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TRAUMA SURGERY

Clinical application of BMP 7 in long bone non-unions

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Abstract
Background Non-unions of long bone fractures are a therapeutic and economic problem of increasing frequency. Aside from conservative treatment options such as ultrasound, impulse waves, and casts, the basic surgical options are autogenous cancellous bone grafting, rod dynamization, reamed nailing, plate fixation, and bone transport techniques. If these methods fail to work, there is a need for alternative treatment options.
Methods Since May 2001, treatment with recombinant human bone morphogenic protein 7 (BMP 7 or osteogenic protein 1) in combination with a type-one collagen carrier has been the subject of increasing interest. BMP 7 induces the formation of new bone by stem cell differentiation, thereby initiating the reaction cascade of osteogenesis. Non-unions over 9 months and unsuccessful bone grafting constitute the indication for this treatment.
Results We report our experience with 54 patients who had atrophic non-union of long bone fractures. Between May 2002 and May 2006, 57 units of BMP 7 were used. The localization of the non-unions included 21 in the femur, 26 in the tibia, 3 in the humerus and 7 in the forearm. In 36 cases, BMP 7 was used in combination with osteosynthesis revision and bone grafting; in 9 additional patients, BMP 7 was used with bone grafting alone. In 12 patients, BMP 7 was applied as a single procedure without any bone grafting or any change in osteosynthesis.
Conclusions There were no perioperative or postoperative complications. Follow-up was obtained for a minimum of 6 months. 47 of the 57 (82%) implantations were successful, with bony healing confirmed by clinical and radiological evaluation. In summary, our results support BMP 7 as an additional innovative therapy for long bone non-unions.

Keywords Bone morphogenetic protein 7 · Fracture healing · Non-union · Osteoinductive materials · Pseudoarthrosis

Introduction

Physiological healing of fractures is a complex process and involves an interplay of multiple biomechanical and biological factors [32]. In about 10% of cases [11], the healing process is delayed; for certain at-risk patients, this number rises to over 30% [35]. The system balance is very fragile and, in accordance with its complexity, can be disturbed on numerous levels. Because fractures in older patients, who are at risk for the development of pseudoarthrosis, are expected to increase by 300% in the next years, treatment of delayed fracture healing is immensely important on an economic level [31].

Established and epidemiologically probable causes for delayed fracture healing are systemic deficits, e.g., advanced age of patient [38], nicotine abuse [5], undernourishment or malnourishment [12], anemia [35], diabetes mellitus [27], and hormonal deficits [40]; prior local impairment of the extremity, i.e., chronic impairment of the soft tissue or the blood circulation [36], local adiposity [21], and reduced oxygen saturation [20]; and characteristics

The protocol was formally approved by the ethics committee of "Landesärztekammer Mainz".

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of the traumatic impact itself, i.e., fracture localization [13, 17, 25, 29, 39], degree of soft tissue damage [4], and neural damage [23]. Other factors may also pertain to the therapy of the fracture, such as frequent lavage [20], size of the fracture gap [7, 14], and stability and exposure of the fracture [2, 41]. Relevant pharmacological variables include corticosteroids [9], heparin [37], non-steroid antiphlogistics [1], ciprofloxacin [20], and nicotine abuse [8, 10, 24, 29].

Non-operative treatment options have included ultrasound since 1983 (micromechanic cell pressure with a success rate of 80%), impulse wave since 1988 (selective destruction of the osteocytes with a success rate of 50%), and magnetic field therapy since 1973 (changing the membrane load of cells). All these options have a high success rate, but are applicable only to the small number of patients with stable osteosynthesis and without infection. Moreover, there has not yet been a prospective randomized trial for this treatment.

In most cases, the therapy for delayed or non-union fractures is often satisfactorily achieved with conventional surgical methods (e.g., dynamization of a nail, changing osteosynthesis using a reamed nail or plate, and, of course, autologous bone). If these methods have no effect, more intricate surgical techniques must be considered, such as segmental resection or segmental transport, which are accompanied by a correspondingly higher risk for complications [3, 6].

The substantial number of patients for whom even these methods fails to achieve bony consolidation and healing poses a problem. Often, complications occur because of the high number of follow-up surgical interventions, especially for autologous bone transplantation, where donor site morbidity rates reach up to 30% for minor complications such as pain and up to 10% for major complications such as nerve palsy and infections [3]. Moreover, the success rate of autologous bone grafting varies from 50 to 80% in the literature. The socio-economic consequences of the resulting long-lasting suffering and inability to work are enormous. For the last few years, local or systemic growth factor therapy has been gaining attention. The BMPs belong to the super family of the "transforming growth factor β" (TGF β) and, like other cytokines, seem to play a major role in controlling fracture healing [22, 42, 44]. The osteoinductive effects of BMP 7 established in animal experiments may also be able to demonstrate in human patients with delayed fracture healing [15, 19].

