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

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Disclosures

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

Materials & Methods

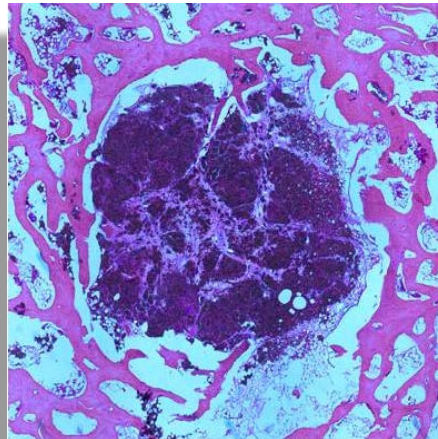
Bone graft substitute with vancomycin (CERAMENT™ |V, BONESUPPORT, Sweden)

- 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



Post-op



12 months

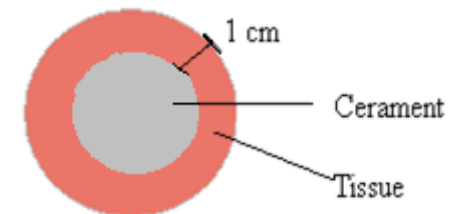
Rapid bone remodelling²

1. Bone healing using a bi-phasic ceramic bone substitute demonstrated in human vertebroplasty and with histology in a rabbit cancellous bone defect model. Hatten HP Jr, Voor MJ. *Interv Neuroradiol.* 2012 Mar;18(1):105-13.

2. Osteotomy of Distal Radius Fracture Malunion Using a Fast Remodeling Bone Substitute Consisting of Calcium Sulphate and Calcium Phosphate. Abramo A, et al. *J Biomed Mater Res Part B: Appl Biomater* 92B: 281–286, 2010

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



* Adopted from:

In Vitro Elution Characteristics of Vancomycin in a Composite Calcium Phosphate/Calcium Sulfate Bone Substitute. Xu Yang, Liza Osagie & Mathias P. Bostrom. HSS Journal, 2012

Materials & Methods

Three types of samples

- **Low surface area** - pre-hardened paste (**LS**)

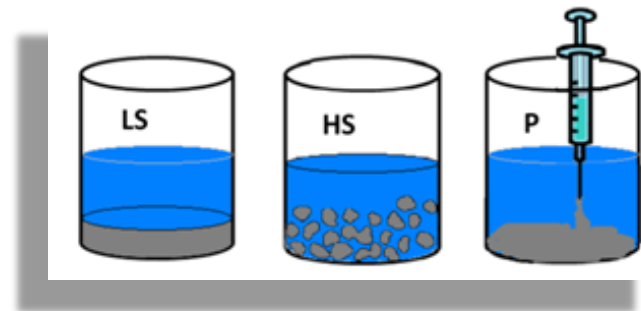
The surface area of the sample was $\sim 24 \text{ cm}^2$

- **High surface area** –beads prepared in a bead mold (**HS**)

