FEATURE

Approaches to Using Biologic Solutions for Nonunions of Bone Fractures

Written by Mary Mosley

In patients with a delayed union or malunion of a bone fracture, an autograft or other biologic solution has been shown to be beneficial. Not all nonunions require an autograft, stated J. Scott Broderick, MD, Spartanburg Regional Hospital, Spartanburg, South Carolina, USA; some need mechanical support, some a biologic, and some both.

When a biologic is needed for a nonunion, an autograft is considered the standard because it is biocompatible, provides structural support, fills voids, and is biologically active. Importantly, an autograft is osteogenic, osteoconductive, and osteoinductive. However, there are limitations with autografts, including the supply because of limited donor sites (especially in a patient with multiple injuries) and the historically high rate of morbidity at the donor site, stated Dr Broderick. Some approaches to address these limitations include using alternative donor sites, improving harvest techniques, lowering donor site morbidity, and achieving a higher yield.

The primary source for a bone autograft is the iliac crest. For the anterior crest, minimal disruption of the anatomy is required, including staying on the outside of the crest to minimize postoperative bleeding and maintaining a distance of ≥ 3 cm from the anterior superior iliac spine to avoid its fracture. About 2% of patients have persistent pain at the donor site [Loeffler BJ et al. *J Bone Joint Surg Am*. 2012]. The posterior iliac crest can provide more volume for the autograft, but care is needed to avoid penetrating the sacroiliac joint and not extend beyond the inner cortex. Alternate donor sites are the proximal tibia and the distal femur via the lateral epicondyle, both of which provide a significant volume of bone, any metaphysis, and the Gerdy tubercle.

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Harvesting methods include curettes, pituitary, drill sleeve, commercial harvesters, and intramedullary (IM) harvest. IM harvest provides a similar volume of bone as well as similar rates of union and complications [Dawson J et al. *J Orthop Trauma*. 2014]. However, IM harvesting is complex, and Dr Broderick recommends training at an experienced center and not to use this approach if performing < 1 annually. Complications associated with IM harvest are insertion site pain and femoral fracture because of the technically challenging procedure. It may be possible to maximize the graft by optimizing the recipient bed or by using a graft extender, such as demineralized bone matrix, which can double the graft volume. The Masquelet technique is another potential option; it was shown in animal studies to create an area with a large amount of vascularization for the graft—namely, by placement of a cement spacer into the defect for 4 to 6 weeks and then its exchange for an autologous cancellous bone graft [Pelissier P et al. *J Orthop Res*. 2004]. This technique is being used clinically.

BIOLOGICS: ALTERNATIVE TO AUTOGRAFTS

Biologics, such as growth factors and bone morphogenic proteins (BMPs), are an option in patients with delayed or no healing of the bone, rather than femoral or iliac crest autografts. However, biologics are not a panacea for poor surgical technique or capacity, cautioned Samir Mehta, MD, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania, USA. When selecting a biologic, surgeons should ensure that it best suits the specific setting and goals. Furthermore, surgeons should consider the host resources and graft properties to ensure that the biologic is complementary; the guiding principle is that the graft must supply what the host lacks, and the host must supply what is not inherent to the graft. Host factors must be corrected or optimized. Noninvasive and minimally invasive options are available, and all options, including surgery, should be considered, Dr Mehta stated.

Characteristics of the ideal bone graft substitute include its being biocompatible, bioresorbable, osteoconductive, osteoinductive, easy to use, structural, and cost-effective. Osteoconduction involves the graft's provision of scaffolding, invasion of the capillary and mesenchymal tissue, and gradual population by osteoprogenitor cells to provide a foundation for the bone formation. In osteoinduction, a biologic stimulus induces cells to differentiate into osteoblasts, which form bone. This revascularization and remodeling allows for capillaries to permeate the graft and living bone to replace biomaterial, and the mechanical stresses contribute to repair and realignment.

Orthobiologic options are bone allografts and graft alternatives, such as bone minerals, bone scaffolds, growth factors, cells, ultrasonography or electricity to stimulate the patient's biology, and a combination of these. Cell-based therapies, such as fibroblast growth factor (FGF) and platelet-derived growth factor, are an alternative solution. A single injection of FGF embedded in a gelatin hydrogel resulted in higher rates of radiographic bone union at 24 weeks in patients with a tibial shaft fracture as compared with placebo; there was no difference between the low and high doses of FGF [Kawaguchi H et al. *J Bone Miner Res*. 2010].

BMPs assist the migration of stem cells to the graft site, cell proliferation, differentiation of cells into osteoblasts, and production of bone from osteoblasts. The US Food and Drug Administration has approved recombinant human bone morphogenic protein (rhBMP)-2 for open tibia fractures with IM nail stabilization and anterior spinal fusions. In a prospective randomized study, rhBMP-2 was added to standard of care with IM nail fixation and compared with standard of care in 450 patients with an open tibial fracture. It reduced the risk of nonunion or delayed union by 44% with the high dose ($P = .0005$) and led to significantly faster fracture healing ($P = .0022$) and fewer invasive interventions ($P = .0264$) and hardware failures ($P = .0174$) [Govender S et al. *J Bone Joint Surg Am*. 2002]. Although the investigators reported less infection with rhBMP-2 in this study, a reanalysis of the data by others showed that it increased the rate of infection, stated Dr Mehta.

The US Food and Drug Administration–approved indications for rhBMP-7 are recalcitrant long bone nonunions and revision of posterolateral lumbar spine fusions. In a study comparing rhBMP-7 with the gold standard of fresh bone autograft, the results were similar at 9 months for clinical success, defined as full weight bearing with less-than-severe pain (81% vs 85%, respectively; $P = .524$) and radiographic healing (75% vs 84%; $P = .218$) [Friedlaender GE et al. *J Bone Joint Surg Am*. 2001].

Alternative solutions have recently become more commonplace. Grafting with autologous bone marrow drawn percutaneously from the anterior iliac crest resulted in 53 of 60 patients obtaining bone union of their noninfected fractured tibias [Hernigou P et al. *J Bone Joint Surg Am*. 2005]. The number and concentration of fibroblast colony-forming units in the graft was positively correlated with the volume of mineralized callus at 4 months. Bone marrow is a source of osteogenic stem cells; however, the proportion of stem cells is limited and declines with age. Centrifugation may increase concentration, and cell cultures may increase the numbers, said Dr Mehta.

Ultimately, several options exist for fracture healing augmentation. The choice of graft is based on the surgeon's understanding of the biology of healing or, rather, the lack of healing as well as the properties of the graft being applied. In addition, the surgeon must take into account the surgical technique necessary to provide access for application of the biologic agent while limiting further injury.