The exact mechanism behind the effects of BMP 7 is currently being investigated and is not yet precisely understood. From what is known currently, BMP 7 seems to increase the activity of the osteoblasts and the infiltration and differentiation of stem cells locally. In addition, a gene expression study following application of BMP 7 was able to show that several other osteogenic growth factors are expressed and thus a chain reaction toward fracture healing initiated [43].

Since May 2001, implanting BMP 7 at the tibia has been available as a licensed treatment in Europe. In its pharmaceutical form, one implantation unit of BMP 7 consists of 3.5 μg protein powder attached to 1 mg collagen 1. Prior to implantation, the unit must be enriched using 3–5 ml of either the patient's blood or a saline solution to attain a consistency comparable to wet sand.

As the amount of implanted protein exceeds the normal physiological existing concentration in the fracture area by far, no increased effectiveness can be expected from using a higher local dose. The legal maximum dose consists of two simultaneously implanted units of BMP 7.

In the licensing study, the same osteoinductive effect was demonstrated for BMP 7 and an autologous bone graft [15]. Moreover, clinical and animal experimental studies indicate the superiority of BMP 7 in patients at risk due to nicotine abuse. Additionally, rates of infection and osteitis are reduced when implanting BMP 7 as compared to an autologous bone graft, and complications associated with bone grafting at the donor side are avoided.

Possible side effects include local erythema and swelling, heterotopic ossification and immune reactions. The use of BMP 7 is contraindicated in children and patients who are pregnant have autoimmune deficiencies, or are on immunosuppressive regiments. So far, no grave complications have been reported. However, the use of the therapy off-label (i.e., in locations apart from the tibia) places responsibility with the executing surgeon.

In our prospective study, BMP 7 is used mostly on therapy-resistant patients, where multiple previous attempts to treat the fracture have failed. Due to the one-time high costs of BMP 7, routine administration is unfeasible.

In the following paper, we report our experiences with 54 patients showing delayed unions in long bones treated by in our clinic local implantation of BMP 7 between June 2002 and June 2006.

Materials and methods

Fifty-seven units of BMP 7(OP-1, Osigraft®) were implanted in 54 patients in our hospital between June 2002 and June 2006. The following inclusion criteria were applied:

- no bony consolidation visible on CT scan or conventional tomography 4 months after the last surgery,
- at least one failed autologous bone graft transplantation, and
- limited bone defect (<1.5 cm).

We used BMP 7 for all long bones of the extremities. At the time of BMP 7 implantation, all patients had already undergone several surgeries. There had been up to seven prior

surgeries, of which only major procedures and bone transplantations are considered here (Fig. 1). Forty-five of the 54 patients had had more than one prior surgery. Nine of these patients had been treated permanently in our clinic. Six of those were treated with one dose of BMP 7 each after the first failed autologous bone graft, and three received an additional re-osteosynthesis procedure prior to the failed autologous bone graft.

At the time of the BMP 7 implantation, all patients showed no signs of infection. The mean age was 45 years (range 23–75); the male–female ratio was 4:1. All patients remained in our consented clinics. Radiographies were performed at 3, 6, and 9 months and, if necessary, tomography or a CT scan was taken to verify bony consolidation. Union was considered the ability to be full weight-bearing without pain and the presence of bridging cortices in two views of conventional radiographs or CT scans. In the case of off-label use of BMP 7, the patients were informed and had to sign a consent form.

Not more than two units of BMP 7 were used at any one surgery. The BMP 7 was applied as the last step before closing the skin and was covered with a collagen sponge to prevent its distribution in the surrounding tissue (Fig. 2a). Drains were only used subcutaneously.