The surface area of the sample was $> 100 \text{ cm}^2$

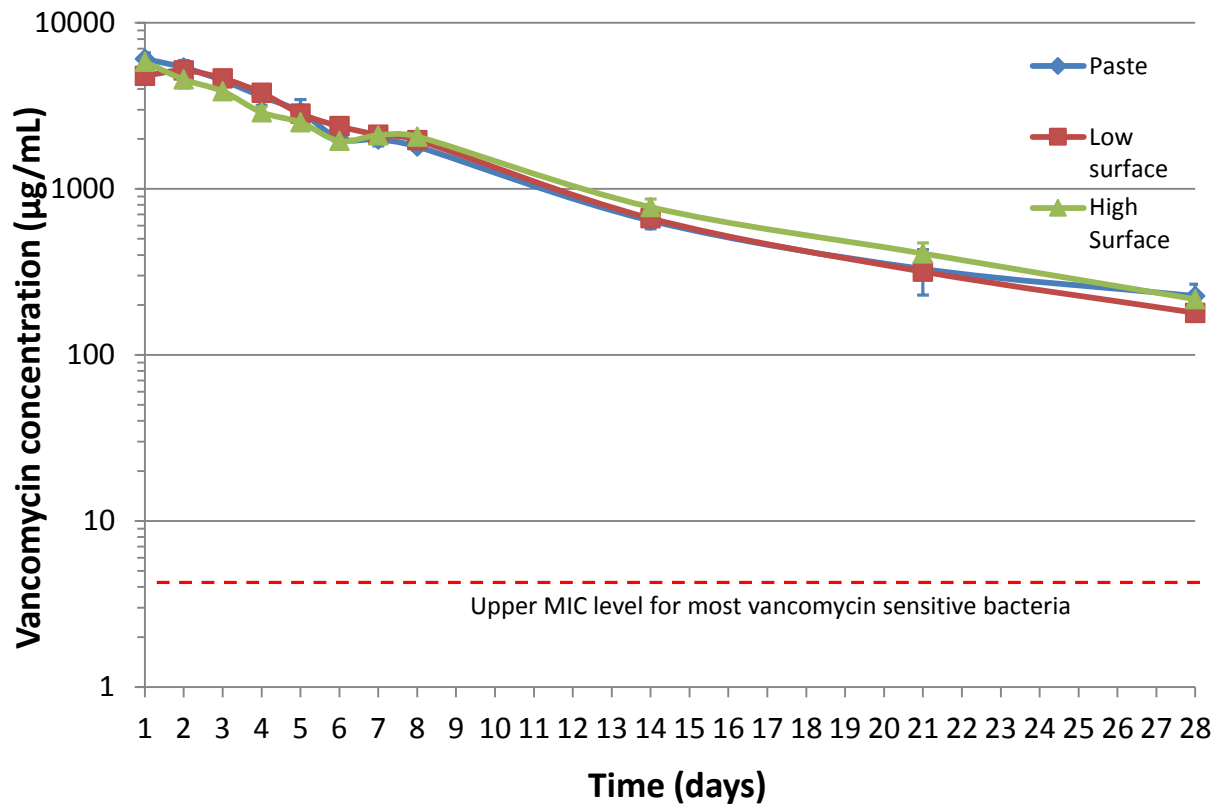
- **Low surface area** – injected as paste (**P**)

