Osteogenic Protein-1 (Bone Morphogenetic Protein-7) Combined with Various Adjuncts in the Treatment of Humeral Diaphyseal Nonunions


Abstract
A prospective study was conducted to determine the efficacy of using recombinant BMP-7 (rhOP-1) as an adjuvant in the treatment of diaphyseal humeral nonunions. Twenty-three consecutive patients with atrophic humeral diaphyseal nonunions were treated at seven separate institutions. All nonunions were fixed with either a compression plate or an intramedullary nail in conjunction with various bone grafting techniques. Recombinant OP-1 was delivered to the fracture site in a Type I collagen carrier at the time of fixation. All fractures went on to eventual union. There were no serious complications and no adverse reactions to the rhOP-1 implant. Our study suggests that rhOP-1 may be a safe and effective adjuvant for the treatment of humeral diaphyseal nonunions.

Fractures of the humeral shaft are a major source of morbidity, comprising about 3% of all fractures. While the vast majority of these fractures will unite with closed treatment, surgical fixation may be warranted in certain cases. Nonunion of the humeral diaphysis occurs after 3% to 12% of fractures, and can be a debilitating condition that leaves the patient with severe pain and leads to stiffness of both the shoulder and elbow joints. In the rare event of a humeral shaft nonunion, compression plate fixation or intramedullary nailing combined with bone grafting of defects or atrophic nonunions results in a 95% healing rate. While these results have been good, there is significant donor site morbidity associated with the harvest of autogenous iliac crest bone graft.

In the past decade, a considerable amount of effort has been directed toward identifying biologic osteoinductive agents to aid in the healing of osseous fractures. Specifically, studies into bone specific differentiation of local tissue have highlighted the role of the bone morphogenic proteins (BMP). Multiple animal studies have shown that recombinant BMP-7 combined with a collagen carrier can induce both heterotopic bone formation at various sites as well as aid in the healing of significant bone defects. Human studies have also shown the benefits of using recombinant BMP-7 (osteogenic protein-1) in the treatment of tibial nonunions and bone defects. This study was performed to determine the efficacy of using recombinant BMP-7 as an adjuvant in the treatment of diaphyseal humeral nonunions.

Materials and Methods
Twenty-three consecutive patients with 23 humeral nonunions were enrolled in an industry sponsored (Stryker Biotech, Hopkinton, MA) clinical study under a Food and Drug Administration (FDA) approved Investigational Device Exemption (IDE) in which they were assigned to treatment with recombinant OP-1 (rhOP-1). Each patient had a humeral nonunion based on a 1988 FDA guidance document definition requiring nine months duration of the nonunited fracture with no evidence of progressive healing over the previous three months. Patients who, in the judgment of their treating orthopaedic surgeon, were candidates
for internal fixation alone, had a hypertrophic nonunion, or had a clinically apparent infection at the fracture site were excluded from this study.

All patients were treated between March, 2002, and July, 2003, at one of seven medical centers in the United States after institutional review board approval had been obtained at the local healthcare facility and with the patient’s informed consent. Once a diagnosis of nonunion had been established, all of the patients underwent plate and screw or intramedullary nail fixation in conjunction with either allograft or autograft bone grafting or demineralized bone matrix (DBM). In addition patients were treated with rhOP-1 contained within a Type I collagen matrix implant.

Each sterile unit of the rhOP-1 implant (Stryker Biotech, Hopkinton, MA) contained 3.5 milligrams of the rhOP-1 mixed with one gram of Type I bovine bone-derived collagen (the total reconstituted volume was approximately four milliliters per unit). Each patient was dosed with one unit of the rhOP-1 implant in addition to the bone graft.

Clinical diagnosis of union was determined by the absence of pain at the fracture site, no motion at fracture site on manual three-point stressing in the sagittal and coronal planes, and functional recovery of range of motion with the involved extremity. The primary end-point of the study was the nine-month visit. Standard radiographs were obtained in the anteroposterior and lateral projections. Patients were assessed for radiographic healing by the treating surgeon and an independent examiner. Radiographic healing required bridging of three out of four cortices on anteroposterior and lateral views.

All preoperative and postoperative adverse events were reported and classified as non-serious or serious according to the International Conference of Harmonization (ICH) Guideline for Good Clinical Practice. Serious adverse events included any untoward medical occurrence temporally related to the use of rhOP-1 implant that resulted in death, was life-threatening, required inpatient hospitalization or prolonged current hospitalization, or resulted in significant or persistent disability. Non-serious adverse events are any untoward medical occurrence that did not fulfill the definition of a serious adverse event.

Results

Twenty-three patients (23 nonunions) were enrolled into the study. There were nine males and fourteen females with an age range of 21 to 87 years (mean: 56.6 years). Eight patients were smokers and three patients were chronic alcoholics; no patient in the study had diabetes mellitus. The average patient weight was 76 kg (range: 55.5 to 108.6 kg). All but two of the fractures were closed, with thirteen occurring in the right upper extremity and ten on the left. Eleven of the fractures occurred in the proximal third of the shaft, five in the middle third, five in the distal third, and two were segmental. Sixteen of the fractures resulted from low-velocity falls, three from high-energy falls from a height, three from motor vehicle accidents, two from blunt trauma, and two from penetrating trauma. There was an average of 1.3 surgical procedures (range: 0 to 3) conducted prior to the index procedure of the nonunion. One of the patients with a nonunion had been previously diagnosed with an infection.

