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PERSPECTIVES

The Role of BMPs in Current Orthopedic Practice

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Abstract

Bone morphogenetic proteins (BMPs) have been applied successfully in the clinic for the treatment of spinal fusion, fracture healing, and delayed and non-unions. Demographic data reveal that because of the steadily rising age of the population, complications related to the musculoskeletal system will increase during the coming years. Multiple *in vitro* and *in vivo* studies, as well as clinical trials, clearly show a strong osteoinductive effect of BMP-2 and BMP-7. In comparison to the "gold standard" autologous bone graft, BMPs seem to be as good as the iliac crest bone graft (ICBG) or even more effective, and the side effects are moderate. Today BMPs play an increasingly important role in orthopedic practice. Further improvement of application systems might lower the risk of side effects and could improve outcome parameters. *IBMS BoneKEy*. 2009 July;6(7):244-253.

Introduction

Bone morphogenetic proteins (BMPs), as members of the TGF-β superfamily, are known to have osteo- and chondro-inductive effects (1). After a landmark study in 1965 demonstrated that demineralized bone induces ectopic bone formation (2), twenty-three years passed before BMP DNA was isolated and the BMP proteins were expressed (1). BMPs have been investigated extensively, with multiple experimental studies demonstrating a strong osteoinductive effect (3). The clinical application of the BMPs, however, is restricted: BMP-2 is used for open tibial fractures and spinal fusion, while BMP-7/OP-1 is used for non-union with limited indication for spinal fusion (4).

During the last decades the development of new orthopedic devices has clearly improved outcomes in trauma and orthopedic surgery; however, a high rate of complications, often caused by biological reasons, remains. A literature review on tibial fracture healing revealed that 16.7% of patients showed delayed fracture healing or a non-union after unreamed tibia nailing, 11.8% developed a malunion, and 0.5% suffered from infections. Up to 23.1% of patients required an operative re-intervention (5). Aside from health-related problems for the patient, these complications can negatively affect the ability to work and result in social and economic problems; the costs for management of complications can increase dramatically, and the aging of the population predicted by demographic data will result in a growing burden of musculoskeletal disorders and complications. Hence, the World Health Organization declared 2000-2010 as the "Bone and Joint Decade" to create awareness, and to advance the understanding, of these problems through research in order to improve prevention and treatment.

Clinical Use of BMPs for the Treatment of Fracture Healing, Delayed Unions, and Non-Unions

Successful bone healing depends greatly on mechanical stability and can be enhanced by biophysical stimulation such as ultrasound, shockwaves, or electromagnetic

fields (6), or by biological substances like bone grafts, hormones or growth factors (7).

Hypertrophic non-unions can be treated with dynamization of intramedullary (IM) nails or a change of the primary implant used for fixation. However, the treatment of atrophic non-unions caused by biological reasons is very challenging. Re-operation with debridement of the atrophic tissue, restabilization and use of biological techniques, such as local application of stimulating factors, are often necessary. The combination of dynamic stabilization, osteoconductive scaffolds in combination with osteoinductive growth factors, and osteogenic cells could be a successful strategy for treatment according to the "diamond concept" (see below) (8).

BMP-2 and BMP-7 have received approval for restricted clinical use (4). In addition to spinal application (9;10), BMP-2 is approved for open tibial fractures (4) and BMP-7 is approved for the treatment of tibial non-unions (11;12) and has limited indication for spinal fusion. Nevertheless, both growth factors are often used "off label" to stimulate bone and defect healing in the upper and lower extremities (13;14) and also in craniofacial surgery (15). While the results are promising, the variability of the treatment strategies makes a comparison of the studies difficult and there is a substantial need for prospective investigations to define clear indications, the optimal timing of application, dosage and application technique.

The osteoinductive potential of BMPs is beneficial for atrophic non-unions resulting from biological problems, but it might also be useful, in some cases, for the treatment of hypertrophic non-unions that evolve from mechanical reasons. However, in both cases adequate osteosynthetic stabilization is fundamental. Users must realize that BMPs stimulate bone formation and do not compensate for an inadequate stabilization.

