Eight-Centimeter Segmental Ulnar Defect Treated With Recombinant Human Bone Morphogenetic Protein-2

Niles D. Schwartz, MD, and B. Matthew Hicks, MD

Management of segmental bone defects resulting from trauma can present the surgeon with an uncommon challenge because of the potential complications and poor prognosis associated with this type of injury. The impact on the patient is often significant and may result in permanent disability or loss of limb. Treatment recommendations for long-bone defects have included autogenous bone grafting, bone transport, acute bone shortening, and amputation.[1-5] The disadvantages of using autograft bone include the blood loss associated with harvest and the morbidity at the iliac crest donor site.[6-8] For bone defects larger than 5 cm, historical options have included amputation, bone transport, and vascularized fibular transfers.[9-12] All these options have potentially significant morbidity associated with treatment. Donor-site morbidity of fibular graft site was reported in 19% of cases,[13] and secondary fracture through fibular graft was reported in 23% of cases.[14]

Use of recombinant human bone morphogenetic proteins (rhBMPs) may be a viable alternative to autogenous bone grafting. With its significant osteoinductive effects,[15,16] rhBMP-2 has already been found effective in bone formation in critical-size bone defects in multiple animal models.[17-20] Johnson and colleagues[21] reported on use of human BMP extracts combined with autograft to treat 6 tibial segmental defects; all patients developed solid union, and mean time to union was 4.7 months.

Here we describe the off-label use of rhBMP-2 on a posttraumatic 8-cm bone defect in an ulna successfully treated with rhBMP-2/absorbable collagen sponge (ACS) along with calcium phosphate ceramic granules (Infuse®/MasterGraft, Medtronic Sofamor Danek, Memphis, Tenn).

Case Report

A left-hand–dominant 16-year-old boy initially presented with grade II open radial and ulnar midshaft fractures, in addition to other injuries, including pulmonary contusion, facial lacerations, and right hand extensor tendon injury, all sustained in a motor vehicle collision. Left forearm injuries were treated with IV antibiotics as well as multiple surgeries for irrigation and débridement and for compression plating. The other injuries were addressed.

The patient subsequently developed osteomyelitis of the left ulna and underwent multiple irrigations and débridements, sequestrum removal, and placement of tobramycin and vancomycin antibiotic beads. He was left with an 8-cm bone defect in the midshaft of the left ulna (Figure 1). Cultures had grown *Serratia marcescens* and *Enterobacter aerogenes*. For 8 weeks, an infectious disease physician treated the patient with piperacillin/tazobactam and gentamicin antibiotics through a peripherally inserted central catheter.

We have obtained the patient's informed, written consent to publish his case report.

Surgical Procedure

After informed consent for the procedure and for rhBMP use was obtained, surgery was begun. A longitudinal incision was made over the left ulna using the previous incision. The antibiotic beads were removed, and the wound was thoroughly irrigated. A burr was used to recanalize the proximal and distal ends of the defect, obtaining good bleeding bone. The bed was clinically clean.

To fill the 8-cm longitudinal deficiency, a macropore sheath (Interpore multiple polylactic absorbable scaffold; Interpore Cross International, Irvine, Calif) was cut to 10 cm and contoured into a half-tube longitudinally. The

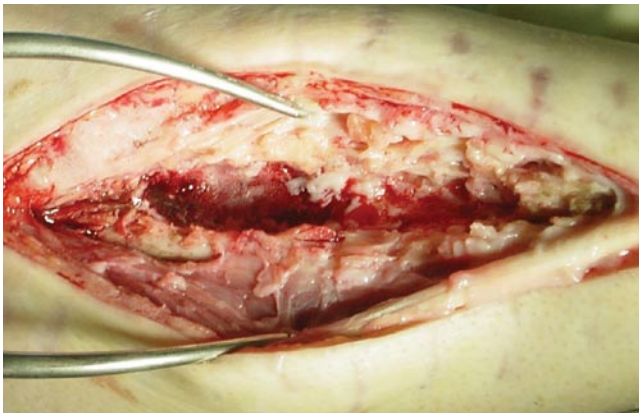

Figure 1. Intraoperative photograph shows 8-cm defect in ulna.