The surface area of the sample was $\sim 24 \text{ cm}^2$



Vancomycin– *in vitro* elution

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**

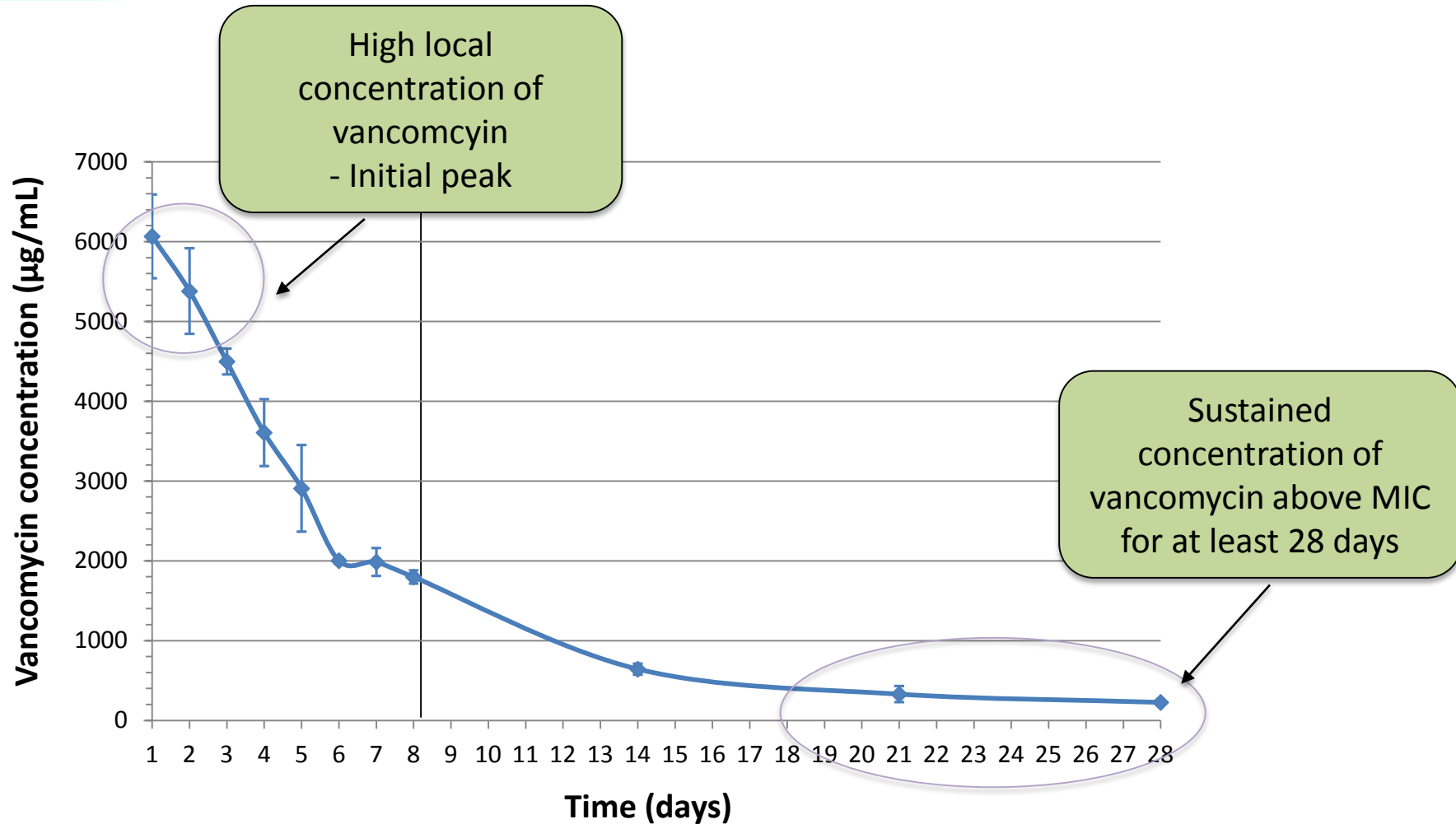


Paste = Low surface area of injected paste
'Paste block'

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

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

Vancomycin *in-vitro* elution



Vancomycin release in vitro from setting CERAMENT™IV paste

MICROBIOLOGICAL ASSAY according to monograph 2.7.2 in the European Pharmacopoeia 5.0



Sample 1

Sample 2

Sample 3

- 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:



Sample 1

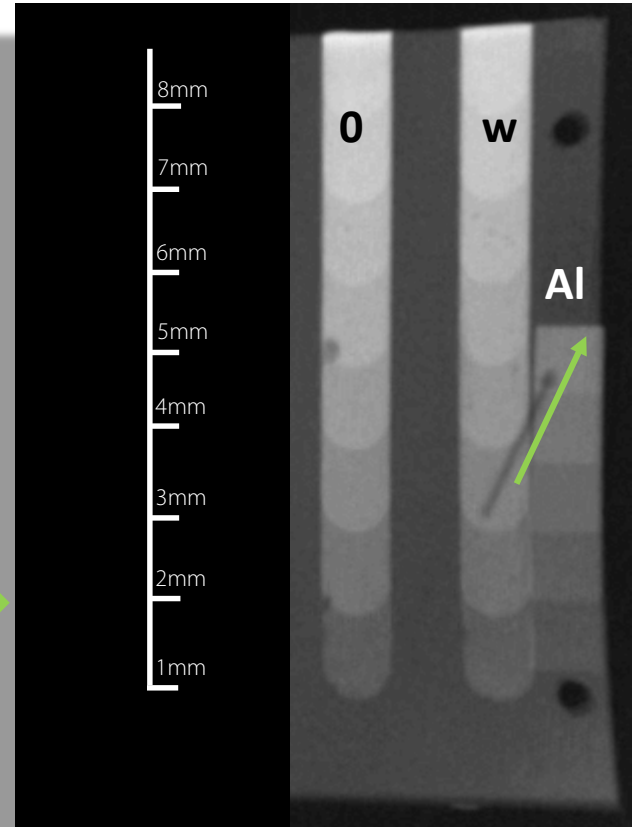
Sample 2

Sample 3

Radiopacity

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 ¹⁾
- 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

