Physical and Biological Properties of a New Antibiotic-Eluting Resorbable Bone Void Filler

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Purpose: A resorbable composite antibiotic-eluting bone void filler was developed to address the growing problem of orthopaedic device-related infection. Prior studies demonstrate the efficacy of local antibiotic delivery in the context of osteomyelitis, but current methods lack degradable, osteoconductive materials. We hypothesized that a polymer/ceramic composite could restore bone volume while addressing periprosthetic infections using a controlled release antimicrobial.

Methods: Prior to device fabrication, polymers were characterized to ensure thermostability. Three groups of devices were fabricated using commercial synthetic calcium-based bone graft granules and varying combinations of biodegradable polymers. Differential scanning calorimetry analyzed polymer blend stability. Polymer device aqueous degradation was assessed qualitatively using scanning electron microscopy (SEM). Antibiotic (tobramycin) release used Kirby-Bauer (KB) sensitivity testing and liquid chromatography tandem mass spectrometry (LC-MS/MS). An IACUC (Institutional Animal Care and Use Committee)-approved rabbit radial window defect model was used to assess healing and antimicrobial efficacy in vivo with *Staphylococcus aureus* inocula. Bone remodeling was assessed with micro-CT, backscatter electron microscopy (BSE), fluorescence, and light microscopic imaging.

Results: No adverse effects of processing temperatures used for device fabrication were noted. SEM device surface inspection showed considerable in vitro device degradation after 90 days in phosphate-buffered saline at 37°C. KB analysis showed bacterial growth inhibition for up to 9 weeks. LC-MS/MS validated KB testing, as antibiotic concentrations exceeded the minimum bactericidal concentration (MBC) for ~8 weeks (Figure 1). In vivo rabbit implant outcomes of the antibiotic-eluting bone void filler supported osteoconductivity and strong antimicrobial properties in a lethal infection model with *S. aureus*. Micro-CT showed restoration of the medullary canal after 12 weeks in situ (Figure 2). These results were corroborated by BSE, showing new bone bridging the implant surgical defect. Fluorescent microscopy revealed up to 50.36% mineralizing bone surface and $3.36 \pm 0.23\ \mu$m of new bone formation per day.

Conclusion: The antibiotic-eluting composite bone void filler demonstrated the ability to release broad-spectrum tobramycin above the MBC for up to 8 weeks in vitro. In vivo implants demonstrated substantial device degradation, restoration of the medullary canal, an accelerated rate of bone remodeling, and rescue from lethal *S. aureus* infections at high CFU (colony-forming units) inocula.

- The FDA has not cleared this drug and/or medical device for the use described in this presentation (i.e., the drug or medical device is being discussed for an "off label" use). For full information, refer to page 600.

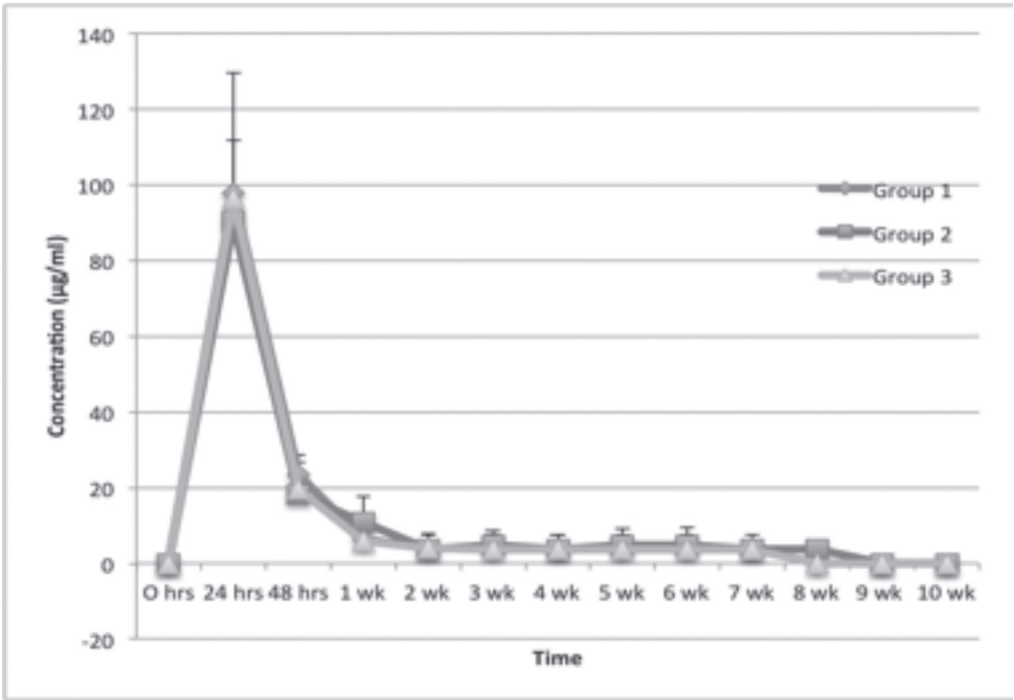

Figure 1. Antibiotic-eluting composite devices release tobramycin in vitro above the tobramycin MBC for *S. aureus* up to 8 weeks.

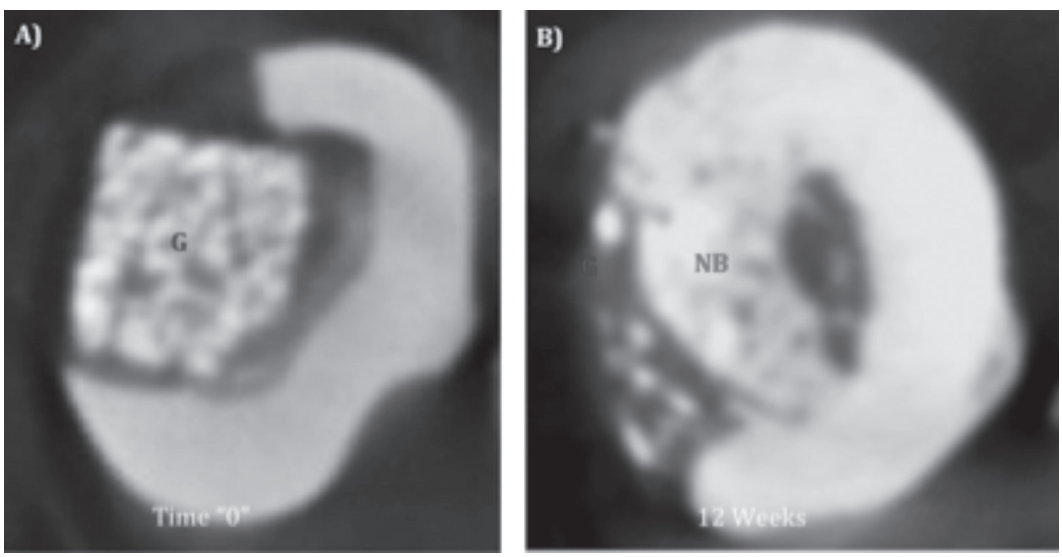

Figure 2. A, Time "0" micro-CT image of ElutiBone implants (G). Note the breach of the medullary canal. B, 12-week postoperative micro-CT image of implanted bone void filler. Note the new bone (NB) and restoration of the medullary canal.

See pages 99 - 147 for financial disclosure information.