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CASE REPORTS

Treatment of a segmental defect in open radial and ulnar shaft fractures using rhBMP-2 and iliac crest bone graft: a case report

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Introduction

Segmental defects and delayed healing of long bone fracture remains a major problem among orthopedic surgeons. Nonunion of the forearm as a result of complex open fracture can result in imbalance in the main anatomical structures, leading to impaired function [17]. Therefore, the treatment of these defects must include the restoration of length and alignment in order to restore functional forearm motion [21]. Current treatment options for segmental long bone defects includes autogenous bone grafting, bone shortening, plate fixation combined with either intercalary non-vascularized structural (corticocancellous) bone grafts, vascularized grafts, or amputation [9]. The identification of recombinant human bone morphogenetic protein-2 (rhBMP-2) has led to revolutionary treatment options in certain orthopedic procedures. Currently, rhBMP-2 is approved by the United States Food and Drug Administration (FDA) for spine fusion [7, 11, 13, 16], tibial fractures [12, 14], and oral maxillofacial [4–6] procedures.

The reported use of BMP-2 in cases of forearm shaft fractures has been limited. In our case report, we describe an off-label use of rhBMP-2 used in combination with iliac crest bone graft to treat segmental defects in a man with open radius and ulna fractures.

Case Report

A 35-year-old right hand dominant male sustained an open ipsilateral radius and ulna fracture with significant bone loss after a motorcycle accident (Fig. 1). On the day of presentation, the patient was taken to the operating room for irrigation and debridement of the open fractures. After the wounds were copiously irrigated, a dynamic compression plate was first placed on the extensor aspect of the ulna. Next, the radius was approached through a volar Henry interval. After initial reduction with dynamic compression plate, it was noted that the ulna was 12 mm longer than the radius. Contralateral fluoroscopic images were then taken in the operating room to assess the ulnar variance, which was noted to be neutral. The radius was then brought out to the appropriate length and the plate was reapplied. This resulted in a 3-cm gap in the mid-radial shaft. The ulnar shaft fracture had an approximately 1-cm defect, but had one point of cortical contact (Fig. 2). The wound was then closed with all bone and tendon being covered. The wound healed with dressing changes over the next 2 weeks without any signs of infection. He was seen several times in the office and underwent therapy to promote forearm, wrist, and finger range of motion. The soft tissue healed completely, and the ulna and radius stayed in good alignment; however, the bony defects persisted at the fracture sights. At 10 weeks postoperatively, the ulna fracture showed some signs of partial bridging, but the radius fracture defect was persistent. He was then scheduled for revision of his hardware and bone grafting.

The patient was taken to the operating room and the left upper extremity was prepped and draped; the arm was exsanguinated and the tourniquet on the upper arm was inflated. The ulnar shaft was addressed first and exposed. There was found to be some bridging cortical bone dorsally and ulnarly and this was left intact. The fibrous tissue in the defect was removed down to intact cortical bone. Due to a concern of metal fatigue and eventual failure, the original plate was removed and a longer plate in different screw holes was applied. The radial shaft was then exposed through the previous

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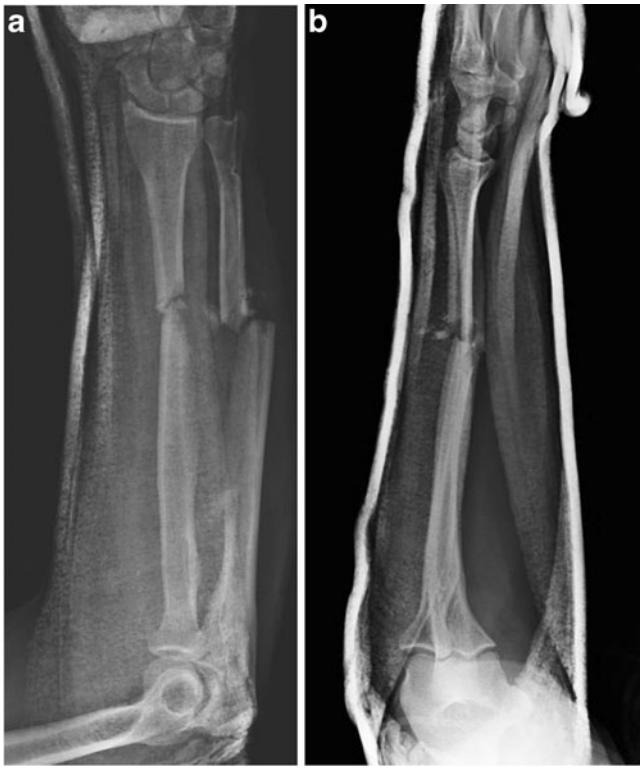