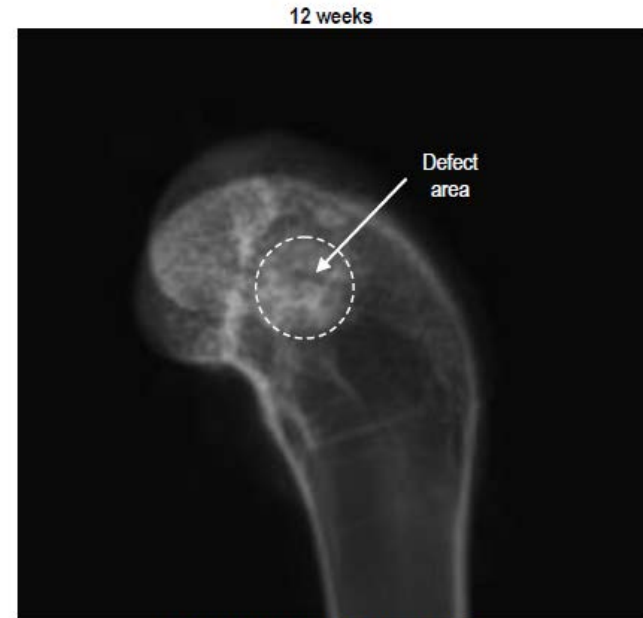
1) *Cancellous Bone Defect Healing with a novel Bi-Phasic calcium Sulphate-Hydroxyapatite Composite Injectable Bone Substitute; Voor MJ, Burden RL, Borden J, Nilsson M. Poster presentation ORS New Orleans 2009*

Radiological bone formation after 12 weeks



Sham - Rabbit X1740 - right femur

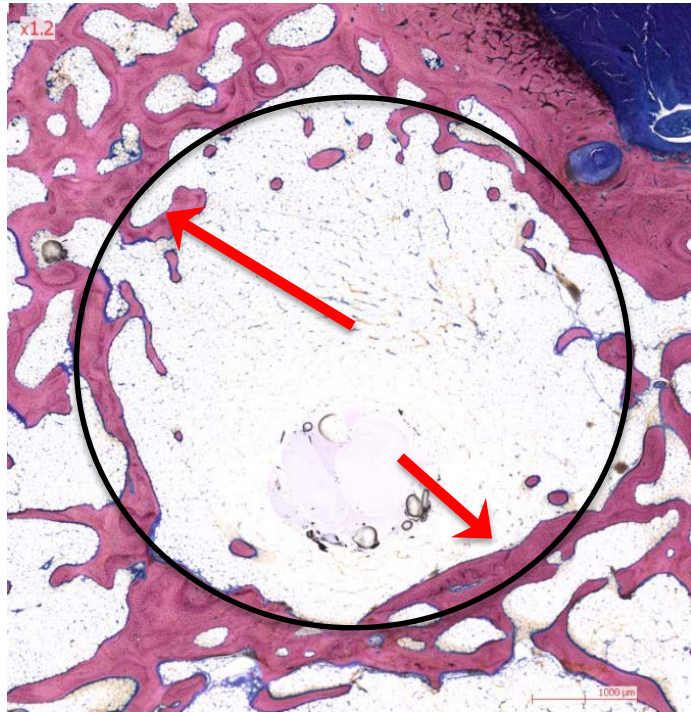
Empty defect



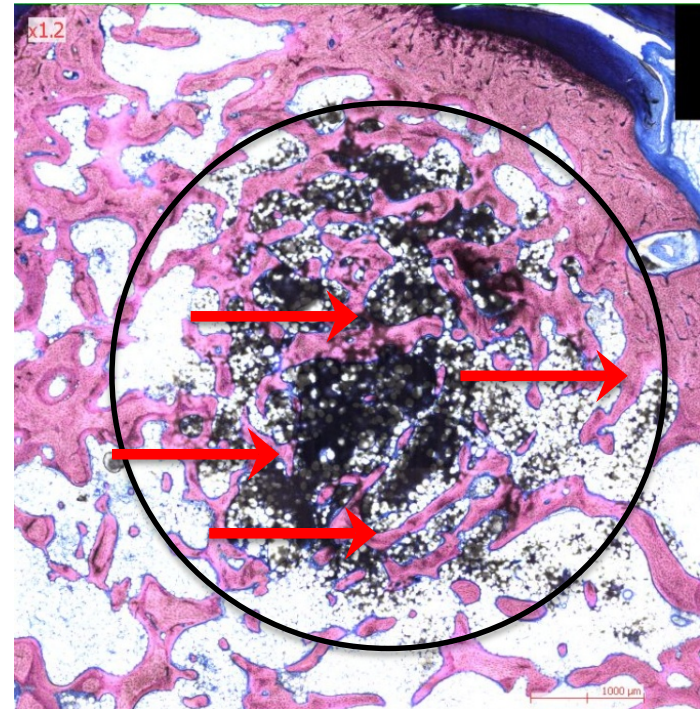
Test article - Rabbit X1735 - left femur