Dr. Schwartz is Attending Surgeon, Fort Wayne Orthopaedics, Fort Wayne, Indiana.
Dr. Hicks is Program Director, Fort Wayne Orthopaedic Residency Program, Fort Wayne, Indiana.

Address correspondence to: B. Matthew Hicks, MD, 7601 W Jefferson Blvd, Fort Wayne, IN 46804 (tel, 260-436-8686; fax, 260-436-8326).

Am J Orthop. 2008;37(11):569-571.

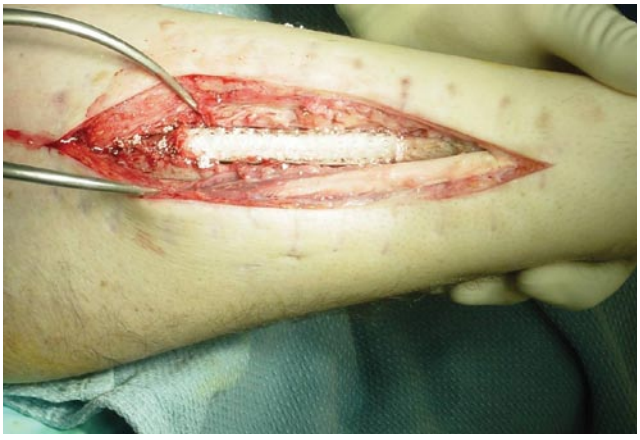

Figure 2. Intraoperative photograph of segmental defect with Infuse/MasterGraft (Medtronic Sofamor Danek, Memphis, Tenn) within macropore sheath (Interpore multiple polylactic absorbable scaffold; Interpore Cross International, Irvine, Calif).

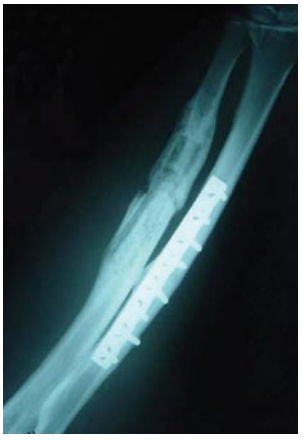

Figure 3. Radiograph shows ulnar graft 12 months after placement of recombinant human bone morphogenetic protein-2/absorbable collagen sponge. Ulna appears to be healing well. Radial plate is from original injury.

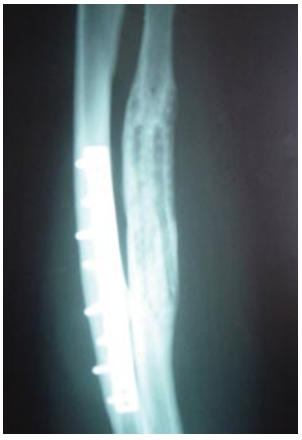

Figure 4. Radiograph shows ulnar graft 22 months after placement of recombinant human bone morphogenetic protein-2/absorbable collagen sponge. Ulna shows continued healing and remodeling.

rhBMP-2 solution was prepared and soaked onto the ACS carrier per manufacturer instructions. Next, 30 cm^3 of MasterGraft granules were folded up into 5.6 cm^3 of rhBMP-2/ACS, and this combined graft was placed into the defect (Figure 2). The MasterGraft granules were used for their osteoconductive properties. After the defect was completely filled, another macropore sheath was placed over the top of the graft to form a temporary cage to prevent collapse of soft tissues onto the ACSs. Although a possible risk for infection, the macropore sheath was thought necessary to preserve proper space for subsequent bone formation in this particular case. We now perform this type of bone grafting without a macropore sheath, as it seems unnecessary. This sheath was then stabilized into the ulna both proximally and distally with 4 bioabsorbable 3.5-mm bicortical screws. The wound was then closed in the usual fashion, and the extremity was placed in a bulky dressing with long-arm posterior splint immobilization.