Fig. 1 Anteroposterior (**a**) and lateral (**b**) initial injury radiographs of the left forearm demonstrating comminution at the fracture sites

incision. The plate and radial shaft were exposed. At this point, the tourniquet was let down and a 3-cm corticocancellous bone graft, with approximately an additional 20-cc of cancellous graft, was taken from the iliac crest. The graft site was closed and attention was then turned to the arm. The arm was exsanguinated again and the tourniquet was again elevated. The volar–radial interval was opened and the corticocancellous graft was fashioned to fit the graft. The plate was removed and the graft was inserted into the defect. A BMP-2 (INFUSE Bone Graft; Medtronic Sofamor Danek, Memphis, TN, USA)-soaked collagen sponge was placed around the bone graft. The graft was then compressed through a new plate and secured with a screw into the cortex of the graft. The sponge was held in place by drilling screws from the plate through it and compressing it under the plate. The ulnar defect was next filled with cancellous graft and a BMP-2-soaked sponge was wrapped around the graft and held by the plate in a similar fashion (Fig. 3). The wounds were closed in a standard technique and the patient was placed in a volar splint.

The patient's forearm was placed in a removable volar splint and started on gentle range of motion exercises at 2 weeks postoperatively. At 4 weeks following the surgery, radiographs showed signs of early healing with some bridging callus. At 3 months, the radius and ulna were completely healed (Fig. 4). At 9 months postoperative, the radiographs showed further remodeling of the callus with a restoration of the cortices in the radius and ulna. On exam, he had no pain over the left forearm and his wounds were healed. Range of motion of the elbow was full extension to 130° of flexion, and forearm pronation to 70° and supination of 70°. He had returned to full work activities.

Discussion

Discovered in 1965 by Dr. Marshall Urist [25], bone morphogenetic proteins, as endogenous growth factors naturally found within the bone matrix [19], are able to induce mesenchymal stem cells to differentiate into osteoblasts and chondrocytes. In vitro studies have shown that mesenchymal stem cells incubated with rhBMP-2 have

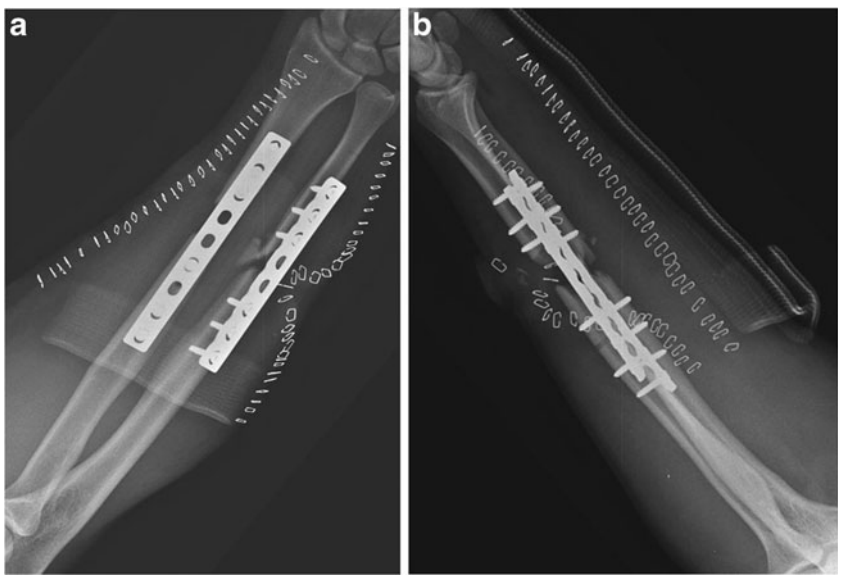

Fig. 2 Postoperative radiographic in the anteroposterior (**a**) and lateral (**b**) views showing the radial and ulnar shaft fractures stabilized with compression plates with resulting 3-cm defect in radius and 1-cm defect in ulna