In a non-union situation, possible mechanical reasons must be analyzed and addressed; BMP application may happen either simultaneously or at a later time point. The treatment of atrophic non-unions is challenging and requires meticulous planning (13). All possible systemic and local reasons must be considered, especially vascular problems. In most situations, however, no obvious reason for failure can be detected. According to the "diamond concept," a simultaneous application of vital cells, *e.g.*, mesenchymal stem cells, might be necessary if the defect zone appears avital. Today most authors recommend a complete debridement of avital and necrotic material (14).

The treatment of bone defects and non-unions often requires the use of additional grafting material. Ideally the graft provides an osteoconductive structure and contains osteoinductive growth factors and osteogenic cells, and in addition, the material must be biocompatible and, if required, should be biodegradable and provide stability (16). Currently it is thought that only autogenous bone meets most of these requirements and therefore it is still considered the gold standard (17). The disadvantage of the use of autogenous material is the additional surgical intervention and the morbidity associated with the harvest procedure, including donor site pain, local infection and paresthesia, and in addition, the amount of bone available for autografting is limited (18-20). Consequently, there is increased interest in bone graft substitutes such as allogenous or xenogenous grafts, demineralized bone matrix and various synthetic materials (21-24). Osteoinductive factors can be applied exogenously to the materials.

For clinical use BMP-7 (Osigraft®, Stryker Biotech, USA) is available as 1 g lyophilized powder containing 3.4 mg eptotermin alfa with bovine collagen I and can be applied as a suspension. According to the manufacturer not more than 2 g (6.8 mg eptotermin alfa) should be applied per patient (European Medicines Agency [EMEA]). BMP-7 is often used in combination with resorbable synthetic carriers based on tricalcium phosphate (TCP). This combination can be applied directly into the defect or non-union after debridement (Fig. 1 and Fig. 2).

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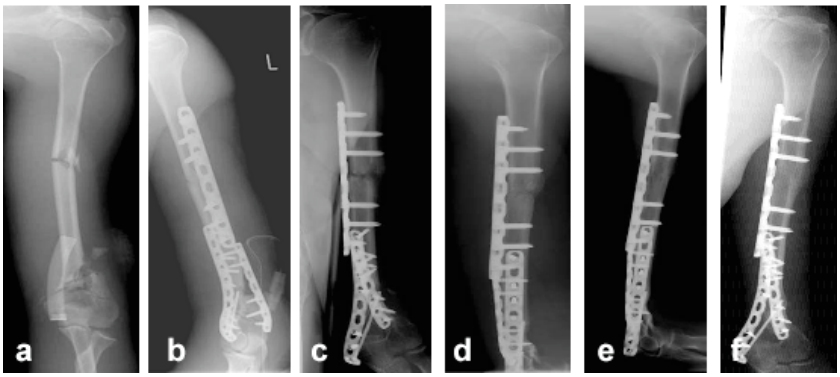

Fig. 1. A 25-year-old male with a 3° open complex humerus fracture after a working accident. a) complex humerus fracture; b) stabilization with locking compression plate (LCP) (Synthes, USA) and soft tissue coverage; c) 6 months after initial surgery; d) 3 months after debridement and application of BMP-7 + tricalcium phosphate (TCP); e) 6 months after debridement and application of BMP-7 +TCP (lateral view); f) 6 months after debridement and application of BMP-7 +TCP (a.p. view).