The postoperative course was uncomplicated. The patient was initially immobilized in the long-arm splint for 2 weeks. Then, gentle range of motion of the elbow and long-forearm splint was initiated with no other activity of the extremity for the next 4 weeks. Gradual return to activities was then allowed over several months. The patient achieved full active elbow and wrist motion and was playing sports 15 weeks after the grafting procedure (against the surgeon's wishes). Sequential radiographs continued to show consolidation of the defect graft over time, with a 12-month radiograph showing consolidation (Figure 3). At the last follow-up, 22 months after the grafting procedure, there were no reported symptoms from the injury (Figure 4), according to radiographs and a clinical report from elsewhere.

Discussion

We report here on the use of rhBMP-2/ACS combined with calcium phosphate ceramic in an 8-cm posttraumatic, postinfectious ulnar defect with excellent clinical results. Treatment of posttraumatic, postinfectious segmental bone defects continues to be difficult. Clinicians continue to search for new treatments given the frequent complications associated with current treatment regimens. Bone morphogenetic protein grafting has the potential to become a valuable new option for segmental defects, as it has already been shown useful in other types of orthopedic procedures, such as spinal fusion and tibial nonunion.[22,23]

Bone morphogenetic protein has been studied extensively in segmental defects in animals. Bostrom and colleagues[17] used a 2-cm ulnar defect model in rabbits to show dose-dependent bone formation, including union in all defects given the highest dosage. Moreover, histologic analysis demonstrated normal bone formation with use of rhBMP-2/ACS. Yasko and colleagues[19] also found dose-related healing in a rat model. Sciadini and Johnson[20] found comparable healing with autograft and rhBMP-2/ACS in the same canine defect model.

Recently, Jones and colleagues[24] presented results from a small clinical trial involving rhBMP-2/ACS used as part of a staged bone grafting procedure. Their study involved treatment of 30 tibial fractures with traumatic bone loss of 1 to 5 cm in length. Patients were randomized to receive iliac crest autograft or allograft plus rhBMP-2/ACS. The authors concluded that rhBMP-2/ACS combined with allograft yielded healing similar to that occurring with autogenous bone graft.

The rhBMP-2/ACS implant has been found to be safe in humans and to have excellent osteoinductive effects. Bone morphogenetic protein grafting has the potential to become a valuable new option for the treatment of segmental defects, and we will continue to evaluate patients critically for possible use of this technique.

Authors' Disclosure Statement

Dr. Schwartz reports no actual or potential conflict of interest in relation to this article.

Dr. Hicks wishes to note that he is a paid consultant and speaker for Medtronic Sofamor Danek.