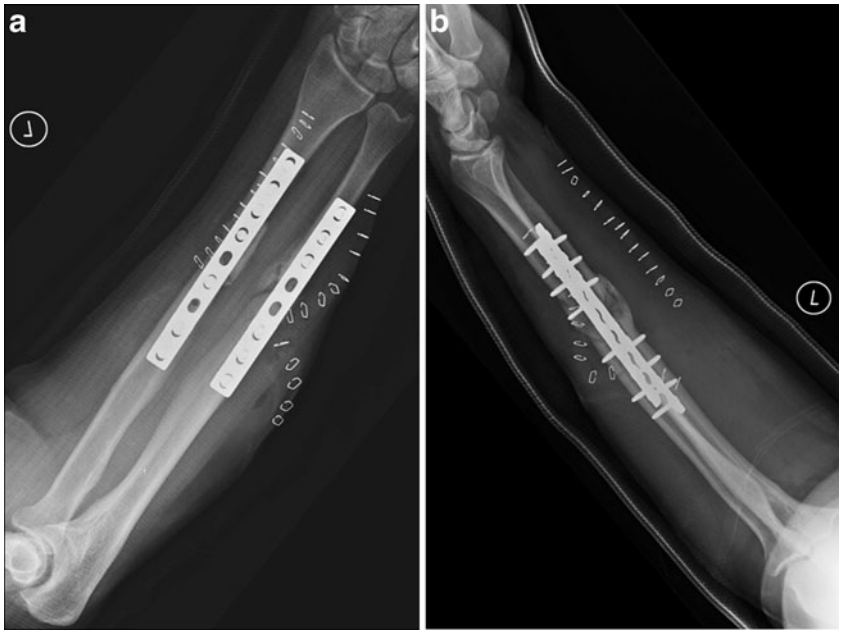

Fig. 3 Anteroposterior (**a**) and lateral (**b**) radiographs after re-plating and bone graft insertion and application of BMP-2 to the radial and ulnar nonunion site

increased alkaline phosphatase activity and undergo matrix mineralization [20]. When implanted in vivo, rhBMP-2 induced the proliferation and differentiation of these mesenchymal stem cells into an osteoprogenitor lineage. The bone formed had exactly the same composition as bone elsewhere in the body [26].

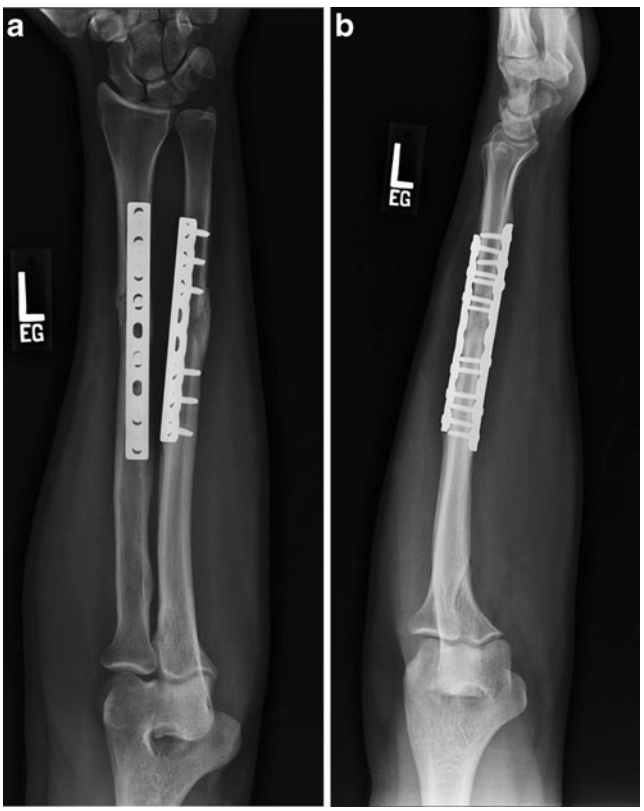

Fig. 4 Radiographs at 3 months postoperatively demonstrating healing of the radial and ulnar defects with full consolidation of graft material in the anteroposterior (**a**) and lateral (**b**) views

Preclinical research had clearly demonstrated the capability of rhBMP-2 to induce new bone formation in a number of different fracture locations in animal models [1–3, 8, 10, 23]. The first clinical reports on the use of purified mixture of human BMP extracts from demineralized bone were published in the 1980s. Johnson and Urist [14] achieved healing of femoral nonunion in 24 of 30 patients treated with BMP extracted from human bone at a mean of 6 months.