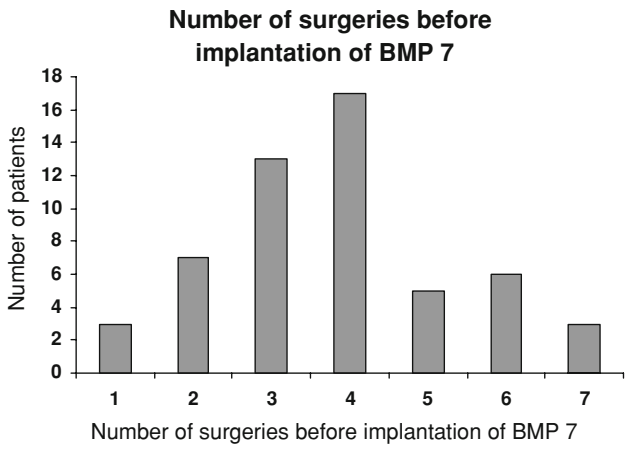

Fig. 1 In up to seven incidences, patients had unsuccessful procedures before implantation of BMP 7 was performed

Results

A total of 54 patients received 57 units of BMP 7 at 57 different sites. Three patients with a non-union in two different long bones received one unit of BMP 7 at each bone site. In two of these three cases, bilateral distal femur fractures had not healed following plating, re-osteosynthesis, and an autologous bone graft. In one incidence, a combination of a non-healing distal tibia fracture and a proximal humeral fracture was treated simultaneously with two units of BMP 7 after failed autologous bone grafting.

Twelve implantations were carried out without additional autologous bone grafting or changes to the osteosynthesis. In these cases, the only procedures performed were debridement of the non-union, and BMP 7 implantation (Fig. 3). In this subgroup, bony consolidation of the fracture was achieved in 11 cases after 5 months. Figures 2, 4, and 5 exemplify three of these cases. Another nine patients with large bony defects (more than 5 cc^3) were also treated without re-osteosynthesis, but with additional autologous bone grafting. In all but one of these nine cases, healing was accomplished within 4 months. Besides autologous bone graft and BMP 7 implantation, re-osteosynthesis was done in 36 cases. In 23 of these cases, loosening of the implant, breakage of the screws, and dislocation of the fragments required revision of the implant; in the remaining 13 cases, implant failure occurred. In 28 of the 36 cases, the fracture was successfully consolidated in 4.7 months. The average healing time for all 57 cases was 4.8 months (range 2.4–5.6).

Postoperative complications did not occur. In particular, heterotopic ossifications could not be identified in the radiographic follow-up until complete healing. However, a prolonged swelling of the implantation area, especially in the distal tibia, was apparent, yet did not lead to a revision

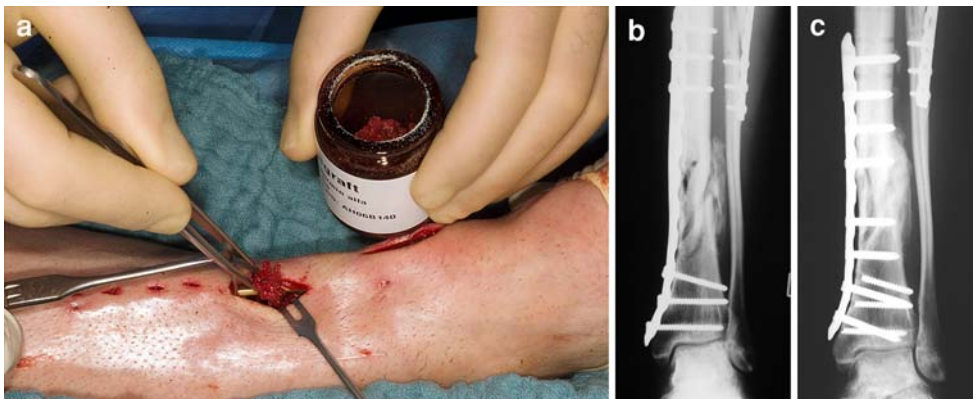

Fig. 2 Autologous bone graft is added to BMP 7 (**a**), then implanted in the defect after re-osteosynthesis is finished (**b**). Postoperative swelling and redness 10 days after implanting BMP 7 is quite usual. Five months after implanting BMP 7, the non-union shows bony consolidation and good remodeling (**c**)