Defect filled with bone graft substitute containing vancomycin

Bone healing after 12 weeks



Without bone graft substitute



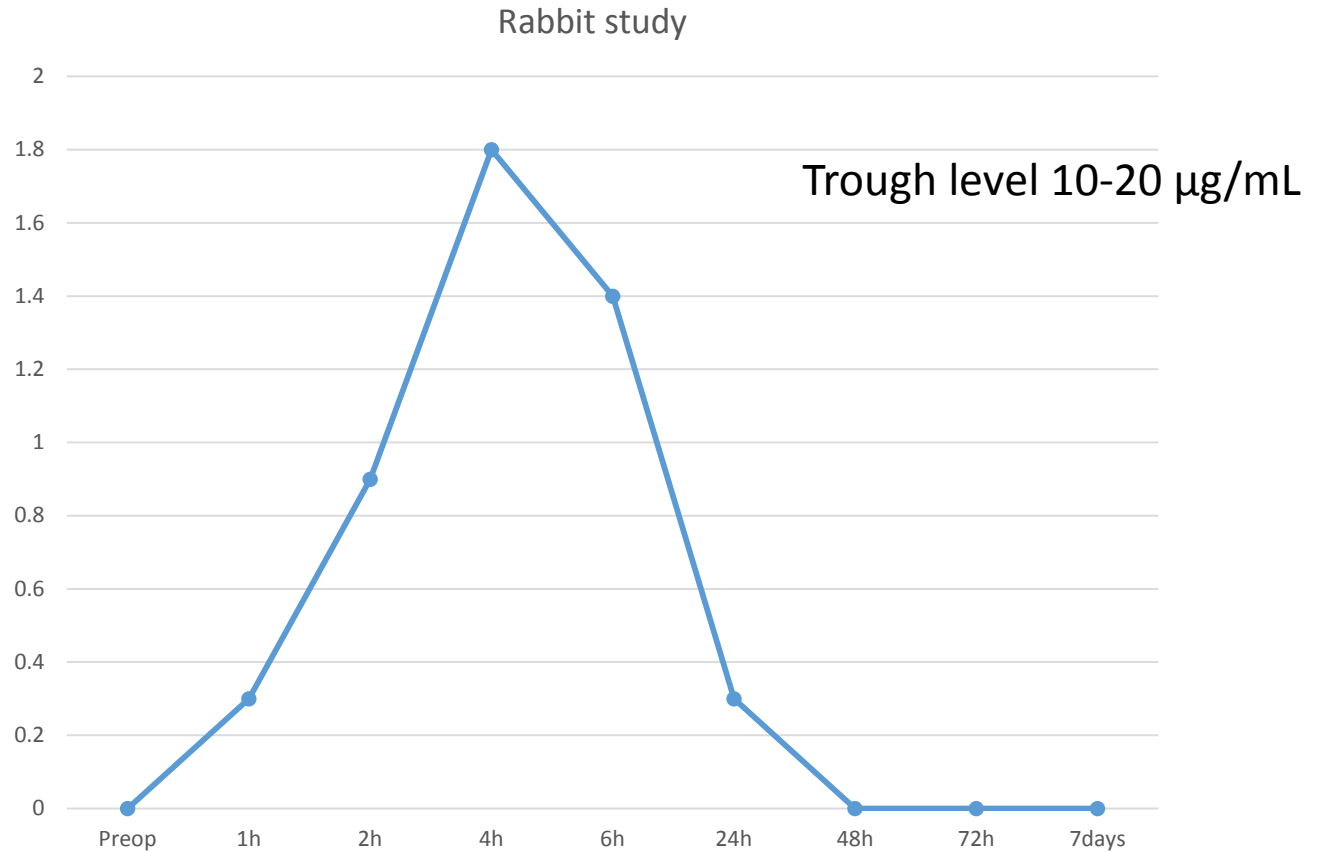
Bone graft substitute with vancomycin



New Bone

Magnification × 4

Plasma-vancomycin ($\mu\text{g}/\text{mL}$)



Mean value (n=5)

- The investigated bone graft substitute has previously been shown to be effective in long bone osteomyelitis, when impregnated with gentamicin¹
- 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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