

OTA Annual Meeting
Basic Science Focus Forum

Bone grafting Symposium #3

Bone Graft Extenders: Which Ones Work?

INTRODUCTION AND BASIC SCIENCE OVERVIEW

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 or nonunions. This is especially true 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) 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

DO THEY WORK?.....WHAT DO YOU WANT THEM TO DO?

- Simple void filler? (dead space management)(delivery vehicle)
- Mechanical support?
- Augment routine bone graft i.e bone graft extender? With inductive potential?

- 2) Extracellular matrix:
 - a) Properties for function
 - i) Space filler (biocompatibility)
 - ii) Structural properties (mechanical)
 - iii) Microstructural (biological for cell surface adhesion/healing)
 - b) ECM scaffolding characteristics
 - i) Substrates for bone replacement
 - ii) Resorption over time
 - iii) Requires cells for cytokines or potency
 - iv) Dependent upon defect types or loads
 - v) Clinical studies frequently compare efficacy of osteobiologics to cancellous autograft as gold standard
 - (a) Late subsidence reported with autograft when used as bone void filler for plateau / pilon fx.
 - vi) DBM as bone void filler
 - (a) Conductive due to tremendous surface area afforded by particulate nature of material

- (b) No inherent mechanical stability
 - 1) Cannot be utilized as bone void filler in *wt. bearing locations*...
 - 2) Satisfactory for “contained “ defects i.e solitary bone cyst.

 - 3) Metaphyseal defects
 - a) Experimentally it has been shown 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. $\text{CaSO}_4 / \text{CaPO}_4 / \text{Ca PO}_3\text{Si} / \text{composite SO}_4\text{- PO}_4$
 - (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) Allograft / Allograft composites
 - (a) Conductive substrate
 - (b) Moldable / may instrument and provide mechanical support metaphyseal cortical defects , transitional zone from metaphysis to diaphysis
 - (c) Compressive strength approximates cancellous bone for wt. bearing
 - (i) Relative mechanical deficiency of Allograft “croutons” for bone void filler in peri-articular situations (i.e plateau fx void filler)
 - (3) 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.
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- 4) Diaphyseal fractures
 - a) Use of adjuvant *EXTENDER* 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) Flap / soft tissue coverage.....reconstitution of inflammatory phase of Fx healing (neo vascularization)
- (4) Graft *EXTENDER* 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)
- ii) 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 (Buchholz, 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)
 - iii) 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.. Masquelet technique)
 - (i) Grafting directly into vascularized pseudo membrane Using RIA derived bone graft.
 - (ii) Membrane directed bone regeneration
 - (2) Bone transport
 - (3) Free tissue transfer
 - (a) Combination methodologies with bone transport and inductive factor augmentation
 - (b) Vascularized fibula

