outcomes, pain, or ability to perform ADLs at 52 weeks. For patients who underwent internal fixation with pi-plate, the mean healing time was 18 weeks (range: 4 to 46 weeks) in the rhBMP-7 group compared to 7 weeks (range 4 to 13 weeks) with autogenous bone graft (p=0.019). As well, there was a difference in the proportion of patients who achieved partial union, with six patients in the rhBMP-7 group having partial union compared to 0 patients in the autogenous bone graft group (p=0.015). Differences between groups in pain, ability to perform ADLs, and functional outcomes were not statistically significant after 52 weeks. From these results the authors concluded that that in human metaphyseal bone, rhBMP-7 is less effective than autograft because rhBMP-7 did not confer the same stability as bone graft when used in conjunction with non-bridging external fixation, and when used with a pi-plate had a slower rate of healing than autogenous bone graft. Limitations to this study included its small sample size, which could affect the ability to detect statistically significant differences between groups and the generalizability of the results. A further limitation to this study was the switching of surgical techniques part way through the trial. The generalizability of the results may also be limited by the use of a single surgeon as outcomes may differ according to surgical skill.

Limitations

There were three relevant HTA reports, one meta-analysis, and one RCT that assessed the clinical-effectiveness of BMPs in nonunion of fractures or acute fracture healing. No controlled clinical trials or evidence-based guidelines for the use of BMPs in fracture healing were identified. Thus, there was some higher quality evidence available to answer the question of clinical-effectiveness, but some limitations to this evidence should be noted. Few studies met the inclusion criteria for the HTA reports; thus, the evidence base from which conclusions of the reports were drawn was limited. As well, most of the included studies had fewer than 150 patients and were of lower quality according to the authors of the HTA reports. Further, one of the three HTA reports assessed the efficacy for rhBMP-2 and rhBMP-7 combined. It is not known whether the results of this combined assessment of clinical efficacy would be directly
generalizable to either rhBMP-2 (INFUSE) or rhBMP-7 (OP-1) alone. The remaining two HTA reports focused specifically on rhBMP-7,\(^4\)\(^5\) as did the RCT.\(^7\) The meta-analysis that provided evidence of the efficacy of rhBMP-2 was in acute fracture healing, as opposed to nonunion.\(^6\) As such, most of the included studies on the healing of nonunion of fractures assessed the effectiveness of rhBMP-7. It is not known whether it is possible to generalize these results to rhBMP-2. Generalizability of the individual studies may also be limited by surgical skill and training, which may not be the same outside of the context of clinical trials. Different carriers can be used to apply BMPs. Outcomes could differ depending on the carrier used, which could impact the generalizability of the results. Finally, the majority of evidence was generated from studies of tibial fractures and may not be generalizable to other fracture sites.

**CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:**

Based on the available evidence, rhBMP-7 appears to produce similar results as autogenous bone graft in healing long bone fractures and may have a lower risk of osteomyelitis. Thus, rhBMP-7 may provide an alternative to autogenous bone graft in long bone fracture healing, particularly when autogenous bone graft fails to correct nonunion. Given that rhBMP-7 was not superior to autogenous bone graft for many outcomes, it could be premature to consider it a replacement for autogenous bone graft. Further, rhBMP-7 was inferior to autogenous bone graft in metaphyseal bone healing. The majority of studies were with rhBMP-7, and rhBMP-2 may provide similar results. As such, rhBMP-2 could be a reasonable alternative for nonunion of fractures and for healing acute type-III tibial fractures. Unfortunately, no guidelines were identified that could clarify the precise role of BMPs in fracture healing. The use of BMPs in fracture healing can potentially avoid the morbidity and costs associated with harvesting bone for autogenous bone grafts. As such, the cost-effectiveness of rhBMP-2 and rhBMP-7 may also be an important consideration in policy decisions about their adoption.

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