Bone Graft Substitutes: Is Anything as Effective as Autograft?

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Disclosures

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• Research Support:
  • Synthes

• Consultant:
  • Exactech

Goals and Objectives

• Describe scope of issue

• Discuss the physiology of fracture healing

• Examine the various properties of bone grafts and bone graft substitutes
It All Depends

Background

- Nonunion estimated in 5-10% of all fractures (Calori, Injury, 2011)
- Significant economic burden
- $23,000 to $58,000 (Kanakaris, Injury 2007)

Fracture Healing

- Fundamental Prerequisites:
  - Mechanical Stability
    - Adequate reduction and fixation
  - Favorable Environment
    - Blood supply to fracture site
    - Sequential activation of cell type and bioactive molecules
Bone Grafting

- 2.2 million bone grafting procedures/year  
  (Calori, Injury, 2011)
- Autologous bone graft/bone marrow aspirate
- Allograft
- Synthetic bone graft
Cancellous Autograft

- Iliac Crest Bone Graft
  - Gold standard
  - Corticocancellous
  - Osteoconductive, osteoinductive, osteogenic

- Hernigou et al: IC rich in colony forming cells; number of cells directly correlates with healing

Materials and Methods

Quantitative Assessment of the Bone Morphogenetic Protein Expression From Harvested Bone Graft

Image: Kenneth A. Egol, MD

Hospital for Joint Diseases ● Department of Orthopaedic Surgery
Materials and Methods

- RNA isolated
- Microarray analysis of three bone harvest graft sites
- RT-PCR analysis of BMP and antagonist expression

Results

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<tr>
<th>Gene of Interest</th>
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<th>BMP-4</th>
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Summary

- Genetic expression of BMP-2 and BMP-5 was found to be 33% higher than other BMP types at IC
- BMPr2 and BMPr1A (BMP receptors) were also upregulated 2 and 5 times respectively in the iliac crest compared to the tibia and humerus
- The genetic expression of the other BMPs were equivalent in the three potential bone graft harvest sites
- Connexin 43, FGF-6, PDGF demonstrated increased expression compared to tibia and humerus
Cancellous Autograft

• Cons
  • Donor site morbidity
  • Newer techniques have better outcomes
  • Increased operating time, hospital stay
  • Can’t use in some patients
    • Inadequate volume (osteoporosis)
    • Compromised bone (recent harvest or fracture)

Bone Graft Substitutes

Bone Bank Allograft

• Pros
  • Large experience
  • Readily available
  • Many forms: freeze dried, fresh frozen, demineralized
  • Greater supply than demand

Bone bank allograft
• DBM
• Coraline hydroxyapatite
• Calcium phosphate
• Calcium Sulfate
• Collagraft (collagen graft)
• BMP2, BMP7

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**Bone Bank Allograft**

- **Cons**
  - Disease transmission
  - Procurement costs
  - Rejection (*contain marrow and vascular components*)
  - Inconsistent incorporation
  - Late resorption
  - Processing affects strength and incorporation

**Demineralized Bone Matrix**

- Demineralized bone matrix
- Urist (1965) placed DBM in muscle pouch of rat \(\Rightarrow\) new bone formation
- BMPs extracted
- Osteoconductive, weakly osteoinductive

**Demineralized Bone Matrix**

- A number of commercial preparations of DBM
  - AlloFuse, Intergro, Optefil, Opteform, Optecure, Grafton, Viagraft, etc.
- Prepared from allograft
- Poor handling
- No structure
- Osteoconductive
- Weakly osteoinductive
Synthetic Bone Graft

• Bone graft use in US increasing
• Shortage of bone graft donors
• Increasing need for synthetic bone graft substitutes

Synthetic Osteoconductive Material

Hydroxyapatite
• Porous structure similar to cancellous bone
• Effective osteoconductive matrix
• Mineralization and remodeling → mature bone

Coralline hydroxyapatite
• South Sea coral skeletons converted to pure, crystalline HA
• Good compressive, low tensile strength
• Limited remodeling potential

