Treatment of Humeral Shaft Aseptic Nonunions in Elderly Patients With Opposite Structural Allograft, BMP-7, and Mesenchymal Stem Cells

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abstract

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Humeral shaft aseptic nonunions occur in 2% to 10% of patients managed conservatively and 10% to 15% of patients treated surgically. The complex muscular and neurovascular anatomy of the upper limb makes the surgical approach to the fracture site demanding and risky, especially when previous surgeries have been attempted. The clinical consequence of atrophic humeral shaft nonunions is a severe functional limitation that may significantly affect activities of daily living, especially in the elderly. The surgical treatment of humeral shaft nonunions is challenging for orthopedic surgeons. Patients with atrophic nonunions require both a stable fixation and enhancement of the biologic response because of the weak biologic reaction observed at the fracture site. The gold standard of treatment in elderly patients has not been described. Nonetheless, older age and comorbidities are associated with potentially malignant nonunions. This study reports the authors’ experience using opposite cortical allograft combined with bone morphogenetic protein 7 and mesenchymal stem cells to treat humeral shaft atrophic nonunions in 2 elderly patients. The nonunion site healed at 4 months (patient 1) and 8 months (patient 2) postoperatively, with full return to activities of daily living and no pain. Neither patient reported complications of the radial nerve, which is at high risk of injury during this type of surgery. The only reported complication (patient 2) was an intraoperative longitudinal partial distal humeral fracture, probably caused by compression screw overtightening. The use of a locking plate and opposite cortical allograft, combined with BMP-7 and mesenchymal stem cells, represents a safe and effective treatment for malignant nonunions in older patients.
Humeral shaft aseptic nonunions occur in 2% to 10% of patients managed conservatively and 10% to 15% of patients treated surgically. Risk factors for nonunion include the type of fracture (ie, transverse and short oblique fractures), smoking, osteoporosis, alcoholism, obesity, previous surgeries, and inadequate treatment.1–3

The surgical treatment of humeral shaft fractures is challenging. The loss of mechanical stability may lead to severe nonuse osteopenia and stiffness of the adjacent joints. Furthermore, the complex muscular and neurovascular anatomy of the upper limb makes the surgical approach to the fracture site demanding and risky, especially when previous surgeries have been attempted.4

The clinical consequence of humeral shaft nonunions is a severe functional limitation that may significantly affect activities of daily living. Therefore, surgical treatment should always be an option, even in older patients.2,3

Patients affected by hypertrophic nonunion may heal if a stable fixation is achieved. However, patients with atrophic nonunions require both a stable fixation and enhancement of the biologic response because of the weak biologic reaction observed at the fracture site.3,4

The literature reports several techniques address humeral shaft nonunions, both in terms of fixation (ie, plates, nails, external fixators) and biological enhancement (ie, autologous or homologous bone graft, demineralized bone matrix, mesenchymal stem cells, bone morphogenetic proteins, platelet-rich plasma).2,5–10 Overall the results are good, especially for open reduction and internal fixation and autologous bone grafting (success rate, 70%–92%).1

Few studies assess treatment of humeral shaft nonunion in the elderly. The gold standard of treatment in this patient population has yet to be described. Nonetheless, older age and comorbidities are associated with potentially malignant nonunions.2,3,11

The current authors report their experience using opposite cortical allograft combined with bone morphogenetic protein 7 (BMP-7) and mesenchymal stem cells to treat humeral shaft atrophic nonunions in 2 elderly patients.

Case Reports
Patient 1
A 77-year-old man presented 19 months after having a humeral shaft spiroid fracture of the right arm. His medical history included hypertension, dysrhythmia, ischemic cardiopathy, type 2 diabetes mellitus, obesity, and severe hip and knee osteoarthritis that forced him to walk using crutches.

The patient reported right-sided functional impotence and preternatural mobility. The humeral shaft fracture had been previously treated elsewhere with 4 months of functional bracing. On clinical examination, both deformity of the arm and preternatural mobility were evident. Range of motion of the elbow was unremarkable, as opposed to the stiff shoulder joint. Radiographic examination revealed atrophic nonunion of the proximal/middle third of the humeral shaft associated with severe nonuse osteopenia (Figures 1A–1B).