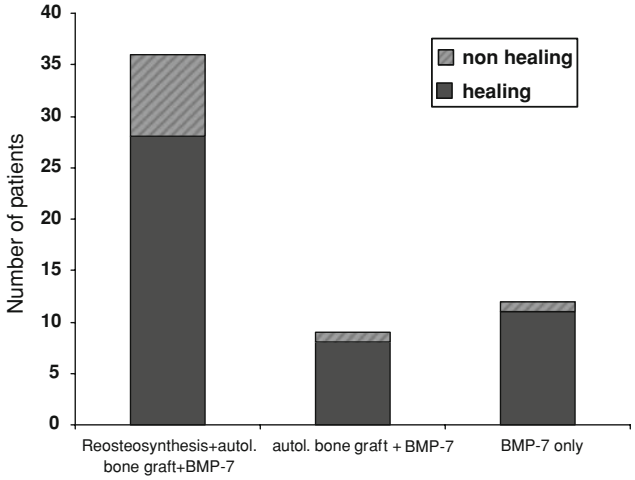

Fig. 3 In 12 cases, BMP 7 without any osteosynthesis changes or additional implantation of autologous bone grafting was performed. Additional bone grafting was done in the case of bony defects; in case of loosening of the implant, re-osteosynthesis was the method of choice

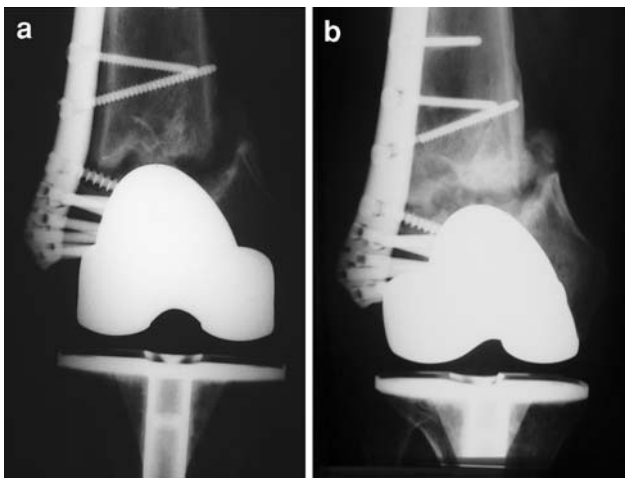

Fig. 4 After two failed autologous bone grafts and a broken plate, BMP 7 was implanted without changing the plate or additional bone grafting (**a**). Six months later, the non-union showed bony consolidation in this 50-year-old man (**b**)

in any case. Forty-one out of 54 patients showed risk factors for delayed fracture healing. Thirty-one patients were heavy smokers, consuming an average of about 20 cigarettes a day for a period of longer than 10 years; nine additional patients suffered from diabetes mellitus (insulin-dependent in four cases). Ten patients were permanently medicated with non-steroid antiphlogistics (all because of persistent pains from their pseudoarthroses).

Discussion

The osteoinductive potency of BMP 7 has been unambiguously demonstrated in vitro and in animal experiments.

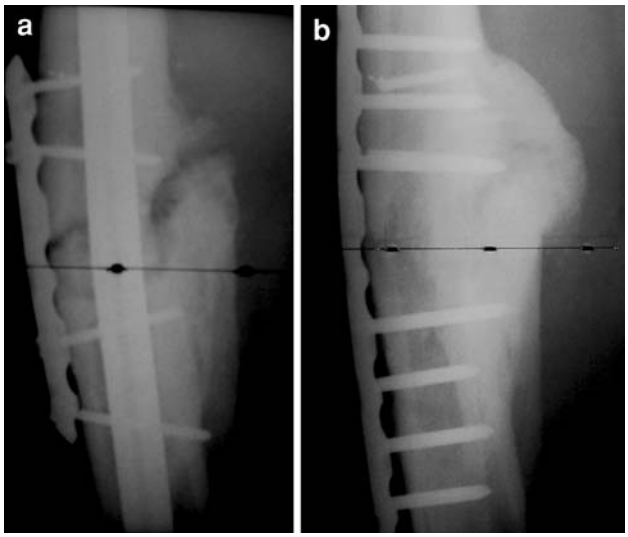

Fig. 5 After unreamed nailing of the fracture, two procedures for non-union fractures were done: first, reamed nailing, and second, autologous bone grafting and anti-rotation plate implantation (**a**). Next, BMP 7 without additional autologous bone grafting in combination with plating showed regular healing over a period of 5 months (**b**)

However, it has to be kept in mind that animal models cannot reflect human in vivo situation. In addition, those animals had not undergone prior surgeries; generally did not feature other comorbidities, soft tissue damage, or pre-existing osteoporosis over months; and were frequently adolescents with a high healing rate. Moreover, different animals have shown completely different healing tendencies for identical fracture patterns. Nor are the pharmacokinetics, i.e., whether growth factors are released faster or more slowly in humans, clearly understood [26, 30]. Furthermore, fracture healing is known to be a complex process varying from patient to patient influenced by many factors, only some of which have been identified.

