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Autograft versus BMPs for the treatment of non-unions: What is the evidence?

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ABSTRACT

Autograft is considered the gold standard in non-union treatment. However, it is associated with significant morbidity and limited biological activity. The introduction of bone morphogenetic proteins (BMPs) has added a valuable tool to the surgeon's possibilities. The initial expectations of the effectiveness of BMPs were high, but over the years the union rate of BMPs was shown to be comparable with autograft. In this overview, both treatment modalities are compared. The off-label use of BMPs, the combination of BMPs and autograft, and the economic perspective of BMP use are summarized. In their current formulation, BMPs are an effective alternative for autograft in selected cases. The beneficial effect outweighs the economic costs. Widening of the indication to other long bone non-unions and new formulations are expected in the nearby future.

Introduction

Since the clinical introduction of BMPs their application has become more and more common in clinical practice. The registration of BMP-7 for tibia non-unions was based largely upon one of the first randomized clinical trials (RCT) on BMP-7, published more than 10 years ago.[1] The registration of BMP-2 for open tibial fractures was obtained after another RCT was performed on this subject[2] in the same time period. These registrations, supported by a large amount of pre-clinical data, marked a turning point in orthopaedics. Surgeons now had a biologically active specimen available on the shelf as an adjunct in difficult cases, and possibly the need for autograft and other adjuncts was minimized. The number of applied units has increased substantially over the past decades, and is still increasing. However, the largest number of units is applied off-label, in patients with complicated bone healing in long bones or pelvis.

As the BMPs are strong osteoinductive drugs, the initial expectations of the medical community were high. The negative effects of autograft, such as long term morbidity, limited biological activity, and availability[3] could be avoided, and the success rate of treating non-unions would be increased. Over the past decade, however, these expectations were lowered. Surgeons were still faced with challenging biological situations, where other aspects of the treatment strategy turned out to be equally important as the administration of exogenous BMPs.[4] Moreover, negative publications on the application of BMPs started to emerge. In spinal fusion, BMP associated radiculitis, ectopic bone formation, and neurological complications were described.[5] In periarticular administration, BMP-2 has recently been associated with increased heterotopic bone formation, leading to more reoperations in tibial plateau fractures.[6]

Concerns about the costs and effectiveness of BMPs in treatment of non-unions could influence their use for this indication. The aim of this overview is to describe the current evidence for the use of BMPs, especially in non-union treatment. Where possible, a comparison with autograft will be made.

BMP-7 or autograft in non-unions

In a non-union situation at first possible mechanical reasons have to be analyzed and addressed and BMP application may happen either simultaneously or at a later time point. The treatment of atrophic non-unions is challenging and it requires an exact planning.[7] All possible systemic and local reasons – especially vascular problems – have to be analyzed first. In most situations though, no obvious reason for failure can be detected. Today most authors recommend a complete debridement of the avital and necrotic material.[8] According to the "Diamond Concept"[4] a simultaneous application of vital cells, e.g. mesenchymal stem cells, can be considered in combination with revision of fixation material and application of exogenous growth factors, specifically BMPs.

The first randomized clinical trial (RCT) comparing the use of autograft and BMP-7 in non-unions was the trial published in 2001 by Friedlaender et al.[1] In this trial, tibial non-unions were randomized between standard of care combined with BMP-7 ($n=63$) versus standard of care with autograft ($n=61$). In the endpoints used for healing at 9 months (clinical and radiographic) no difference between the groups was found (81% vs. 85%, $p=0.524$,

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and 75% vs. 84%, $p = 0.218$, respectively). The authors also reported a rate of more than 20% chronic pain at the donor site in the autograft group. The conclusion of this study was that BMP-7 is a safe and effective treatment for tibial non-unions.

The results achieved in the study by Friedlaender et al. were later confirmed in other studies. In tibia non-unions, similar and even higher success rates were obtained by Zimmermann et al. in 2007,[9] Kanakaris et al. in 2008,[10] Calori et al. in 2008,[11] and others. The interpretation of these results is hampered by the design of these studies, or inclusion criteria, with the exception of the study by Calori et al.[11] In their RCT on long bone non-unions, tibia non-unions with the same definition as the non-unions in the trial by Friedlaender et al. were included: no healing during at least nine months after the fracture and no progress of healing during at least three months prior to inclusion. In this RCT, randomization between BMP-7 treatment and platelet rich plasma (PRP) took place. The success rate in the BMP-7 group was 87% and time to union was shorter than in the PRP group.