References

1. Dabezies EJ, Stewart WE, Goodman FG, Deffer PA. Management of segmental defects of the radius and ulna. *J Trauma.* 1971;11(9):778-788.
2. Grace TG, Eversmann WW Jr. The management of segmental bone loss associated with forearm fractures. *J Bone Joint Surg Am.* 1980;62(7):1150-1155.
3. Cierny G 3rd, Zorn KE. Segmental tibial defects. Comparing conventional and Ilizarov methodologies. *Clin Orthop*. 1994;(301):118-123.
4. Green SA. Skeletal defects. A comparison of bone grafting and bone transport for segmental skeletal defects. *Clin Orthop*. 1994;(301):111-117.
5. Prokuski LJ, Marsh JL. Segmental bone deficiency after acute trauma. The role of bone transport. *Orthop Clin North Am*. 1994;25(4):753-763.
6. Younger EM, Chapman MW. Morbidity at bone graft donor sites. *J Orthop Trauma.* 1989;3(3):192-195.
7. Goulet JA, Senunas LE, DeSilva GL, Greenfield ML. Autogenous iliac crest bone graft. Complications and functional assessment. *Clin Orthop*. 1997;(339):76-81.
8. Robertson PA, Wray AC. Natural history of posterior iliac crest bone graft donation for spinal surgery: a prospective analysis of morbidity. *Spine*. 2001;26(13):1473-1476.
9. Jupiter JB, Bour CJ, May JW Jr. The reconstruction of defects in the femoral shaft with vascularized transfers of fibular bone. *J Bone Joint Surg Am*. 1987;69(3):365-374.
10. Heitmann C, Erdmann D, Levin LS. Treatment of segmental defects of the humerus with an osteoseptocutaneous fibular transplant. *J Bone Joint Surg Am*. 2002;84(12):2216-2223.
11. Song HR, Kale A, Park HB, et al. Comparison of internal bone transport and vascularized fibular grafting for femoral bone defects. *J Orthop Trauma*. 2003;17(3):203-211.
12. Bowers KW, Edmonds JL, Girod DA, Jayaraman G, Chua CP, Toby EB. Osteocutaneous radial forearm free flaps. The necessity of internal fixation of the donor-site defect to prevent pathological fracture. *J Bone Joint Surg Am*. 2000;82(5):694-704.
13. Vail TP, Urbaniak JR. Donor-site morbidity with use of vascularized autogenous fibular grafts. *J Bone Joint Surg Am.* 1996;78(2):204-211.
14. Minami A, Kimura T, Matsumoto O, Kutsumi K. Fracture through united vascularized bone grafts. *J Reconstr Microsurg*. 1993;9(3):227-232.
15. Zegzula HD, Buck DC, Brekke J, Wozney JM, Hollinger JO. Bone formation with use of rhBMP-2 (recombinant human bone morphogenetic protein-2). *J Bone Joint Surg Am*. 1997;79(12):1778-1790.
16. Cheng H, Jiang W, Phillips FM, et al. Osteogenic activity of the fourteen types of human bone morphogenetic proteins (BMPs) [published correction appears in *J Bone Joint Surg Am*. 2004;86(1):141]. *J Bone Joint Surg Am*. 2003;85(8):1544-1552.
17. Bostrom M, Lane JM, Tomin E, et al. Use of bone morphogenetic protein-2 in the rabbit ulnar nonunion model. *Clin Orthop*. 1996;(327):272-282.
18. Cook SD, Salkeld SL, Brinker MR, Wolfe MW, Rueger DC. Use of an osteoinductive biomaterial (rhOP-1) in healing large segmental bone defects. *J Orthop Trauma*. 1998;12(6):407-412.
19. Yasko AW, Lane JM, Fellinger EJ, Rosen V, Wozney JM, Wang EA. The healing of segmental bone defects, induced by recombinant human bone morphogenetic protein (rhBMP-2). A radiographic, histological, and biomechanical study in rats [published correction appears in *J Bone Joint Surg Am*. 1992;74(7):1111]. *J Bone Joint Surg Am*. 1992;74(5):659-670.
20. Sciadini MF, Johnson KD. Evaluation of recombinant human bone morphogenetic protein-2 as a bone-graft substitute in a canine segmental defect model. *J Orthop Res*. 2000;18(2):289-302.
21. Johnson EE, Urist MR, Finerman GA. Repair of segmental defects of the tibia with cancellous bone grafts augmented with human bone morphogenetic protein. A preliminary report. *Clin Orthop*. 1988;(236):249-257.
22. Burkus JK, Gornet MF, Dickman CA, Zdeblick TA. Anterior lumbar interbody fusion using rhBMP-2 with tapered interbody cages. *J Spinal Disord Tech*. 2002;15(5):337-349.
23. Friedlaender GE, Perry CR, Cole JD, et al. Osteogenic protein-1 (bone morphogenetic protein-7) in the treatment of tibial nonunions. *J Bone Joint Surg Am*. 2001;83(suppl 1, pt 2):S151-S158.
24. Jones AL, Bucholz RW, Bosse MJ, et al; BMP-2 Evaluation in Surgery for Tibial Trauma-Allgraft (BESTT-ALL) Study Group. Recombinant human BMP-2 and allograft compared with autogenous bone graft for reconstruction of diaphyseal tibial fractures with cortical defects. A randomized, controlled trial. *J Bone Joint Surg Am*. 2006;88(7):1431-1441.