References

1. Tiedeman JJ, Garvin KL, Kile TA, et al. The role of a composite, demineralized bone matrix and bone marrow in the treatment of osseous defects. *Orthopaedics* 1995;18:12:1153-1158.
2. Johnson EE, Urist MR, Finerman GAM. Bone morphogenetic protein augmentation grafting of resistant femoral non-unions. A preliminary report. *Clin. Orthop.*, 230:257-265, 1988.
3. Friedlaender GE, Perry CR, Cole JD, et al. Osteogenic protein 1 (bone morphogenetic protein 7) in the treatment of tibial nonunions. *J Bone Joint Surg Am* 2001;83:S151-158.
4. Govender S, Csimma C, Genant HK et al. Recombinant human bone morphogenetic protein 2 for treatment of open tibial fractures. A prospective, controlled, randomized study of four hundred and fifty patients. *J Bone Joint Surg Am* 2002,84:12:2123-2134.
5. McKee MD, Schemitsch EH, Waddell JP, Kreder HJ, Stephen DJG, Leighton RK, Buckley RE, Powell JN, Wild LM, Blachut PA, O'Brien PJ, Pirani S, McCormack RG. The effect of rhBMP-7 on the healing of open tibial shaft fractures: Results of a multicenter, prospective randomized clinical trial. Proceedings of the 18th Annual Meeting of the Orthopaedic Trauma Association, Oct 12, 2002, p157-158.
6. Bucholz RW, Carlton A and Holmes R. Interporous hydroxyapatite as a bone graft substitute in tibial plateau fractures. *Clin Orthop*, (240): 53-62, 1989.
7. Larsson S and Bauer TW. Use of injectable calcium phosphate cement for fracture fixation: a review. *Clin Orthop*, (395): 23-32, 2002.
8. Kopylov P, Runnqvist K, Jonsson K and Aspenberg P. Norian SRS versus external fixation in redisplaced distal radial fractures. A randomized study in 40 patients. *Acta Orthop Scand*, 70(1): 1-5, 1999.
9. Zimmerman R, Gabl M, Lutz M, Angermann P, Gschwentner M and Pechlaner S. Injectable calcium phosphate bone cement Norian SRS for the treatment of intra-articular compression fractures of the distal radius in osteoporotic women. *Arch Orthop Trauma Surg*, 123(1): 22-7, 2003.
10. Cassidy C, et al. Norian SRS cement compared with conventional fixation in distal radial fractures. A randomized study. *J Bone Joint Surg Am*, 84-A(11): 2127-37, 2003.
11. Lobenhoffer P, Gerich T, Witte F and Tscherne H. Use of an injectable calcium phosphate bone cement in the treatment of tibial plateau fractures: a prospective study of twenty-six cases with twenty-month mean follow-up. *J Orthop Trauma*, 16(3): 143-9, 2002.
12. Watson JT. The Use of an Injectable Bone Graft Substitute in Tibial Metaphyseal Fractures. *Orthopedics* 27(1): 103-105, 2004.
13. Horstmann WG, Verheyen CC and Leemans R. An injectable calcium phosphate cement as a bone-graft substitute in the treatment of displaced lateral tibial plateau fractures. *Injury*, 34(2): 141-4, 2003.
14. Schildhauer TA, Bauer TW, Josten C and Muhr G. Open reduction and augmentation of internal fixation with an injectable skeletal cement for the treatment of complex calcaneal fractures. *J Orthop Trauma*, 14(5): 309-17, 2000.

15. Muschler GF, Midura MJ. Connective Tissue Progenitors: Practical Concepts for Clinical Applications. *Clin Orthop* 2002; 395:66-80.
16. Muschler, GF, Midura RJ, Nakamoto C. Practical modeling concepts for connective tissue stem cell and progenitor compartment kinetics. *J Biomed Biotechnol.* 2003;3(2003)1-20.
17. Hernigou P et al; Percutaneous Autologous Bone-Marrow Grafting for Nonunions. *J. Bone and Joint Surg.*, 87-A No. 7 July 2005
18. Hernigou P et al; Treatment of Osteonecrosis with Autologous Bone Marrow Grafting. *Clin Orthopaedics and Rel Res.*, 405: 14 – 23, 2002
19. Muschler GF, Nakamoto C, Griffith LG. Engineering principles of clinical cell-based tissue engineering. *J Bone Joint Surg Am.* 2004 Jul; 86-A (7):1541-1558.
20. 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
21. Connolly JF, Guse R, Tiedeman J, Dehne R. Autologous marrow injection as a substitute for operative grafting of tibial nonunions. *Clin Orthop* 1991; 266:259-269.
22. Connolly J, Guse R, Lippiello L, Dehne R. Development of an osteogenic bone-marrow preparation. *J. Bone and Joint Surg.* 1998; 5:684-690.
23. Tiedeman JJ, Connolly JF, Strates BS, Lippiello L. Treatment of nonunion by percutaneous injection of bone marrow and demineralized bone matrix. An experimental study in dogs. *Clin Orthop.*1991 Jul ;(268):294-302.
24. Brude Slater M, et al. Involvement of Platelets in Stimulating Osteogenic Activity *J Ortho Research* 13:655-663, 1995.
25. Marx RE, Carlson ER, Eichstaaedt RM, et. al, Platelet Rich Plasma; Growth Factor Enhancement for Bone Grafts. June 1998, *J Ortho Research* 85(6) 13:655-663, 1995.
26. Cierny G, Zorn KL. Segmental tibial defects, comparing conventional and Ilizarov methodologies. *Clin. Orthop.* 301: 118-133, 1994.
27. Green SA, Jackson JM, Wall DM, Marinow H, Ishkanian J. Management of segmental defects by the Ilizarov intercalary bone transport method. *Clin Orthop*: 280:136-142, 1992.
28. Gold SM, Wasserman R. Preliminary results of tibial bone transports with pulsed low intensity ultrasound (Exogen). *J Orthop Trauma.* 19(1):10-6, 2005.
29. Lowenberg DW, Feibel RJ, Louie KW, Eshima I. Combined muscle flap and Ilizarov reconstruction for bone and soft tissue defects. *Clin Orthop.* 332:37-51, 1996.
30. Mahaluxmivala J, Nadarajah R, Allen PW, Hill RA.: Ilizarov external fixator: acute shortening and lengthening versus bone transport in the management of tibial non-unions. *Injury.* 36(5):662-668, 2005.
31. Matsuyama J, Ohnishi I, Kageyama T, Oshida H, Suwabe T, Nakamura K. Osteogenesis and angiogenesis in regenerating bone during transverse distraction: quantitative evaluation using a canine model. *Clin Orthop.* 433: 243-250, 2005.
32. Mekhail AO, Abraham E, Gruber B, Gonzalez M. Bone transport in the management of posttraumatic bone defects in the lower extremity. *J Trauma.* 56(2):368-378, 2004.

