In Vivo Antibiotic Release Profile from an Antibiotic Coated Orthopaedic Implant

BioInterface
October 2010
Presentation Overview

- Orthopaedic Device Colonisation
- Product Hypothesis
- In vitro efficacy data
- In vivo release data
- Study Limitations
- Next steps
Colonisation of the orthopaedic device

Colonisation of orthopaedic devices is a major clinical issue

**Infection**

- Systemic antibiotics are not effective
- Revision surgery usually requires:
  - Multiple re-operations
  - Long hospital stay
  - High case costs (up to $100k) with financial penalties
- High associated morbidity, amputation sometimes an end-point

**Aseptic Loosening**

- Implant failure occurs in the absence of any infectious process
- Cases may be initiated by bacteria or their products.
- Rate of false negatives

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of explants</th>
<th>Joint culture positive</th>
<th>False negative</th>
<th>Diagnosed Aseptic with positive results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dobbins et al</td>
<td>26</td>
<td>6</td>
<td>14</td>
<td>70%</td>
</tr>
<tr>
<td>Moussa et al</td>
<td>21</td>
<td>9</td>
<td>2</td>
<td>17%</td>
</tr>
<tr>
<td>Tunney et al</td>
<td>120</td>
<td>5</td>
<td>21 (Culture)/71 (PCR)</td>
<td>18%/62%</td>
</tr>
</tbody>
</table>
## AB Bone Cement - Australian Registry Results

<table>
<thead>
<tr>
<th>Revision Diagnosis</th>
<th>Antibiotic Cement</th>
<th>Plain Cement</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>% Primary</td>
</tr>
<tr>
<td>Loosening/Lysis</td>
<td>78</td>
<td>0.80</td>
</tr>
<tr>
<td>Dislocation Of Prosthesis</td>
<td>75</td>
<td>0.77</td>
</tr>
<tr>
<td>Infection</td>
<td>49</td>
<td>0.50</td>
</tr>
<tr>
<td>Fracture</td>
<td>30</td>
<td>0.31</td>
</tr>
<tr>
<td>Other</td>
<td>11</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>243</td>
<td>2.48</td>
</tr>
</tbody>
</table>

- Lower incidence of infection with AB cement (not significant)
- Lower incidence of loosening with AB cement

*Australian National Joint Registry Report 2009*
Hypothesis

- Produce a cementless implant with anti-colonisation properties – with the objective of similar clinical performance to AB bone cement.
Technology Concept

- Cementless primary hips – femoral and acetabular components
- Gentamicin coating: Similar release profile to AB cement
- Resorbable PLGA overcoat: Short term residence to maintain osteointegration performance
Proposed mechanism of action
In vitro Coating Efficacy Studies

• Dosing and Efficacy Studies
• Comparison to antibiotic bone cement
• Development of an in vitro anti colonisation model
Coating Efficacy compared to bone cement

Key points:

• **1mg/cm²**: Effective against all bacterial strains inc. Resistant strains.
• 0.1mg/cm²: Effective against sensitive strains antimicrobial effect no longer observed @ 4days
• Equivalent or superior efficacy to BC

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SA: Staphylococcus aureus  
CNS: Coagulase Negative  
EF: Enterococcus faecium  
PA: Pseudomonas aeruginosa
In vivo Gentamicin Release Studies

- Phase I: Dosing Study
- Phase II:
  - Antibiotic bone cement
  - Coated Implant
Phase 1: Dosing Study

Model:

• Canine
• Intramedullary bolus injection

Study Design:

• 96hr study duration
• Test Samples:
  • 0.848mg gentamicin solution (0.1mg/cm²)
  • 8.48 mg gentamicin solution (1mg/cm²)

• Samples analysed:
  • Blood
  • Urine
  • Synovial fluid
  • Kidney
Phase I: Dosing Study

Main Findings:

• Gentamicin was not detected in synovial fluid.
• Understanding of excretion mechanism of Gentamicin.
• Larger gentamicin concentration resulted in detectable levels systemically over a longer time period.
• Samples were coated with 1mg/cm² of Gentamicin for Phase II study.
Phase II: In vivo Gentamicin Release

Model:

• Canine
• Intramedullary Implantation

Study Design:

• 10 day study duration
• Test Samples:
  o Gentamicin Coated GritBlast (GB) Implant (n=4)
  o Smartset GHV Bone Cement (n=2)

• Samples analysed:
  • Blood
  • Urine
  • Bone Marrow
  • Kidney
  • Retrieved Implant
Surgical Technique Outline

- Coated Implant
- Implantation Device
- Positioning of implant
- Coated Implant *in situ*
- Fluoroscopic Image
- Bone Marrow harvest
Gentamicin Release Data (Blood)

Gentamicin levels are undetectable in both bone cement and coated implant samples 24 hours following implantation.

Overall, the Gentamicin Release Profile in both antibiotic bone cement and coated implants are similar in blood samples.
Gentamicin Release Data

**Urine Gentamicin (ng/mL) Results**

- Pre-dose
- 6h
- SD 1
- SD 4
- SD 7
- SD 10

**Bone Marrow Gentamicin (ng/mL) Results**

- GBC
- GCI

**Gentamicin Concentration on Implant**

- Treatment Group:
  - BC
  - CI
  - GCI
  - 91775
  - 79545
  - 04371

**Gentamicin Concentration in Kidney**

- Treatment Group:
  - BC
  - CI
  - GCI
  - 91775
  - 79545
  - 04371
Key Points:

• Understanding of excretion mechanism of gentamicin
• Demonstrated burst release similar to antibiotic bone cement.
• Gentamicin no longer detectable in blood 24hrs following implantation.
• Low levels of gentamicin detected in both bone cement and coated implant samples out to 10 days.
• Very low levels of gentamicin remain on implant at 10 days.

Gentamicin Release Profiles from AB cement and coated implant are similar in blood, urine and kidney samples
Study Limitations.

- Low n numbers
- Gritblast implants
- Limited intermediate data
- BM collection
- Variability in AB bone cement data
Next Steps

- Determine coating effects on osteointegration and bone fixation
- Coating characterisation
- In vivo efficacy studies