

OTA ANNUAL MEETING 2016
ORTHOPAEDIC TRAUMA BOOTCAMP

ORTHOBIOLOGICS FOR ORTHOPAEDICS AND TRAUMATOLOGY

There are clearly no well defined indications for use of a specific type of bone graft substitute or use of inductive factor when dealing with complex fractures, especially when dealing with acute bone and soft tissue defects. The use of all of these materials should be based on contemporary fracture management principles and current levels of evidence for use of these materials

1) Osteoinductive Bone Substitutes

- a) Autologous Bone...considered the GOLD STANDARD...
 - i) There are few reports that actually provide the evidence for the clinical efficacy of autograft.
- b) Allogeneic Bone and Demineralized Bone Matrix
 - i) No reports that carefully evaluate the osteoinductive properties of allograft bone.
 - ii) Animal studies have documented DBM's osteoinductive effects, there is a paucity of clinical information with similar findings.
 - (1) Only one prospective controlled study showing equivalent rates of spinal fusion in the same patients treated with autograft versus a 2:1 ratio composite DBM(gel)/autograft, suggesting potential use DBM as a bone-graft extender. Only anecdotal information is available regarding similar applications in long bone fractures and nonunions.
 - (2) Evidence of differential potencies of DBM preparations based on the manufacturer and manufacturing process.
- c) Bone Morphogenetic Proteins
 - i) Urist, Johnson and colleagues first used the protein in clinical settings. Uncontrolled retrospective series (Level 4 evidence) had encouraging results and stimulated further investigation in this area.
 - ii) Two recombinant BMPs have been developed for clinical use; rhBMP-2 and rhBMP-7 Each has been evaluated in randomized, controlled trials in trauma patients and these studies provide data that qualify as Level 1 evidence.
 - (1) Clinical use for diaphyseal open tibia fractures, long bone nonunion, and spinal fusion.

2) Osteoconductive Bone Graft Substitutes

- a) Allograft
 - i) Level 4 evidence exists for use of cortical allograft in reconstructive and trauma surgery of the humerus and femur. Further research is needed to determine the ideal material for encouraging bone formation with these applications.
 - ii) Calcium ceramic synthetic substitutes

- (1) Bone formation by providing an osteoconductive matrix for host osteogenic cells to create bone under the influence of host osteoinductive factors, for use in metaphyseal defects
- (2) **Recommendations for use**
 - (a) **CaPO₄**: Level I-II for use as an adjunct to internal or external fixation in fractures of the tibial plateau, intertrochanteric hip fractures and calcaneus fractures. Level I for use in distal radius fractures
 - (b) **CaSO₄**: Level I-II for use as a resorbable antibiotic bead in infected nonunions
 - (i) Level III for use as an adjunct to internal fixation in tibial plateau fractures
 - (ii) **Allograft**: Level IV : no significant published evidence for use in non spinal skeletal Fractures
 - (iii) **Hydroxyapatite** Level I for use in tibial plateaus as an adjunct to internal fixation

3) **Materials With Osteogenic Properties**

- a) Bone marrow aspirate has a high concentration of CTPs. One milliliter of iliac aspirate contains approximately 40 million nucleated cells 1500 of which are CTPs..Clinical use with concentration and implantation for Fx and nonunions.
 - i) Human data is limited, only case reports treating a limited number of patients demonstrating successful treatment in spinal fusion and nonunion patients (Level 4).
- b) Use of Platelet – Rich Plasma and Related Peripheral Blood Concentrates
 - i) Level 1 evidence in the Basic science literature to strongly support the positive effects and cellular stimulation by these adjuvants as a mechanism for bone repair.
 - (1) Published prospective comparative studies are currently lacking.
 - (a) Indications for foot and ankle surgery , diabetics, and smokers. (level 3/4)

SPECIFIC INDICATIONS.....

- 1) **Metaphyseal defects**
 - a) For most metaphyseal defects, it has been shown experimentally that a simple cancellous void will reconstitute on its own and heal completely given a sound biologic environment without the addition of any further grafting material. The danger here is that the subchondral surface will collapse if this defect does not reconstitute fast enough to provide subchondral support with the initiation of wt. bearing
 - i) **Conductive substrates**
 - (1) **Ca ceramics. CaSO₄/ CaPO₄**
 - (a) Incorporation characteristics...i.e rates of osteointegration
 - (b) Ultimate compressive strength mPa
 - (c) Delivery mechanism. Particulate vs self setting “cements”
 - (d) Incorporation time vs bone regenerated into defect
 - (i) Cellular mediated vs chemical degradation of materials