Off-label

BMP-2 and BMP-7 have received approval for restricted clinical use. Nevertheless both growth factors are often used "*off label*" to stimulate bone and defect healing in the upper and lower extremities,[7,8,12] but also in craniofacial surgery.[13]

Moghaddam et al.[14] recently published a study on 101 BMP-7 treatments in 101 non-unions of 98 patients. The average age of the patients was 50 years (18–88 years). Before BMP-7 application, patients had already underwent surgical treatement an average of 3.3 times (median 3, 1- to 13-times). BMP-7 was used "off-label" in all long bones. In 93 cases (92%), they observed proper bone healing. The average healing time was 4.8 months (range 1.5–11 months). The average time from injury to BMP-7 application was 18.4 months (3–84 months). In 65 cases, BMP-7 application was combined with re-osteosynthesis and autologous bone grafting. Serious side effects were not observed.

These and other results are promising, but due to the variability of the treatment strategies a comparison of the studies is difficult. There is a substantial need for prospective investigations to define a clear indication, the right timing of application, the correct dosage and application technique.

Economic perspective

The economic discussion on use of BMPs in non-unions is ongoing. Several studies on cost-effectiveness of BMP application have been published recently.[15,16] In their study on cost-effectiveness, Garrison et al.[16] evaluated fresh fractures, spinal fusion, and fracture non-unions. The conclusion of this publication was that cost-effectiveness in fracture non-unions was not clear, and that further research, including proper economic evaluation, was necessary. These findings are in line with another review by the same group on effectiveness of BMP treatment in non-unions,[17] although this review deals with all indications for both BMP-2 and BMP-7, and no proper economic evaluation could be performed on the available data. Another attempt for economic evaluation was done by Dahabreh et al. in 2007.[15] In their analysis, Dahabreh et al. compared the medical costs before and after BMP-7 administration, to find that the costs in persistent non-unions decrease dramatically after application of BMP-7. Before BMP-7 treatment, the total costs in treating non-unions are £13,845, and £7,338 thereafter. So far, the effectiveness of BMP treatment of non-unions has been demonstrated, and the cost-effectiveness is not clear. This should be one of the key issues in the BMP research area in the years to come.

Combination of BMP-7 and autograft

The treatment of bone defects and non-unions often requires the use of additional grafting material. In the ideal case the graft is biocompatible, provides an osteoconductive structure, contains osteoinductive growth factors and osteogenic cells, and in addition the material should be biodegradable and provide stability.[18] At the moment it is supposed that only autograft meets most of these requirements and therefore it is still considered the gold standard.[18] 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 paraesthesia; additionally the amount of bone available for autografting is limited[18–21] and the biological activity of MSCs in autograft decreases as the donor ages.[22] Still, some of the mentioned drawbacks can be overcome by adding BMPs to autograft, and as autograft is easily available, at least in the surgeon's perspective, the combination of BMPs and autograft is subject of several studies.

Recently, a retrospective analysis of 45 patients treated with both BMP-7 and autograft was published.[23] These patients underwent a mean of 2 prior operations (range 1–7), and the non-unions were located in long bones (seven humerus, 19 femur, and 19 tibia). All non-unions healed after a median of 5 months, with radiological union occurring after 6 months. Although the study design is not optimal, the results are very promising. Other studies have looked at the combination of BMP-7 and autograft as well, most with success rates higher than BMP-7 or autograft alone. The biggest disadvantage of this successful combination is that it still brings about the drawbacks associated with autograft harvesting. New harvesting methods, specifically the Reamer-Irrigator-Aspirator (RIA) system (Synthes, Davos, Switzerland), are designed to overcome these problems and may improve the results in this area significantly. Future research will evaluate this development.

Conclusions

After an initial promising start, second thoughts on the use of BMPs have emerged. Concerns about safety and costs have arisen, as well as the reality that the application of BMPs does not guarantee union in difficult cases. This implicates that BMP application is not the final solution in the challenging field of non-union treatment. Still, the introduction of BMPs has added a biological component to the treatment options available. Emerging evidence supports its use as an alternative for autograft, with at least comparable effectiveness and no harvesting morbidity. Also, economic evaluations show a favourable outcome. In the nearby future, ongoing evaluation will determine the true position of this adjunct in our treatment palette.

Conflict of interest

The authors have no conflicts of interest for this manuscript.

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