The largest and most critical study that evaluated the use of rhBMP-2 in the treatment of open fractures of the tibial shaft was an international investigation termed BESTT (BMP-2 Evaluation in Surgery for Tibial Trauma) [12]. This prospective randomized, controlled, single-blind study of 450 patients with an open tibial fracture was carried out at 49 centers (11 countries) to evaluate the safety and efficacy of rhBMP-2. Patients with an open tibia fracture were assigned to one of three treatment groups: group I treated with standard care (intramedullary nail fixation and routine soft tissue management) and was considered to be the control group, group II had the addition of 0.75 mg/ml rhBMP-2, and group III had 1.5 mg/ml rhBMP-2 placed at the fracture site. The percentages of patients requiring secondary interventions were 26% and 37% in the 1.50- and 0.75-mg/ml groups, respectively, compared with 46% in the control group ($p=0.0004$). The patients who received 1.5 mg/ml rhBMP-2 also had significantly more rapid fracture healing ($p=0.0022$) than did the 0.75-mg/ml and control groups. The implantation of rhBMP-2 in those patients with a Gustilo–Anderson type III open fracture significantly reduced the rate of infections ($p=0.0219$) and

had faster wound healing (p=0.0010) compared to the control group. No associated adverse events were reported with the use of rhBMP-2. The data from this study led to FDA approval of rhBMP-2 in 2004 for open tibial fractures stabilized with an intramedullary nail.

Following the BESTT study, Swiontkowski et al. [24] combined the data from the BESTT trial and another prospective, randomized, controlled study of 60 patients from ten level 1 trauma centers in the USA to evaluate the use of rhBMP-2 in patients with type III open tibial fractures. Patients that were treated with 1.5 mg/ml rhBMP-2 had fewer secondary interventions (9% vs. 28%, p=0.0065) and lower rates of infection compared to the control group (21% vs. 40%, p=0.0234).

BMPs have also been investigated in the setting of large bone defects requiring bone grafting. In a randomized, controlled, prospective clinical investigation [15], patients with a tibial diaphyseal fracture with cortical defect were randomly assigned to receive either autogenous bone graft or allograft with rhBMP-2. The fractures healed in 13 of 15 patients in the rhBMP-2 group and 10 of 15 in the autograft group without any need for secondary intervention. The rhBMP-2 group had less blood loss (p=0.0073) due to the bone graft harvesting in the autogenous bone graft group. The authors concluded that the use of rhBMP-2 in combination with allograft demonstrated clinical results equivalent with those of autogenous bone grafting for these large posttraumatic tibial bone defects.

Most of the literature involving the use of rhBMP-2 in orthopedic trauma involves fractures of the lower extremities. In the literature, there appears to be only one previous case of the use of BMP-2 in the upper extremity. This describes the treatment of a posttraumatic 8-cm segmental defect of the ulna in a 16-year-old boy [22]. The patient had grade II open ulna and radial shaft fractures that were treated with irrigation and debridement and plating. He subsequently developed osteomyelitis of the ulna, which required extensive irrigation and debridement followed by placement of antibiotic beads. This resulted in an 8-cm mid-shaft defect in the ulna. The defect was filled with a macropore polylactic scaffold (Interpore multiple polylactic absorbable scaffold; Interpore Cross International, Irvine, CA, USA) combined with BMP-2 and then the ulna was plated. Radiograph at 12 months showed early consolidation, and complete healing was seen at 22 months.

The management of segmental bone loss can present the treating physician with many challenges. There are many different treatment options to address segmental defects. Currently, the use of autogenous bone graft is the gold standard for the treatment of segmental defects up to a certain length. In our case, we found that BMP-2 combined with autogenous iliac crest graft resulted in rapid healing of large bony defects in the bones of the forearm. The time for healing of segmental defects is directly related to the length of the defect and the bone grafting technique used. Our patient had radiographic evidence of union at 3 months, which is relatively rapid for such a large defect.

Since its approval by the Food and Drug Administration for autograft replacement in spinal fusions in 2002 and open tibia fractures in 2004, BMP-2 has been successfully used in multiple spine, orthopedic, and maxofacial trauma cases. Although it is an expensive treatment option, with a single dose costing approximately $5,000, a recent cost–benefit analysis has shown that the use of BMP-2 in high grade open fractures (types III A and III B) actually lowers the total cost from a health insurer's perspective [18]. With increasing data demonstrating its potential to improve healing for bony defects after extremity trauma, there will be a growing interest in applying rhBMP-2 in these difficult cases. However, its use must be balanced against the high cost and should also be compared to the use of less expensive bone healing augmentation products.

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