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OTA Basic Science Forum  
October 17<sup>th</sup>-18<sup>th</sup>, 2018

***Cell based Therapies for Fractures***

**Bone marrow Aspirate Concentrate in the Treatment of Fractures**

Cellular therapy has been described, promoted, and marketed as facilitating all aspects of skeletal repair. For the practicing surgeon it is difficult to integrate the basic science material with clinically relevant indications and techniques for the application of these materials. We hope to provide the practitioner with a common-sense approach regarding the indications and application of this evolving technology.

- 1) Common biological requirements for bone regeneration
  - a. Cells: Adult progenitor cells from the marrow, periosteum, and other sources
  - b. Blood supply: For the delivery of nutrients, oxygen, and systemic factors required for cell survival
  - c. Molecules and their receptors: Provides for the induction of cells to proliferate and differentiate into osseous tissue (osteinduction)
  - d. Extracellular matrix: To provide a scaffold for cells (osteoconduction), and storage site for growth factors
- 2) Marrow aspirates have been utilized in three primary techniques for delivery.
  - a. Cells selected by withdrawal from bone marrow, subsequent culture in the laboratory, and ultimately transplant at the site of injury;
  - b. Bone marrow aspirate, concentrated and directly implanted into the injury site;
  - c. Systemic mobilization of stem cells and other bone marrow precursors by the use of growth factors. (Marmotti A)
- 3) Fracture / nonunion location
  - a. Use thoughtful use of cellular adjuvant materials in this location depends on numerous factors
    - i) Evaluation of fx site. Mid shaft tibia fracture is usually a biologically “challenged” region
      - (1) The appropriate migration of cellular components to the site of bone graft or fracture is crucial in continuing the progression of the fracture healing cascade. Consideration of delivering these cells to the region in question.
      - (2) Condition of soft tissues and “zone of injury” local environment  
Placing graft in a “dead zone”

- 4) Specific technique of aspiration and delivery
  - a. Muschler, GF, Boehm, C, Easley K. Aspiration to obtain osteoblast progenitor cells from human bone marrow: the influence of aspiration volume. *J Bone Joint Surg Am* 1997Nov (11):1699-1709
- 5) Graft delivery
  - (a) **Composite grafts**
    - (i) DBM + Autogenous cellular concentrates, BMAC +, - platelet gels (as carrier)
      1. Limited success with centrifuged aspirate **alone** (Connelly, Watson)
      2. Concentration of CFU's in conjunction with carrier materials (Hernigou)
      3. Augmentation of regenerate with BMAC (100% consolidation)
 

Need to achieve threshold concentrating of viable CFU's (Gessmann J, et.al. *Orthop Rev (Pavia)*. 2012 Jan 2;4(1):e14.)
    - (b) Providing scaffolding for mesenchymal cell infiltration. Depending on the temporal relationship of the delivery of the inductive factor to the cell population in question, will determine the specific effect that each protein has on the fracture healing cascade. It is important that these stem cells have the appropriate conductive surface to migrate on to initiate the further production of their specific induced function.
    - (c) Providing Colony forming units (CFU's) (Hernigou)( Tideman / Lindsay
 

Meta analysis for *BMAC* application nonunion  
 100% showed significant increase in bone formation in theBMAC group on radiograph. 90% reported significant improvement in earlier bone healing on histologic/histomorphometric assessment. 81% reported a significant increase in bone area on micro-computed tomography. 78% showed a higher torsional stiffness for the BMAC treated defects. (*J Orthop Trauma*. 2015 Sep 14)
- 6) At this time, there is much to be learned regarding the role of cell therapies for hard tissue repair. Several reports have suggested success of some of these therapies and the quality of the evidence is good (levels II and III). Further investigation, particularly the development of effectively powered randomized controlled trials, is needed to truly advance this field of study and provide reliable treatments for patients

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