In vitro characterization of a vancomycin eluting injectable bone graft substitute with examination of concomitant bone remodeling in rabbit

Fredrik Lindberg MD, PhD
BONESUPPORT, Sweden
Disclosures

• Employee and co-founder of BONESUPPORT
• Shareholder in BONESUPPORT
• CERAMENT™ | V is a non-CE marked device
Materials & Methods

Bone graft substitute with vancomycin

(\textit{CERAMENT}^\textregistered \textsc{V}, BONESUPPORT, Sweden)

- Injectable
- bi-phasic composition
- hydroxyapatite (40%)
- calcium sulphate (60%),
- water soluble radiocontrast agent (iohexol 180 mg iodine /mL)
- vancomycin 66 mg / mL bone graft substitute paste
Material characteristics

Injectable & curable paste

Macroporosity created by osteoclasts and macrophages¹

Rapid bone remodelling²

Vancomycin elution – Material & Methods

- 10 mL of bone graft substitute was placed in a glass cylinder filled with 50 mL Ringer solution and allowed to cure

- 20 % exchange of the liquid every 24th hour

- The experimental set-up assumes a two-compartment model with initial distribution into a central compartment, followed by a gradual equilibration with a peripheral compartment*

- The collected samples were analysed for vancomycin

Materials & Methods

*Three types of samples*

- **Low surface area** - pre-hardened paste (LS)
  The surface area of the sample was $\sim 24 \text{ cm}^2$

- **High surface area** – beads prepared in a bead mold (HS)
  The surface area of the sample was $> 100 \text{ cm}^2$

- **Low surface area** – injected as paste (P)
  The surface area of the sample was $\sim 24 \text{ cm}^2$
All samples (of 10 mL), regardless of if they had a high or low surface area or if they contained pre-hardened (beads) or paste-like material, resulted in similar local concentration of vancomycin.

**Paste** = Low surface area of injected paste 'Paste block'

**Low surface** = Low surface area of pre-set beads 'Large beads'

**High surface** = High surface area of pre-set beads 'Small beads'

Upper MIC level for most vancomycin sensitive bacteria
Vancomycin *in-vitro* elution

High local concentration of vancomycin - Initial peak

Sustained concentration of vancomycin above MIC for at least 28 days

Vancomycin release *in vitro* from setting CERAMENT™IV paste
MICROBIOLOGICAL ASSAY according to monograph 2.7.2 in the European Pharmacopoeia 5.0

- 10 mL of bone graft substitute with vancomycin, corresponding to 660 mg of vancomycin.
- Pre-set discs in triplicate were exposed to agar plates with *Staphylococcus aureus* (ATCC 6538)
- The single disc was moved to a new agar plate every day for 18 days, and the zone of inhibition was recorded
- CERAMENT™ discs without vancomycin were similarly tested as a control:
The bone graft substitute also contains the water-soluble radiocontrast agent iohexol, to enable controlled mini-invasive injections under fluoroscopy.

The radiopacity of the bone graft substitute with (w) or without (0) vancomycin in a 3 mm thick layer, corresponds to that of a 5 mm Aluminium (Al) disc.
Comparative rabbit study to investigate:

- Bone formation
- Osteoblast activity
- Non-toxicity

- Critical defect (5x8 mm) with very slow spontaneous bone formation
  
- Drilled bilaterally in the femoral condyles of New Zealand White Rabbits (2 sites in 5 animals/group)

- Filled with bone graft substitute with vancomycin or left empty

- Analysis of plasma-vancomycin

Radiological bone formation after 12 weeks

Defect filled with bone graft substitute containing vancomycin
Bone healing after 12 weeks

Without bone graft substitute

Bone graft substitute with vancomycin

New Bone

Magnification × 4
Plasma-vancomycin (µg/mL)

Rabbit study

Trough level 10-20 µg/mL

Mean value (n=5)
• The investigated bone graft substitute has previously been shown to be effective in long bone osteomyelitis, when impregnated with gentamicin\(^1\)

• In the present study it is shown that also vancomycin elutes at a high initial concentration, followed by at least 4 weeks of a therapeutic local concentrations in vitro

• The rapid concomitant bone remodelling without local toxic effects, together with the vancomycin elution, indicates that the product might be a suitable bone graft substitute in environments with Gram + contamination or in high risk patients

\(^1\)A Prospective Evaluation of CERAMENT™/G Bone Void Filler with Gentamicin in the Treatment of Chronic Osteomyelitis with Cavitary Defects. Martin McNally, Jamie Ferguson, Ryan Giordmaina, Marion Sutherland, David Stubbs, Andrew Woodhouse. Oral Presentation at OBIC, 2014
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