The patient was admitted for surgery. The approach to the humeral shaft was performed through a deltopectoral incision extended to the mid-arm. The nonunion site was exposed and debrided. Then, 1.5 cm of necrotic stump was resected and intramedullary canal reaming performed. At the same time, another surgeon aspirated 60 cc of bone marrow from the iliac crest of the patient. The aspirate was processed and concentrated using the SmartPReP 2 bone marrow aspirate concentrate (BMAC) (Harvest Technologies, Plymouth, Massachusetts) to obtain 10 cc of BMAC. A sample (0.5–1 cc) of BMAC was sent to the microbiology laboratory to assess cellularity. Pre- and postconcentration nucleated cells were 16.7×10^3/µL and 75.1×10^3/µL, respectively; pre- and postconcentration platelets were 142×10^3/µL and 502×10^3/µL, respectively. The non-
union site was stabilized (Figure 1C) with an opposite cortical strut (homologous tibial diaphysis), fixed with 2 tricortical compression screws at both sides of the nonunion, and filled with fresh-frozen cadaver cancellous bone, BMP-7 (Osigraft OP-1; Stryker, Mahwah, New Jersey), and BMAC. The nonunion site was stabilized with a locking compression plate (LCP) (Synthes, West Chester, Pennsylvania). The wound was closed as usual, and no drain was inserted.

The arm was protected in a sling for pain control during the first few days postoperatively. The postoperative protocol consisted of early active range of motion of the shoulder and elbow. Radiographic evaluation revealed full healing of the nonunion site 8 months postoperatively. The cortical graft appeared to be fully integrated 11 months postoperatively (Figure 2). At final follow-up 1 year postoperatively, the patient had full functional recovery of the shoulder and return to all activities of daily living. No pain or other complications were associated with BMAC harvesting.

**Patient 2**

An 81-year-old woman presented 23 months after having a transverse fracture of the mid-distal third of the right humeral shaft. Her medical history was significant for hypertension, severe stenosis of the supra-aortic trunks, chronic renal insufficiency, and pulmonary emphysema.

Two years prior to the humeral shaft fracture, the patient had been treated elsewhere for a right-sided proximal humeral fracture that healed with a locking plate. The latter was removed before fixing the midshaft fracture with Ender nails and cerclages. The humeral shaft nonunion was observed on serial radiographs, ultimately resulting in the rupture of the nails 15 months postoperatively (Figure 3A). On physical examination, right arm impotence, preternatural mobility, and elbow stiffness (40° of passive range of motion) were observed (Figure 3B). Radiographic examination was also remarkable for severe nonuse osteoporosis.

The patient underwent surgery to treat the humeral shaft nonunion. The nonunion site was exposed through an extensile posterior approach to the humerus (C). Radiographic (A) and clinical assessment (B) of the nonunion. Intraoperative photograph showing the metal cerclages stabilizing the partial longitudinal distal fracture of the humerus (C).
intramedullary canal was reamed. The nonunion site was filled with fresh-frozen cadaver bone, BMP-7, and BMAC and stabilized with a Synthes LCP plate and opposite tibial cortical allograft. A sample (0.5-1 cc) of BMAC was sent to the microbiology laboratory to assess cellularity. Pre- and postconcentration nucleated cells were $14.3 \times 10^3/\mu L$ and $68.6 \times 10^3/\mu L$, respectively; pre- and postconcentration platelets were $159 \times 10^3/\mu L$ and $492 \times 10^3/\mu L$, respectively. Intraoperatively, a longitudinal incomplete fracture of the distal humerus, most probably caused by compression screw overtightening, was observed. This fracture was treated with metal cerclages (Figure 3C) and 2 months of splint immobilization. Eight weeks postoperatively, the patient started physical therapy to recover both shoulder and elbow range of motion. At about 4 months postoperatively, the nonunion site had healed fully. The cortical strut was stabilized with a Synthes LCP plate and data analyses. A search narrowed to different surgical techniques, advanced and different classifications, treatments, and data analyses. A search narrowed to include only those assessing the treatment of atrophic nonunions of the humeral shaft in the elderly yields even fewer studies. Despite the good results observed with all of these devices, the literature reports satisfactory results with all of these devices. In patients with osteoporotic bone, clinical and biomechanical studies have observed significantly improved stability with the use of a locking plate. In light of these findings, the current 2 patients were treated with a Synthes LCP plate, which allows use of either a locking or a compression screw in any hole. The use of long plates (76% of the total length of the bone or at least 11-hole plates) can enhance the mechanical stability, along with the use of 6.5-mm cancellous (preferably locking) screws, as opposed to 4.5-mm cortical screws in cases of poor grip. Moreover, a cadaver cortical bone graft as an opposite cortical strut, fixed with tricortical screws, may improve the mechanical stability and act as an osteoconductive and osteoinductive scaffold. The potential risks of this procedure are infection and a more aggressive soft tissue stripping required to insert the strut. Marinelli et al reported a cohort of 57 cases of humeral shaft nonunion, 40