Twenty-one of the nonunions were repaired with a plate and screws. Two of the nonunions were fixed with an intramedullary nail. In addition to the standardized dose of rhOP-1, patients were treated with various types of bone graft and other osteoinductive agents. Four patients were treated with iliac crest bone graft alone, one with DBM alone, and 18 were treated with a combination of autograft, allograft cancellous chips, platelet concentrate gel, or DBM. No patients were treated with allograft bone or platelet concentrate gel alone. Patient characteristics and specific treatments are outlined in Table 1.

All fractures went on to eventual union. The mean time from repair to union was 144.3 days (range: 69 to 356 days). Because of the lack of standardization with regards to adjunctive bone graft or bone graft substitutes used, no comparison of healing time after application of rhOP-1 could be made.

There were four perioperative adverse events encountered in three treated patients. Three of the perioperative adverse events were serious and one was non-serious. Serious peri-

Table 1  Patient Demographics

<table>
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<tr>
<th>Sex</th>
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CL-Closed, OP-Open, PRO-Proximal, MID-Midshaft, DIST-Distal, SEG-Segmental, CC-Allogenic cancellous bone chips, STIM-Implantable bone stimulator, DBM-Demineralized bone graft, ICBG-Iliac crest bone graft, SYMPH-Symphony platelet concentrate (Depuy, Warsaw, IN)
operative adverse events include two radial nerve palsy
(one of which eventually resolved) and one brachialis muscle
contracture. One patient developed a superficial cellulitis
that was the lone non-serious perioperative adverse event.
There were four late serious adverse events encountered
at follow-up. The patient with the brachialis contracture
developed severe elbow stiffness and declined further surgi-
cal intervention. One patient developed a superficial wound
infection and was treated medically with a short course of
intravenous antibiotics. Heterotopic ossification developed
near the shoulder in one patient resulting in pain and limita-
tions in range of motion. Finally, one patient developed a
late ulnar nerve palsy.

Discussion
Recently, a considerable amount of research has been con-
ducted to identify specific biologic agents that can be used in
the treatment of difficult fractures and nonunions. Previous
reports on the use of rhOP-1 in the treatment of nonunions
have been encouraging. Friedlander and colleagues reported
their results in a prospective multi-center study comparing
the use of autogenous iliac crest bone grafting to rhOP-1 in
conjunction with a reamed intramedullary nail for treatment
of tibial diaphyseal nonunions.16 They reported comparable
radiographic and clinical results in the rhOP-1 group without
the donor site morbidity associated with harvesting of iliac
crest bone graft. Geesink and associates showed that rhOP-1
in conjunction with a collagen carrier led to the healing of
five out of six fibular defects encountered after high tibial
osteotomy.15 None of the fibular defects treated with only
the collagen carrier went on to heal. In our current study, all
of the diaphyseal humeral nonunions went on to heal and
there was a low rate of complications.

Currently, humeral shaft nonunions are repaired with
surgical fixation. Classically, hypertrophic nonunions have
been treated with compression plating only, while atrophic
nonunions may require bone graft. In 1937, Campbell re-
ported a 94% healing rate in humeral nonunions treated with
plating and autogenous bone grafting.19 Rosen reported a
95% union rate in nonunions treated with operative fixation.6
He used autogenous iliac crest bone graft in atrophic cases
and in nonunions with bone defects. Other investigators have
found similar success in treating humeral nonunions.20-22

Specifically, Ring reported bony union in 14 of 15 patients
with atrophic nonunions containing bony defects treated with
plating and autogenous bone grafting.22 While these results
are excellent, they rely on a separate surgical procedure to
obtain the graft, which carries inherent risks including pain,
infection, hematoma, and residual sensory loss.23,24 In our
current study, union occurred in all 11 patients who did not
have autogenous iliac crest bone grafting.

There are a few potential weaknesses of our study design
that are worth mentioning. The first weakness is the poten-
tial for detection bias when assessing the radiographs for
union. To minimize the detection bias, all of the films were
reviewed by an independent examiner. Another weakness of
the study was the varied use of alternate bone graft and bone
graft substitutes. It is unclear what the role of these adjuncts
had in the healing potential of the nonunions treated in this
group of patients.

Our results, in conjunction with other recent literature,
support the use of rhOP-1 for treating non-unions in con-
junction with conventional plating or intramedullary nailing
techniques. Currently, the cost of a single 3.5 mg dose of
rhOP-1 is $5,000. The benefit of avoiding potential compli-
cations associated with the harvest of autogenous iliac crest
bone graft, however, cannot be overstated. While allogenic
bone grafts avoid donor site morbidity and provide an osteo-
conductive framework, they lack the osteoinductive proper-
ties associated with autogenous bone graft. We believe that
hypertrophic nonunions of the humeral shaft should continue
to be treated with compression plating alone; while atrophic
nonunions can be treated with rhOP-1 and allogeneic bone
graft material instead of using an autogenous bone graft.
While the rhOP-1 can provide osteogenic properties, the
osteoc conducive allogeneic bone graft can act as a scaffold
for new bone formation.

Conclusion
Previous experience has shown the strong osteoinductive
properties of rhOP-1 with a good safety profile; however,
further research is required to more clearly define the indica-
tions and optimum matrix for delivery of the agent. While
the routine use of rhOP-1 in the treatment of hypertrophic
nonunions may not be warranted, it should be considered,
in conjunction with allogeneic bone grafting, for the treat-
ment of atrophic and recalcitrant nonunions of the humeral
diaphysis.

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