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Effect of Osteogenic Progenitor Cell Concentration on the Incidence of Foot and Ankle Fusion

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ABSTRACT

The use of biologics, namely demineralized bone matrix, bone marrow aspirate (BMA), and other growth factors, has gained popularity in foot and ankle surgery for use in compromised hosts or high-risk situations. Our research has shown the concentration of these pluripotent cells was greatest in the iliac crest. A medical record and radiographic review was performed to compare the effect of BMA harvest site osteogenic progenitor cells on the incidence of fusion. Radiographs were reviewed for radiographic evidence of trabecular bridging in 2 or more views. If fusion occurred, the number of osteogenic progenitor cells found in the combined BMA at surgery was recorded. A total of 33 patients were included in the present study. Of the 33 patients, 32 (97.0%) had radiographic fusion at a mean of 13 ± 6 (range 8 to 30) weeks, and 1 (3.0%) experienced nonunion and required revision. The patient procedures were as follows: 18 (54.5%) hindfoot arthrodeses, 8 (24.2%) forefoot arthrodeses, 4 (12.1%) fractures, and 3 (9.1%) isolated ankle fusions. The mean colony-forming units for the patients with fusion was 20.3 ± 23.5 (range 0.0 to 107.0). In the patient with nonunion, it was 0.20 colony-forming unit. Our comparison of the incidence of fusion with the use of osteogenic progenitor cells from 3 anatomic sites showed a low incidence of complications and a high incidence of fusion. No association was found between the BMA concentration and the incidence of fusion, suggesting a minimum concentration and biologic potential of pluripotent cells is necessary to achieve the clinical effect of fusion.

Osseous healing is an extended, complicated process involving multiple cellular signaling lineages interacting with patient and surgical variables. This is a complex relationship of an individual patient's potential to heal, the fixation type, and time. To assist in successful fusion in foot and ankle reconstruction, a biologic adjuvant can be used at surgery. Biologic agents, such as demineralized bone matrix (DBM), bone marrow aspirate (BMA), and other growth factors, have been used in complicated foot and ankle cases to aid in successful outcomes (1–6).

BMA has been harvested from varying sites in the lower extremity, including the anterior inferior iliac crest, medial distal tibia, and lateral calcaneus (Fig.). Autogenous BMA is a safe and potent adjuvant material, because it possesses a greater concentration of hematopoietic, endothelial, and mesenchymal stem cells than does the peripheral whole blood (7). Mesenchymal stem cells have the ability to form osteoblasts and assist in the osseous healing process. Recently, we aimed to assess the exact concentration of osteogenic progenitor cells from these 3 different BMA harvest sites and recorded any site-specific complications (8).

Our research has shown that the concentration of these potent cells was greater in the iliac crest than in the other sites (tibia and calcaneus). However, no statistically significant difference was found in the number or concentration of osteoprogenitor cells located in the distal tibia and the calcaneus (8). To take this one step further, we sought to determine whether this cell concentration had an overall effect on the incidence of fusion in these cases.

The purpose of the present study was to discern whether the incidence of fusion was affected by the concentration or number of osteogenic progenitor cells from BMA harvest. We performed a medical record and radiographic review to compare the effect of the

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Fig. Location of bone marrow aspiration harvest from the lateral calcaneus.

BMA harvest site osteogenic progenitor cells on the incidence of radiographic fusion.

Patients and Methods

The present study was an institutional review board-approved retrospective medical record and radiograph review of patients included in a previously reported prospective analysis ("Assessment of osteoprogenitor cells in bone marrow aspirate obtained from different anatomic locations") (8). This previous study was designed to compare the number and concentration of osteoprogenitor cells among 3 different anatomic harvest sites (ie, iliac crest, tibia, and calcaneus) in the lower extremity from July 2009 to June 2011. Each patient had BMA harvested from all 3 sites. A sample from each site was sent to the laboratory for comparison. The remaining aspirate from each site was mixed together and injected into the surgical site. A statistically significant greater concentration of cells was found from the iliac crest harvest site compared with the other 2 sites, the calcaneus and distal tibia ($p < .0001$ and $p < .0001$, respectively). Also, no statistically significant difference was found between the calcaneus and distal tibia sites ($p = .063$) (8).