**Figure 4:** Postoperative radiographs in complementary views (A). Complementary radiographic views showing bone healing at the nonunion site 4 months postoperatively (B). Complementary radiographic views showing cortical allograft integration 10 months postoperatively (C).
of which were atrophic nonunions. They observed a 93% union rate, whereas the complication rate was comparable to that with other surgical techniques. To limit the soft tissue stripping and to prevent the excessive rigidity of the construct, these authors also recommended using grafts that were shorter than the plate, fixed with 2 proximal and distal screws (with respect to the nonunion site). This allows for early active mobilization. Patient 1 was successfully treated with this technique.

Hypertrophic nonunions are usually secondary to an insufficient biomechanical stability, as opposed to atrophic nonunions, which result from suboptimal biological responses. Therefore, bone healing stimulation in patients affected by atrophic nonunion seems to be crucial. The autologous iliac crest bone graft (ICBG) is the gold standard for providing osteogenic, osteoinductive, and osteoconductive stimuli for bone healing. However, in older patients with age-related comorbidities, ICBG may be associated with potentially severe complications, such as donor site morbidity and blood loss. Furthermore, the quality of ICBG may be too poor in elderly patients to guarantee good mechanical stability and osteogenic potential. Therefore, the authors did not use autologous ICBG for patient 1 or 2. Available options included demineralized bone matrix, cadaver cancellous bone graft, mesenchymal stem cells, and bone morphogenetic proteins. The latter have been successfully used in other bones and districts, including nonunions of the humeral shaft. Despite the satisfactory results reported with these techniques, the most effective bone graft material has yet to be determined through prospective randomized trials.

The 2 cases described here were treated with BMP-7 (osteoinductive stimulus), cadaver bone grafts (osteoconductive stimulus), and mesenchymal stem cells (osteogenic stimulus). Despite previous reports regarding the low cellularity in bone marrow concentrate in the elderly, the BMAC cell count reported demonstrated numerous mesenchymal stem cells in the bone marrow concentrate in these 2 elderly patients.

Both cases reported here showed satisfactory results. The nonunion site healed at 4 months (patient 1) and 8 months (patient 2) postoperatively, with full return to activities of daily living and no pain. Neither patient reported complications of the radial nerve, which is at high risk of injury during this type of surgery. The only reported complication (patient 2) was an intraoperative longitudinal partial distal humeral fracture, probably caused by compression screw overtightening. The fracture was successfully treated with metal cerclages and cast immobilization for 2 months. This complication, previously reported by Ring et al., highlights the technical difficulty of the procedures used to treat these complex cases. It also supports the current authors’ recommendation to use locking screws whenever possible. After 2 months of immobilization, the patient healed successfully without further stiffness in joint motion compared with the preoperative range of motion. King et al. suggested making bone healing (as opposed to allowing early motion) the priority for elderly patients with humeral atrophic nonunions that do not have sufficient mechanical stabilization to allow for early range of motion.

CONCLUSION

The surgical treatment of humeral shaft atrophic nonunions in the elderly represents a challenging scenario for orthopedic surgeons. Successful treatment relies on both mechanical stability and optimal biologic response. The use of a locking plate and opposite cortical allograft, combined with BMP-7 and mesenchymal stem cells, represents a safe and effective treatment for malignant nonunions in older patients.