Regarding the use of BMP 7, there has been one prospective, randomized and partially blinded clinical study investigating 122 patients treated over a time span of 7 years in seven different trauma centers in the USA. Criteria for inclusion in this study included a tibial pseudoarthrosis at least 9 months old, and a surgical technique of intramedullary nailing and autologous bone grafting. The control group received the same intramedullary nailing; however, they were administered BMP 7 instead of spongiosa. Success was evaluated using the clinical criteria of painless full weight-bearing status and radiological consolidation at 9 months after treatment. In the autologous bone grafting group, the success rate was 84%, compared with 75% for the BMP 7 application. However, this difference did not reach statistical significance ($P = 0.218$). In the subgroup of patients with nicotine abuse, BMP 7 showed a markedly higher success rate compared to autologous bone grafting. Also, the frequency of infections was lower in the

group administered BMP 7. Because these were not the criteria the study was designed to evaluate, the results cannot be interpreted as significant [15].

Another prospective, randomized, and double-blinded study was carried out with high tibial and fibular osteotomies. Three groups of six patients each was treated for fibular osteotomy, with BMP 7 plus a collagen carrier (Group 1), demineralized bone matrix (Group 2), or only the collagen carrier (Group 3). Following the application of BMP 7, bony consolidation was visible in five out of the six cases and in four out of six cases following demineralized bone matrix as assessed after 10 weeks. No bony consolidation could be diagnosed following collagen carrier treatment only [16].

A review of the clinical application of BMP 7 was recently published in England. In 60.5% of the documented 653 cases, the indication given was non-union. In 74% of the cases, additional autologous bone grafting was administered, and in 23% of the cases, BMP had been implanted without bone auto-transplantation. The cases healing radiologically and clinically without further measures were considered successful; the success rate by those parameters was 82% [18].

Other clinical follow-up studies also show a success rate as high as our study [28, 33, 34, 45].

In contrast to these clinical studies, the cases we treated can be considered to be negatively selected, i.e., the situation was far more complicated. For nearly all of our patients, not only had previously attempted autologous bone grafts failed, but also much more intricate osteosynthesis techniques had failed. Under these conditions, fracture healing was achieved in 47 of 57 cases after implanting BMP 7.

With regard to how much BMP 7 caused the definitive consolidation in every case, this cannot be evaluated by means of this particular follow-up study. However, in 11 cases, sole implantation of BMP 7 without other measures was successful. In these cases, connective tissue was removed with bone debridement.

Regarding indications for use, it is noteworthy that because BMP in the licensing study was implanted only at the tibia, the European license is restricted to this area, while in the US and Australia, BMP 7 is licensed as an implant, not as a drug, and thus may be used on all bones. In Europe, usage in parts other than the tibia is referred to as off-label use.

These criteria allow some room for interpretation and physician decision to identify the indications for other sites. In the end, the attending physician must offer his patient the best possible therapy while at the same time facing the possible consequences of personal financial accountability. Thus, there is considerable legal uncertainty.

From a financial point of view, the cost for one unit of BMP 7 is much higher than that for autologous bone grafting. Unfortunately, however, there are no valid data on the costs of autologous bone transplantations. Estimates for mere surgical costs begin at 500 Euro for the procedure and rise to 4,000 Euro considering follow-up costs and complications necessitating further treatment.

Disregarding the legal and financial aspects, it must be concluded that BMP 7 therapy is clearly advantageous. In contrast to autologous bone grafting, there is no donor morbidity and the risk for infections is markedly lower, while at the same time the effectiveness for patients at risk is higher.

Conclusions

BMP 7 is an innovative option in treating therapy-resistant non-unions. Its usage is safe and has so far not resulted in any complications with any of our patients. Based on our clinical cases, it can be assumed that BMP 7 is at least comparable to autologous bone grafting and might be superior in multiple failed cases where autologous bone grafting shows success rates lower than 80%, such as 60–80%. Especially, when judging the outcomes of patients solely receiving BMP 7, i.e., no additional autologous bone grafts or changes in osteosynthesis, a positive therapeutic impact for this cytokine can be assumed.

However, BMP 7 cannot be effective if there are an insufficient number of stem cells. The goal of reaching bony consolidation of a non-union can only be facilitated by BMP 7 on the basis of precise surgical technique.

Because BMP 7 was successful in 82% of our patients with therapy-resistant non-union, BMP 7 should be perceived as a therapeutic option that, given specific indications, patients should not be denied.

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