Osteobiologics in Spine Surgery

Basic Science and Mechanisms of Osteobiologics
Clinical Applications-Paradigm for Informed Choice

Spine Day, 2011

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UC San Francisco

Overview

- Basic Science and Molecular Mechanisms in Spine Fusion
- Composition of Osteobiologics
  - Matrix
  - Cell Biology
  - Proteins and Molecular Biology
- Clinical applications
  - Variability in practice patterns
- Matrix for matching bone graft solutions with patients
  - Data from clinical trials

Disclosures

- Research/Institutional Support:
  - NIH, OREF, AOA, Medtronic, DePuy, AO North America
- Consultancies
  - Medtronic, DePuy, Osteotech, Stryker Biologics, US Spine, Biomet, Orthovita
- Stock:
  - Acculif, Baxano, Providence Medical, Loma Vista Medical, Axis Surgical

Constituents of a Bone Graft Material

Scaffolds
Growth/Differentiation Factors
Cells
Spectrum of Bone Graft Options

- Bone graft extenders
  - Osteoconductive matrices, Demineralized matrices
- Bone graft enhancers
  - Osteopromotive materials (AGF, PDGF)
- Bone graft substitutes
  - Osteoinductive-
    - Recombinant proteins, Demineralized Matrices
  - Osteogenic-
    - Cell-based technologies

Consensus in Clinical Practice

- The presence of variability in clinical practice patterns is a clear indication of the absence of an evidence-based approach to treatment.

Basic Science of Spine Fusion

- The molecular events of osteoneogenesis recapitulate the events of embryogenesis
  - Fracture healing
  - Spine Fusion
Biology of Spinal Fusion

- Discrete stages
  - Hemorrhage
  - Inflammatory
  - Revascularization/regenerative
  - Remodelling/maturation

Fracture Healing

Day 7
Day 14
Day 21
Day 28-35

Cho et al. JBMR, 2002; Einhorn JOT, 2005
Spine Fusion Biology

- Dependent upon
  - Composition of the graft
    - Cells
    - Growth factors
    - Matrix/scaffold
  - Host environment
    - vascularity
    - mechanical environment

Composition of the Graft

Cells
Growth Factors
Matrix

Cellular contribution

- Grafted cells comprise a portion of the final fusion mass
- Grafted cells may also contribute to local inflammation
- release factors that promote angiogenesis and cellular recruitment

Murine inter-transverse fusion
Murine spinal fusion: 1 week

Murine spinal fusion: 2 weeks

HBQ Alkaline phosphatase/TRAP

Y-Chromosome

Track graft derived cells
Murine spinal fusion

Y-chromosome stain: murine fusion

Cells as Trophic Implants

- Autogeneic
  - Marrow-derived
    - Fractionated vs. Unfractionated
- Allogeneic
  - Minimally Manipulated Cells
    - DBM with viable cells
    - Placental/Amniotic tissue derived
    - Synovial derived
  - Processed cells
    - Culture expanded
    - Pre-differentiated cells
Composition of the Graft

Cells
Growth Factors
Matrix

BMP Mechanism

- Members of TGF-beta superfamily
- Secreted as dimers
- proteolytically cleaved to activate

Osteoinductive Materials

Bone: Formation by Autoinduction

Marshall R. Urist
Department of Surgery, University of California Center for Health Sciences, Los Angeles 90024
12 November 1965

Sources of MSCs:

- All mesenchymal tissues
- Peripheral blood
- Bone
- Periosteum
- Endosteum
- Bone marrow
- Muscle
- Mesenchymal Stem Cell (MSC)

Differentiation of MSCs:

OSTEOBLAST

PRE-OB

Fibroblast

Chondrocyte

Muscle
Adipocyte

Stratum

Differentiation Factors

Proliferation Factors

IGFs, TGF-β, BMPs

OSTEOBLAST

PRE

PRE-OB
Recombinant Proteins in the Spine Surgery

- BMP-2
- OP-1
- GDF-5

Class I Clinical Data
- FDA-approved pivotal IDE clinical trial
- Prospective
- Multi-center
- Randomized Control
  - Open ALIF with LT-CAGE® device
    - 136 patients INFUSE® Bone Graft (rhBMP-2/ACS)
    - 143 patients autogenous iliac crest bone graft