Forty patients were included in the previously completed study (8). To be included in that study, the following criteria had to be met:

1. Patient age 18 years or older
2. A requirement for arthrodesis or fracture surgery involving augmentation with BMA as a part of our institution's standard of care
3. The ability to understand the study protocol
4. Provision of written informed consent

Exclusion criteria included the following:

1. Previous marrow harvesting from the calcaneus, distal aspect of the tibia, or iliac crest
2. Irradiation of the ipsilateral foot, ankle, or pelvis
3. Presence of an active infection
4. A myeloproliferative disorder or the use of immunosuppressive drugs
5. Surgical revision
6. Inadequate radiographic follow-up data
7. Pregnancy

Thirty-three patients met the inclusion criteria and were included in the current study. The previous cell concentrations for those 33 patients were documented. Seven patients were excluded from the current study due to inadequate radiographic follow-up or a non-osseous index procedure was performed. Those who did not have radiographs taken at their final follow-up examination or did not have any radiographs taken throughout the course of healing were considered to have inadequate radiographic follow-up data. One of us (J.E.M.) reviewed all the patients' medical records and was not involved in any operative care in either study. The other authors' (C.F.H., G.C.B.) practice was the source of the prospective study participants and performed the operations. The primary outcome measure was complete radiographic fusion evident by trabecular bridging of $\geq$2 cortices. The secondary outcomes included the interval to partial and full weightbearing after surgery.

The study variables included basic demographic data, including patient age, sex, body mass index, tobacco use at surgery, history of diabetes mellitus, worker's compensation, number and concentration of osteogenic progenitor cells per patient, surgery type, interval to weightbearing (partial and full), and complications such as nonunion and revision surgery.

A comparison of the mean, standard deviation, and range was performed using Excel®, version 2010 (Microsoft Corporation, Redmond, WA), and the incidence of fusion was determined.

Results

A total of 33 patients were included in the present retrospective review (Table 1). Of the 33 patients, 20 (60.6%) were female and 13 (39.4%) were male, with a mean age of 51 $\pm$ 13 (range 23 to 84) years. Three patients (9.1%) were diabetic, and 8 (24.2%) smoked tobacco at surgery. The mean body mass index was 33 $\pm$ 6.4 (range 19 to 42) kg/m^2. The cases of 4 patients (12.1%) were worker's compensation cases. The patient procedures were as follows: 18 (54.5%) hindfoot arthrodeses, 8 (24.2%) forefoot arthrodeses, 4 (12.1%) fractures, and 3 (9.1%) isolated ankle fusions.

Thirty-two patients (97.0%) had radiographic evidence of fusion at a mean of 13 $\pm$ 6 (range 8 to 30) weeks. However, 1 patient (3.0%) experienced nonunion and required revision surgery. The mean number of colony-forming units (CFUs) for the 32 patients with fusion was 20.3 $\pm$ 23.5. The patient with nonunion had a mean number of CFUs of 0.20. The 1 patient with nonunion was a nondiabetic, nonsmoker, obese individual who had undergone triple arthrodesis (Table 2). The mean interval to partial weightbearing was 5.5 $\pm$ 2.5 (range 0 to 11) weeks and to full weightbearing was 13 $\pm$ 5 (range 3 to 26) weeks.

The 1 notable complication (3.0%) involved a worker's compensation case. The patient was noncompliant and sustained a medial distal tibial diaphyseal stress fracture at the tibial BMA site after continually weightbearing on her lower extremity despite the postoperative instructions. The stress fracture was treated uneventfully in a tall fracture boot. No other complications were noted.

Discussion

The goal of any arthrodesis procedure or fracture care is to attain relative immobility of the articulation between the bone fragments. Some controversy exists regarding the amount of bone healing necessary to achieve the clinical success of fusion. With modern internal fixation techniques, primary bone healing is the goal, although mixed bone healing (primary and secondary) is common. The use of biologic agents in foot and ankle surgery has become a key adjuvant in primary and revision cases, especially when patients are immunocompromised or have poor healing potential. In addition to the various forms of structural bone grafts, BMA has become a source of powerful potent cells, and the harvest and placement can be easily performed with minimal complications (2).

BMA contains bone morphogenic proteins, multiple growth factors, and live mesenchymal stem cells to aid in osseous healing (9). The specific concentration of osteogenic progenitor cells from 3 different anatomic sites has been researched in a previous study (8). Hyer et al (8) provided evidence that the anterior iliac crest has the greatest concentration of osteogenic progenitor cells. In addition, they concluded that the distal tibia and calcaneus both have significant quantities of progenitor cells but found no statistically significant