Effect of Bisphosphonates on Osteochondral Allograft Incorporation

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Characterization of patient specific contact pressures within the talar footprint of retrieved Agility total ankle arthroplasty tibial components

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My disclosure is in the Final AOFAS Program Book.
I have no potential conflicts with this presentation.
Background

• Articular cartilage lesions of the foot and ankle represent a difficult clinical challenge.

• Multiple factors present for lack of intrinsic healing of articular cartilage
  – Absence of direct blood supply, lack of innervation, and degradative local environment.
Background

- Osteochondral transplantation is a viable treatment for larger, full-thickness chondral lesions.

- Bony component allows stable framework when dealing with concomitant osseous defects.

- Allografts composed of cadaveric tissue allows grafting without the need for donor tissue from the patient.
Background

- Osteochondral allografts have good short-term success rates.
- Common failure mechanism: graft collapse.
Background

- Collapse of osteochondral grafts is preceded by osteoclastic resorption of transplanted and host bone.
Bisphosphonates

- Bisphosphonates have shown strong clinical efficacy when used in an anti-resorptive capacity.
  - Risedronate (Actonel) – newer generation, *nitrogenated*
  - Etidronate – older generation, *non-nitrogenated*

- Nitrogenated bisphosphonates (e.g. Risedronate) may not require the onset of apoptosis for their anti-resorptive actions, unlike the non-nitrogenated bisphosphonates (Etidronate).
  - This may confer a higher degree of chondroprotection for the nitrogenated class.
Bisphosphonates

- The ability to mitigate osteoclast-mediated bone resorption and stave off chondrocyte apoptosis suggests promising role in enhancing in vivo performance of osteochondral grafts.

- Muehlman et al. recently showed oral administration of Risedronate lead to improved incorporation of subchondral bone in the knee and also percentage of hyaline cartilage tissue.

- Systemic administration complications:
  - AVN Jaw, Spontaneous Subtroch. Fractures, Digestive Problems
Hypotheses

• LOCAL delivery of bisphosphonates will reduce drug-related complications associated with systemic delivery, while still providing anti-resorptive activity and chondroprotection to osteochondral allografts.

• Addition of nitrogenated and non-nitrogenated bisphosphonates to storage solution will result in an increased chondroprotective effect on the tissue, resulting in increased duration of chondrocyte viability.

• Nitrogenated bisphosphononates will offer a higher level of chondroprotection than non-nitrogenated bisphosphonates.
Methods

- **50 osteochondral cores taken from 5 Cadaver hemicondyle distal femurs donated by MTF.**
  - Two donors: 45 yo. Male. & 21 yo. Male

- **Cores stored in MTF solution at 2-4°C:**
  - Control: MTF solution
  - Group 1: MTF solution + 0.1M Risedronate
  - Group 2: MTF solution + 0.1M Etidronate
  - Group 3: MTF solution + 0.01M Risedronate
  - Group 4: MTF solution + 0.01M Etidronate

- **Histologic evaluation at 16 days, 35 days and 43 days**
  - Safranin-O staining: proteoglycan content
  - TUNEL staining: chondrocyte viability
16 Days After Harvest

Control

Low Dose Etidronate

High Dose Etidronate

Low Dose Risedronate

High Dose Risedronate
35 days After Harvest

Control

Low Dose Etidronate

High Dose Etidronate

High Dose Risedronate

Low Dose Risedronate
43 days After Harvest

Control
Low Dose Etidronate
High Dose Etidronate
High Dose Risedronate

Beaumont Hospitals®
Chondrocyte Viability (TUNEL) Staining 43 Days

Control  
0.01M Risedronate  
0.1M Risedronate

0.01M Risedronate > 0.1M Risedronate > Control >> Etidronate
Ongoing Studies

- **In vitro analysis of direct effect of bisphosphonates on articular chondrocytes.**
  - Cell culture utilizing normal human articular chondrocytes.
  - Expose to varying concentrations of bisphosphonates.
  - Assay ECM production, viability and apoptosis markers.

- **Mini-Pig model of osteochondral allografting in the knee.**
  - Funding obtained: AOFAS Research Grant
References


