The use of recombinant human bone morphogenetic protein-2 for the treatment of a delayed union following femoral neck open-wedge osteotomy

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Abstract

Although the clinical potential of bone morphogenetic proteins (BMPs) has been known for decades, their use in humans has only been approved for a limited number of orthopaedic conditions. Promising results in animals demonstrate the utility of BMP-2 in regional bone repair without using osteoconductors. To our knowledge, no comparable human case has been described. We report the case of a 50-year-old man who suffered a femoral neck fracture. After 9 months of extensive treatment, he was still not pain-free. The following open-wedge osteotomy resulted in a therapy-resistant delayed union. We therefore conducted 4 computer tomography-guided injections of recombinant human (rh) BMP-2 into the bone gap. No osteoconductor was employed. Six weeks later, there was a 55-60% defect filling. Follow-up examination showed a complete union of the bone defect. Our case report shows that in a complicated delayed union rhBMP-2 can be successfully used to induce bone formation without any osteoconductor.

Introduction

Femoral neck fractures (FNF) belong to the most frequent fractures in patients of all ages. In younger patients (<55 years), internal fixation, e.g., by hip-screws, is preferred, while arthroplasty is commonly used in older patients (>70 years).¹ Although the vast majority of human fractures show normal bone healing, approximately 5% per year do not heal and are to be classified as delayed or non-unions.²,³ Delayed and non-unions constitute an obstacle in the treatment of bone defects, since they usually cause pain and possibly result in limb length differences, potentially leading to avascular necrosis and a severe loss of function.¹ Intervention is therefore inevitable: although surgery using internal or external fixation combined with (autologous) bone-grafts is still considered the gold standard in the treatment of non-unions, extracorporeal shock-wave therapy (ESWT) and osteotomy are also said to result in useful outcomes.⁴,⁵ Trochanteric open-wedge osteotomy is invasive in nature and therefore associated with the common operative risks. In addition, the procedure itself can foster trochanteric non-unions.⁶ The advantages of ESWT are its non-invasiveness and low rate of complications.⁷ Results on its efficacy, however, are still controversial.²,⁵ In autologous bone-grafting, there is only a limited quantity of bone available to harvest and the procedure is also associated with significant complications, such as persistent donor-site pain, local infection and paresthesia.²

Recently, bone morphogenetic proteins (BMP) have become available to enhance bone repair. BMP-2 and BMP-7 are supposed to have the greatest osteoinductive capacity both in animal and in human trials. However, little is known about long-term effects, and to date, the use of BMPs in humans has only been approved for the treatment of a limited number of orthopaedic conditions.²,⁸ The benefits of BMPs in the treatment of delayed and non-unions remain unclear.⁹,¹⁰ One of the clinical challenges in the use of BMPs is to transport the growth factors to the bone repair-site and to maintain a sustained, therapeutic concentration at repair site, high enough to evoke an adequate osteoinductive reaction.¹¹ In animal trials, there have been first successful attempts to enhance fracture repair by regional use of BMP-2 without the use of traditional osteoconductors: Baltzer et al.¹² injected adenoviral vectors encoding for BMP-2 into the segmental defect site in femora of rabbits. Schmidmaier et al.¹³ established closed tibial fractures with BMP-2-coated titanium Kirschner wires. Tang et al.¹⁴ used cannulated screws with holes delivering recombinant human BMP-2 (rhBMP-2) to the site of FNFs in dogs. To our knowledge, there is no comparable case in humans like ours in current literature, though.

The purpose of this case report was to show that in a complicated delayed union following a trochanteric open-wedge osteotomy after FNF and treatment with ESWT, rhBMP-2 can be successfully used to induce bone formation via computed tomography-guided injections without any osteoconductor instead of autologous bone-grafting. The patient was informed that data from the case would be submitted for publication, and gave his consent.

Case Report

In a skiing-accident, a 50-year-old man sustained a medial FNF (Pauwels III), initially treated by 2 hip-screws. At presentation in our practice after 4 months, the patient was limping in pain and had leg shortening following incomplete fracture healing (Figure 1). We treated the patient with 4 ESWT-sessions using a PIEZO-Wave 6A-A 236+TQF104G therapeutic device (Richard Wolf Enterprises, Knittlingen, Germany; 2000 impulses, 0.403mJ/mm², 8Hz, each). Treatment resulted in adequate healing of the initial fracture-site and in pain reduction, but with major leg shortening inducing major problems in sports activities, and activities of daily living (ADL). Ten months after the accident/initial surgery, the patient underwent femoral derotational open-wedge osteotomy at an external hospital. Surgery reduced the length difference to 2.5 cm and improved limping; 2.5-month-postoperative radiographs, however, revealed no sign of ossification or calcification in the 1.4-6 cm osteotomy-gap (Figure 2). We repeated 4 ESWT-sessions over 3 weeks which did not at all enhance union. Four months after osteotomy, the open-wedge gap still showed no sign of ossification (Figure 3). Unwilling to undergo another surgery, e.g., autologous bone-grafting, the patient agreed on a minimally-invasive off-label alternative: 4 computed tomography-guided injections of 2 mg of rhBMP-2 (Inductos®) each were
administered into the repair-site. The first 3 injections were given at an interval of 1 week followed by a computed tomography (CT) control. A final injection was given 3 weeks later. No osteoconductor was employed. On follow-up, 6-week-post-treatment CT images showed an approximately 55-60% union (Figure 4), while later radiographs documented a complete union of the osteotomy-gap (Figure 5). During follow-up examination, ADL and sports activities were fully restored, the patient was pain-free and did not report any side-effects.