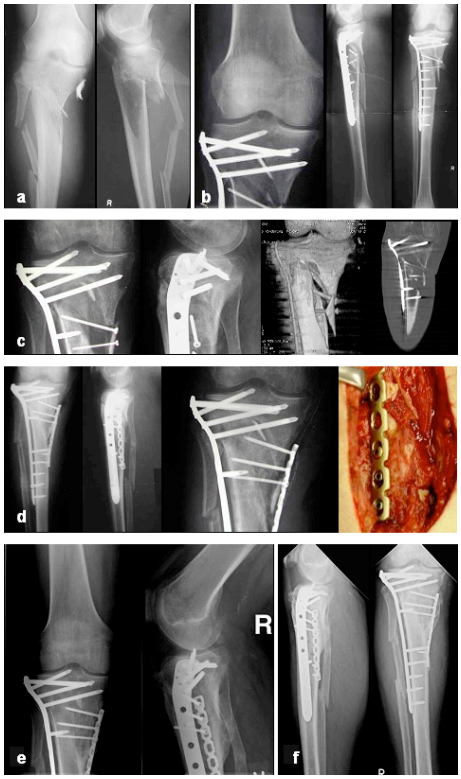

Fig. 2. A 63-year-old man with a 3° open tibial head fracture after a car accident. The fracture was treated in open reduction with an internal fixator (LISS) and gastrocnemius flap. a) Tibial head fracture; b) Stabilization with open reduction internal fixation (ORIF) and defect filling with autologous spongiosa; c) 8 months after initial surgery with atrophic non-union; d) Debridement and intramedullary application of BMP-7 + TCP and autologous spongiosa; e) 12 months after BMP-7 application; f) 18 months after BMP-7 application.

BMP-2 (InductOs®, Wyeth, UK) is available as a KIT containing 12 mg dibotermin alfa (1.5 mg/ml), which will be applied with bovine collagen I matrix. According to the manufacturer, no more than 24 mg dibotermin alfa should be applied per patient (EMEA). For acute fracture situations, BMP-2 should be applied periosteally surrounding the fracture zone. Today, BMP-2 is applied clinically using a bovine collagen sponge as a carrier. The positioning of this collagen sponge is often difficult and in some cases a secondary displacement has been noted. This can lead to ectopic bone formation in the surrounding soft tissue (25-27).

Clinical Use of BMPs for Spinal Fusion

BMP-2 is approved for anterior lumbar interbody fusion but also showed beneficial results in posterolateral, posterior and transforaminal lumbar application in multiple clinical studies.

An analysis of these studies in a total of 679 patients undergoing anterior lumbar fusion demonstrated benefit resulting from BMP-2 treatment in comparison to autologous bone grafting (28). Further clinical studies comparing BMP-2 with iliac crest bone graft (ICBG) for anterior interbody fusion supported these findings (29;30). In posterolateral lumbar fusion the use of BMP-2 was compared to the “gold standard” ICBG and showed in multiple studies a significantly higher fusion rate compared to controls (31-33).

For posterior interbody lumbar fusion, tapered titanium fusion cages with BMP-2 versus ICBG were compared and showed similar outcome scores. However, heterotropic bone formation was found in the spinal canal close to the loaded cage (34), demonstrating the importance of considering safety aspects when BMP is used in spinal fusion; BMP should not be applied too close to the spinal canal. Furthermore, a more controlled application system might reduce the risk of heterotropic bone formation.

Studies on transforaminal lumbar interbody fusion (TLIF) support this view. The use of BMP-2/ACS for TLIF was reported safe and effective when sponges were placed at a distance from the spinal canal (35-37). However, initial vertebral osteolysis (resorption) was found, which resolved radiographically after 3 months with complete resolution of symptoms (38). It must be considered that BMP-2 stimulates osteoblasts and also osteoclasts. Osteoclast stimulation is necessary for successful bone remodeling, however, this could be an explanation for the temporary implant loosening. This possibility must be considered when BMPs are used in spinal fusion and should be investigated in additional clinical trials.

Some studies have also shown that the use of BMP-2 for anterior cervical spine fusion is safe and effective (39). However, other studies describe a more frequent dysphagia in BMP-2-treated patients compared to controls (40). A transient, postoperative, soft tissue swelling has been described in cases with BMP-2 treatment for tibial fractures (41). Normally this swelling disappears without intervention after a few days. Further clinical studies addressing safety in anterior cervical fusion are necessary.