Both lack osteogenic and osteoinductive properties

Image: Biostructures.net
**Synthetic Osteoconductive Material**

**CaPO₄ and CaSO₄ Cement**
- Primarily osteoconductive
- Useful in filling metaphyseal bone gaps
- Compressive strength 15-55 mp
- Weakness in torsion and shear
- Extrusion into soft tissue?
- CaSO₄ resorption >> CaPO₄
- Association w/ serious wound drainage
- $400 - $2,000 per 5ml

**Collagraft (collagen graft)**
- Osteoconductive bone matrix
- Porous beads
  - 60% hydroxyapatite
  - 40% tricalcium phosphate + fibrillar cartilage
- Autograft expander when combined with BMA
- Poor mechanical characteristics

**Osteoinductive Proteins**

**Bone Morphogenetic Proteins**
- Wozney et. al 1988 identified genetic sequence of BMPs
- Cheng et. al 2003, characterized 14 types of human BMPs
  - TGF-β superfamily
  - Commits stem cells to osteoprogenitors
  - Produce H.O.
  - Actively expressed in fracture callus
  - BMP-2 and BMP-7 successful in human trials
Recombinant Human (rh)BMP-2
(Infuse)

rhBMP-2 Animal Studies

- BMP-2 knockout mice show a propensity to develop non-healing extremity fractures
- BMP-2 injected into rats induces new bone growth within 14 days
- Wang et al. (PNAS) suggests BMP-2 is required for initiation of fracture healing

- Einhorn et al. (JBJS) has shown that injection of rhBMP-2 accelerated healing of femoral fractures in rats
- Histological analysis showed rhBMP-2 induced mice had a larger, more vascular fracture callus
rhBMP-2 (Infuse)

Recombinant Human (rh)BMP-7 (OP-1)

- Osteogenic
- Peaks later in fracture healing than BMP-2
- Strong extracellular antagonists: noggin, chordin, follistatin, DRM/gremlin, sclerostatin
rhBMP-7: Initial Animal Trials

- Makino et al. (JOR) was one of the first to show benefit for rhBMP-7 in nonunions
- At 6 weeks, all of control animals had nonunion while all of the treated rats had healed

rhBMP-7: Clinical Trials

- Friedlander et al. (JBJS) looked at 124 patients with tibial nonunions
- Prospective, randomized – rhBMP-7 vs. ICBG
- No difference in outcomes, increased pain with ICBG

rhBMP-7 Clinical Trials

Small studies initially showed benefit in pelvis and humerus fractures
- Higher powered studies have failed to reproduce results

Recent studies have evaluated combination of autograft + rhBMP-7 in fracture healing
- Giannoudis et al. showed a 100% union rate in a small (n=45) 2009 study
- Fewer complications

Upper extremity trials have been less promising
Potential Complications of BMPs

- Small risk of:
  - Immune reaction
  - Ectopic bone formation
- Little data on adverse events for off-label uses
- Long term complications unknown
- Spine surgery: unpublished industry data suggests increased adverse events (Yale YODA Project, 2013)

Cost effectiveness of BMP products

- Limited evidence
- 2010 Cochrane review suggests:
  - BMPs unlikely cost effective in spinal fusion
  - BMPs may be cost effective in acute, open tibial fractures if used in severe cases
  - BMPs unlikely cost effective for tibial non-union as a primary treatment
- However, costs likely to come down
  - Engineering improvements
  - Financial incentives for shorter hospital stays
Is Anything Better Than Autograft?

• Only clinically available graft source that is osteogenic, osteoinductive and osteoconductive

• No sound evidence that any alternative is more effective, or more cost effective, in stimulating bone formation (MK SEN, Injury, 2007)

• Bone graft substitute development driven by ICBG limitations, not increased effectiveness

Summary

• Autogenous Bone graft remains gold standard

• Crest is still best

• Basic science strategies have focused on BMP’s

• As a bone void filler- osteoconductive materials seem OK

Thank You