Discussion

We present the case history of a healthy 50-year-old man who suffered a traumatic medial FNF. Following surgical intervention, he developed a major leg length difference. The correction of this difference by open-wedge osteotomy resulted in a therapy-resistant delayed union at repair-site. We followed an off-label use of a procedure based on a regional and minimally-invasive protocol to treat the bone defect: The administration of 4 CT-guided rhBMP-2 injections into the defect-site without the use of any osteoconductor or viral vectors successfully induced bone repair in the open-wedge osteotomy-defect. Six weeks after the last administration, rhBMP-2 had already triggered the initial spark by initiating a 55-60% union of the repair-site. On follow-up examination, the patient had normal radiographs showing bone healing ad integrum and normal ADL including sports activities.

Although the clinical potential of growth factors to enhance fracture repair has been known for decades, little is known about their long-term effects and they have only been approved for the treatment of a very limited range of orthopaedic conditions. The benefits of BMPs in the treatment of delayed and non-unions are still being discussed controversially. This case report emphasizes that rhBMP-2 can be successfully used for the treatment of complicated delayed unions and possibly non-unions as well as an equivalent alternative to the gold standard of autologous bone grafting. In specific, we have shown that rhBMP-2 can induce and enhance bone repair even without using osteoconductors which contradicts the conventional notion of bone repair. Traditionally, bone healing is supposed to require 3 components: an osteoconductor, i.e., a scaffold over which new bone can form, an osteoinductor, i.e., a growth factor directing cellular differentiation, and pluripotent mesenchymal stem cells, i.e., the target cell for the growth factors. In animal trials, however, Baltzer et al. and Schmidmaier et al. as well as Tang et al. have already demonstrated the capacity of rhBMP-2 to enhance bone repair without osteoconductors - either by using viral vectors encoding for BMP-2 in rabbits, BMP-2-coated Kirschner wires in rats or specific...
delivering devices in dogs\(^1\) ensuring a high therapeutical concentration of BMP-2 at repair-site. In contrast to these efforts in the animal model, we did neither adopt the gene therapeutical approach by Baltzer et al.\(^1\) - which is currently not approved in Germany - nor the invasive techniques by Schmidmaier et al.\(^1\) or Tang et al.\(^1\) Instead, we used CT-guided injections to transport rhBMP-2 directly to the repair-site and administered the injections repeatedly to maintain a sustainable regional concentration of the growth factor. This approach seems technically safe and risk-free. Importantly, it is additionally much less invasive than autologous bone-grafting\(^2\) which was important to our patient, as he did not want to undergo a third surgery within 13 months.

With regard to negative long-term effects, our conclusions are restricted to the (positive) results of the 9-month-post-treatment follow-up. Future studies should use longer follow-up intervals, for patient safety must be our number one priority, as such a new technique is taken from the bench to the bedside.\(^2\) Besides, it is hard to tell whether our positive outcome would have been the same in an older patient, as bone healing is known to be more complicated in the elderly.\(^13,15\) In spite of these limitations, we believe it appropriate to consider the regional use of rhBMP-2 as an alternative to the last resort of autologous bone-grafting. In view of the positive outcome of the present case, further prospective, controlled, randomized studies in a larger patient population seem warranted. In specific, an examination of the appropriate dosage and administration intervals of rhBMP-2 would be desirable.

Delayed or non-unions are a key obstacle in all types of fractures or open-wedge osteotomies.\(^1\) Current treatment recommendations for delayed or union include both invasive procedures, such as autologous bone-graft or osteotomy, and non-invasive techniques, such as ESWT.\(^2,5\) The present case report shows that growth factors, for instance, rhBMP-2, can also be successfully used to treat complicated delayed union following open-wedge osteotomy in a minimally-invasive procedure without the use of traditional osteocductors.

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**Figure 4.** Computed tomography image 6 weeks after the last recombinant human bone morphogenetic protein-2 injection shows an approximately 55–60% union of the bone defect.

**Figure 5.** Nine-month-follow-up anteroposterior (A) and lateral (B) radiographs of the left femur show a complete union of the bone defect.

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**References**