- (ii) Use of marrow concentrates to accelerate incorporation characteristics. “seeding the graft”
 - (e) Multiple studies with good Level I and II evidence support use of both sulfate and phosphate materials for contained metaphyseal defects.
 - (i) Demonstrated superiority over autogenous graft materials.
 - (2) MECHANICAL Factors. Use of conductive substrate materials in metaphyseal defects augmented with use of locking plates for plateau, distal femoral, and pilon fractures
 - (a) MINIMAL evidence currently avail for use of supplementary locking plates in these locations.
- 2) Diaphyseal fractures
- a) Use of 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) Acute bone loss vs non-union defect
 - (3) Condition of soft tissues and “zone of injury” local environment
 - (a) May require angiography / MRI to determine vascularity/viability of host defect. Most graft failures are as a result of inadequate or poor host nutrition to the local graft region as most fx sites and nonunions are often at the site of thick scar and / or relative avascularity. There is no substitute for preparing the host recipient bed appropriately by resecting the avascular / necrotic tissue and providing healthy tissue for eventual revascularization and thus success of the graft.
 - (b) Flap / soft tissue coverage.....reconstitution of inflammatory phase of Fx healing (neo vascularization)
 - (4) Size of defects
 - (5) Infection status
 - (6) Mechanical stability
 - ii) Acute defect / delayed union / subcritical defect (without total segmental loss) With internal fixation i.e. plate / IM nail
 - (1) Graft options
 - (a) Composite grafts
 - (i) DBM + Autogenous cellular concentrates, +, - platelet gels (as carrier)
 1. Limited success with centrifuged aspirate alone (Connelly, Watson)
 2. Concentration of CFU’s in conjunction with carrier materials (Hernigou) (Jimenez....Astrom technique)
 - iii) Acute critical sized defect / nonunion. (segmental loss <4cm)
 - (1) Graft options
 - (a) BMP-2 implantation at time of wound closure (open tibia fx) (BESTT study results)
 - (b) Segmental defects up to 4 cm (Bucholz, Jones et.al)

- (c) OP-1 (McKee ..Canadian open tibial shaft study)
- (d) OP-1 for nonunions (equivalent efficacy between autograft and OP-1)
- (e) 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.
- (f) Providing Colony forming units (CFU's) (Hernigou)
- iv) Large segmental defects
 - (1) Staged reconstruction
 - (a) Antibiotic spacer / beads / rods
 - (i) Carrier for inductive materials
 - (ii) Carrier for antibiotics
 - 1. PMA
 - 2. CaSO⁴
 - (b) Development of vascularized pseudo-membranes.. Masquet technique)
 - (i) Grafting directly into vascularized pseudo membrane
Using RIA derived bone graft.
 - (ii) Membrane directed bone regeneration
 - (2) Bone transport
 - (a) Segmental bone loss remains problematic and usually requires massive quantities of graft material, whether it be a composite graft utilizing transplant of autogenous cellular material in combination with a competent osteoconductive substrate as well as inductive proteins are necessary to bridge large structural defects. Problems here include the lack of rapid remodeling and as such these defects are prone to fatigue failure and stress fracture. Large segmental defects often require bone transport versus free tissue transfer such as vascularized iliac crest or free fibula or combinations of both.
 - (b) Ultrasound directed rapid transport of over nail with autodistractors
 - (c) Augmentation of rapid regenerate with BMP's
 - (3) Free tissue transfer
 - (a) Combination methodologies with bone transport and inductive factor augmentation
 - (4) Ti cage / graft / IM nail.... defect replacement (Lindsey)
- 3) Adjuvant therapies
 - a) Ultrasound...LIPUS (Low Intensity Pulsed Ultrasound) for treatment of fresh fractures
 - i) Heckman. Et al....Fresh tibial shaft fxs. Effective: 24%(clinical) and 38% (clinical and radiographic) acceleration
 - ii) Leung....Tibial shaft fx. With comminution IM nail / ex fix. Effective: 42% Acceleration.
 - b) Ultrasound ...for delayed and nonunions

- i) Prospective cohort studies revealed that the overall success rate of LIPUS for nonunions is 55% to 100%
- c) Ultrasound adjuvant to distraction osteogenesis (Gold et al.)

Many basic science and some clinical trials have shown that LIPUS could be a useful method for enhancement or acceleration of healing in some kinds of fresh fractures and nonunions. However, the role of LIPUS for fracture healing is still unknown because of the heterogeneity of results in clinical trials for fresh fractures and the lack of controlled trials for delayed unions and nonunions. There is still a need for more RCTs with large numbers of participating patients from multiple centers.

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