33. Oedekoven G, Jansen D, Raschke M, Claudi BF: The monorail system--bone segment transport over unreamed interlocking nails. *Chirurg.* 67(11):1069-1079, 1996.
34. Song HR, Kale A, Park HB, Koo KH, Chae DJ, Oh CW, Chung DW: Comparison of internal bone transport and vascularized fibula femoral bone defects. *J Orthop Trauma.* 17(3):203-211, 2003.
35. Watson JT. Treatment of Tibial Fractures with Bone Loss. *Techniques in Orthop.* 11(2): 132-143, 1996.
36. Watson JT, Anders, M, Moed BR: Management Strategies for Bone Loss in Tibial Shaft Fractures. *Clin Orthop.* 315:138-152, 1995.
37. Rozbruch RS, Weitzman AM, Watson JT, Freudigman P, et.al. Simultaneous Treatment of Tibial Bone and Soft –tissue Defects with the Ilizarov Method. *J Ortho Trauma* 20(3):197-205, 2006.
38. Watson JT, Distraction Osteogenesis. *Journal of AAOS* Oct; 14(10) 168-74. 2006.
39. DeLong, W, Einhorn, T, Koval, K, Watson JT, et.al. Bone Grafts and Bone Graft Substitutes in Orthopaedic Trauma Surgery. A critical analysis. *J Bone Joint Surg Am.* 2007 Mar;89(3):649-58. Review.
40. Quigley K, Watson JT, Mudd C, Iliac Crest Aspiration and Injection in the Treatment of Delayed and Nonunion. Paper Presentation. Abstracts of the 22nd Annual Meeting OTA. Phoenix ,AZ. Oct 3-7, 2006.
41. Hernigou P et al; Percutaneous Autologous Bone-Marrow Grafting for Nonunions. *J. Bone and Joint Surg.*, 87-A No. 7 July 2005
42. Hernigou P et al; Treatment of Osteonecrosis with Autologous Bone Marrow Grafting. *Clin Orthopaedics and Rel Res.*, 405: 14 – 23, 2002
43. Heckman JD, Ryaby JP, McCable J, et al. Acceleration of tibial fracture healing by non-invasive, low-intensity pulsed ultrasound. *J Bone Joint Surg Am.* 1994;76:26–34.
44. Leung KS, Lee WS, Tsui HF, et al. Complex tibial fracture outcomes following treatment with low-intensity pulsed ultrasound. *Ultrasound Med Biol.* 2004;22:486–490.
45. Gold SM, Wasserman R. Preliminary results of tibial bone transports with pulsed low intensity ultrasound (Exogen). *J Orthop Trauma.* 2005; 19:10–16.