Comparison of OP-1 Putty (rhBMP-7) to Iliac Crest Autograft for Posterolateral Lumbar Arthrodesis: A Minimum 2-Year Follow-up Pilot Study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>OP-1 Putty</th>
<th>Autograft</th>
<th>Statistical Test</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Success</td>
<td>75/101</td>
<td>94/104</td>
<td>χ²</td>
<td>0.021</td>
</tr>
<tr>
<td>Radiographic Success</td>
<td>7/11</td>
<td>6/40</td>
<td>Fisher’s Exact Test</td>
<td>0.000</td>
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</tbody>
</table>

Note: Clinical success requires a 20% or greater improvement in Oswestry scores from preoperative. Overall radiographic success requires an assessment of less than 5° of angular motion and less than 2 mm of translational movement on lateral flexion and extension radiographic views and bridging bone between the transverse processes on anteroposterior radiograph.

Comparison of BMP-2 vs ICBG in a single-level instrumented posterolateral fusion model

Clinical Outcomes and Fusion Success at 2 Years of Single-Level Instrumented Posterolateral Fusions With Recombinant Human Bone Morphogenetic Protein-2/Compression Resistant Matrix Versus Iliac Crest Bone Graft

John E. Dimar, MD, Steven D. Storlason, MD, Kenneth J. Busnach, MD, and Mark V. Cameron, MD

Comparison of BMP-2 vs ICBG in a single-level instrumented posterolateral fusion model

FDA IDE study

Fusion rates 73% vs 88% (p<0.05) vs ICBG

No difference in clinical outcomes at any timepoint
BMP in Adult Deformity

- Luhmann et al: Spine 2005
  - Posterior at 2mg/ml with BCP (4-36mg/level)
    • 93% fusion overall
    • 71-73% in thoracic spine
  - Posterior at 2mg/ml with BMP and CRM (40mg/level)
    • 100% fusion
  - Anterior with femoral ring at 1.5mg/ml (6-12mg/level)
    • 96% fusion rate
- Fusion defined by plain films
  - Scores lower on subset of patients with CT available
Concerns about BMP in Spine Surgery

- **Cost:**
  - 40mg/level with average of 6.5 levels
  - 20+ large kits/case
- **Anterior use with allograft**
  - Concern regarding early phase of graft resorption
  - Consider use of non-resorbable cage
- **Heterotopic bone formation with TLIF/PLIF**
- **Retropharyngeal swelling in cervical spine**

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67 pts treated with stand-alone PLIF and paired titanium cages
- Randomized between ICBG and BMP-2

Fusion Rates: No statistical difference
- ICBG: 77.8%
- BMP-2: 92.3%

Clinical results similar at 2 years
- Study enrollment suspended due to CT evidence of bone posterior to the cages

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36 consecutive pts treated with ALIF and stand-alone FRA
- Nonunion rate with ICBG=36%
- Nonunion rate with BMP-2=56%
- Noted early and aggressive resorption of FRA in these non-instrumented cases

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Bone was identified posterior to the implants in the ICBG and BMP-2 groups

Risk factors for bone posterior to the cages:
- Residual segmental anterolisthesis
- <3mm cage recession

No clear clinical sequelae identified
Cervical Interbody

- Cervical Interbody applications

INFUSE® Bone Graft in ACDF

ACF + INFUSE® Bone Graft

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Journal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butterman*</td>
<td>2007</td>
<td>Spine J</td>
</tr>
<tr>
<td>Vaidya*</td>
<td>2007</td>
<td>E Spine J</td>
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<td>Perri</td>
<td>2007</td>
<td>Spine J</td>
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<td>Smucker</td>
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<td>Shields</td>
<td>2006</td>
<td>Spine</td>
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<tr>
<td>Boakye*</td>
<td>2005</td>
<td>J Neuro Spine</td>
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<tr>
<td>Lanman*</td>
<td>2004</td>
<td>Neuro Focus</td>
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<tr>
<td>Baskin*</td>
<td>2003</td>
<td>Spine</td>
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</table>

- 282 total patients
- 97-100% fusion success*

Variation in:
- Dose: 0.4 – 1.4 cc/level
- Placement: In and/or around interbody
- Techniques: ACDF/ACVF; single or multi-level
- Interbody Spacer: Bone, PEEK, resorbables

**For more information contact our Office of Medical Affairs**

WARNING: When anterior cervical spinal fusions were performed with INFUSE Bone Graft, some cases of edema have been reported within the first post-operative week. In some of these cases, this swelling has been severe enough to produce airway compromise.