In a human study the safety and efficacy of BMP-7 were compared to autograft in patients who underwent posterolateral spinal arthodesis (42;43). A significantly higher posterolateral fusion was observed in the BMP-7 group compared to controls with a higher Oswestry score. No ectopic bone formation and no adverse events were found in the BMP-7-treated patients. In a larger randomized study, BMP-7 was shown to be statistically equivalent to ICBG in posterolateral single level fusion (44).

Additional Questions

Preclinical and clinical safety assessments have revealed little evidence of toxic effects and there have been few reports of adverse events such as ectopic bone formation, bone resorption, swelling and hematoma primarily in spinal application (10). A low rate of immunological reaction following administration of BMPs, resulting in antibody formation, has been observed in some patients, without clinical consequences, although the long-term implications of this finding are unknown (45). In a further study,

antibody responses to BMP-2 were detected in less than 1% of spine patients. For BMP-7 low immune responses have been observed in 38% of patients without clinical adverse effects (46).

Less information is available regarding how much of the applied growth factors binds to receptors of the effector cells. Controlled application techniques may increase the effect but lower the concentrations that are necessary to stimulate healing.

However, the number of patients studied thus far is too small to draw final conclusions on the optimum method of delivery and utilization of both BMP-2 and BMP-7, as well as the need for mixing them with the various volume extenders. Further clinical studies will have to address these questions.

BMPs can be useful at any time point where additive bone formation may stimulate the healing of bone. In complex fracture situations with large bone loss, soft tissue damage and periosteal destruction, BMPs might stimulate fracture healing and prevent delayed or non-union. It is still unclear if the growth factor should be applied at the time of acute trauma care or later, and it is also uncertain up to which size of defect can be treated successfully with BMPs. Here, too, further clinical trials will need to investigate both questions.

The use of BMPs is still an expensive treatment option. However, studies clearly demonstrate that the total treatment costs for non-unions using BMP-7 are lower compared to standard treatment (47). A cost-benefit analysis showed that, in the long run, the use of BMP-2 in open tibia fractures lowers the total costs from a health insurer's perspective (48).

Future Approaches

Current use of BMPs requires an open approach, and BMPs are applied in combination with collagen. Possible new application strategies might include the local and controlled injection of BMPs in combination with a synthetic carrier, especially in the treatment of delayed and non-unions. A rabbit osteotomy model demonstrated the efficacy of injected BMP-2 in combination with a calcium phosphate paste (alpha-BSM) (49). The injectable techniques are under clinical investigation but are not yet available in the clinic. Promising results were also obtained in animal models using different gene therapy approaches to deliver BMP vectors (50;51).

A further interesting approach might be the local administration of growth factors from coated osteosynthetic implants. This technique could reduce clinical problems in fracture treatment as it eliminates the need for exposure of the fracture; the need for implantation of further devices; the need for injections as the delivery method with the risk of infection; and side effects caused by the carrier. By using the implant coating the implants serve as fracture stabilization devices and as local drug delivery systems. A recently developed cold coating technique based on the polymer poly(D,L-lactide) (PDLLA) for orthopedic implants with growth factors for local protein delivery might fulfill these requirements (52). This application system was investigated in combination with different growth factors and showed efficacy on osteoblast- and osteoclast-like cells (53;54) and in different animal models by using different stabilization systems – IM nails, plates, or cages for spinal fusion. A significant effect on bone healing and spinal fusion was demonstrated (55-57). In the future, such bioactive implants could be used in difficult fracture situations in order to prevent delayed or non-unions.

Conclusion

BMPs have been used successfully for spinal fusion, fracture healing and the treatment of delayed or non-unions. Multiple *in vitro* and *in vivo* studies and clinical trials clearly show a strong osteoinductive effect. In comparison to the “gold standard” autologous bone graft, BMPs seem to be as good as ICBG or even more effective. However, there is a clear need for further clinical studies evaluating cost-benefit and long-term outcome parameters. The described side effects are moderate; however, further improvement of application systems might lower the risk of side effects

and improve outcome parameters even further.

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