Composition of the Graft

Cells
Factors
Matrix
**Graft Matrix**
- provides structure
- occupies space
- provides a surface for adhesion of bone forming cells
- releases osteoinductive agents as it is being broken down by host osteoclasts.

**Structure Drives Biology**
- Structure influences
  - Cellular integration
  - Vascularization
  - Fluid/Nutrient Transport
  - Time-appropriate cellular resorption
- Allograft/Synthetic Matrices

**Constituents of a Bone Graft Material**
- Scaffolds
- Growth/Differentiation Factors
- Cells
Clinical Applications

Informed Decisionmaking in Bone Graft Options

Levels of Proof

• Beyond a Reasonable Doubt
  – Randomized prospective clinical trial

• Preponderance of evidence
  – Preclinical studies
  – Prospective cohort studies; retrospective review
  – Clinical experience

Burden of Proof for Bone Graft Materials

• Hierarchy of credibility:
  – Cell culture assays of bone nodules/markers
  – Athymic rat submuscular assay of osteoneogenesis
  – Rabbit Ulnar defect
  – Rabbit Spine model
  – Large animal long bone or spine model
  – Non-human primate spine
  – Human clinical trials

Questions for Consideration in Evaluating a Bone Graft Product

• What is the current highest level of proof to support the use of the product as a bone graft substitute in the spine?

• As a bone graft enhancer/extender?

• How does the product compare to alternatives?
  – Safety
  – Clinical Efficacy
  – Price
Informed Choice

- Application of the right technology and option to the appropriate clinical needs
- Clinical needs defined by:
  - Host considerations
    - Age
    - Previous surgery
    - Location
    - Comorbidities
  - Surgical Factors
    - Length of fusion
    - Revision vs Primary
    - Interbody vs posterolateral

Bone Graft Applications:

<table>
<thead>
<tr>
<th>Biology</th>
<th>Poor</th>
<th>Moderately Demanding</th>
<th>Most Demanding</th>
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<tbody>
<tr>
<td>Normal</td>
<td>Least Demanding</td>
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<td>Small</td>
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<td>Large</td>
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Bone defect size

Choosing the Right Tool

Selective Application

- When do we need our most potent osteobiologies?
- When are more potent osteobiologics inappropriate?
  - Clinical efficacy
  - Cost
  - Complication profile
### Biologics Applications:

<table>
<thead>
<tr>
<th>Poor Biology</th>
<th>High Grade Surgery</th>
<th>Good Biology</th>
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<tbody>
<tr>
<td>Bone defect size</td>
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<tr>
<td>Posterolateral Fusion</td>
<td>TLIF/PLIF</td>
<td>Adolescent Idiopathic Scoliosis</td>
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<tr>
<td>ACDF</td>
<td>ALIF</td>
<td>Osteoconductive Matrixes</td>
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### Osteoconductive/Osteoinductive Matrices

- High Grade Spondylolisthesis
- Revision Adult Deformity
- Pseudarthrosis
- Osteoinductive Matrixes
- Adolescent Idiopathic Scoliosis

### Osteoinductive Matrices

- Revision posterolateral fusion
- High Grade Spondylolisthesis
- Revision Adult Deformity
- Pseudarthrosis
- Osteoinductive Matrixes
- Adolescent Idiopathic Scoliosis

### Osteoconductive Matrices

- Revision posterolateral fusion
- High Grade Spondylolisthesis
- Revision Adult Deformity
- Pseudarthrosis
- Osteoconductive Matrixes
- Adolescent Idiopathic Scoliosis

### Bone defect size

- Small
- Large

- Posterolateral Fusion
- TLIF/PLIF
- Adolescent Idiopathic Scoliosis

- Osteoconductive Matrices
Adolescent Idiopathic Scoliosis

- Bone Graft Choices
  - Local autograft for thoracic scoliosis
  - Iliac crest for extension to L5 or S1
  - Allograft as extender

- Betz et al: Spine 2005
  - Randomized prospective study allograft vs no graft
  - Multisegmental hook constructs
  - Pseudarthrosis defined as broken implant or gap on plain films with pain
  - 1/37 with allograft
  - 0/39 with no graft

Biologics Applications:

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Conclusion

• There is tremendous variability in the choice of bone graft substitutes for common spine applications
• Decision-making on bone graft materials is often made with incomplete data
• Matching graft choice with patient need may provide a framework for informed choice
• Future use of Incremental Cost Effectiveness Analysis to evaluate utility of osteobiologics in the spine may lend insight into cost-effective solutions

Thank You

UCSF Center for Outcomes Research