•Rifampin and Minocycline-Containing Coating for Orthopaedic Implants with Potent In Vivo Activity

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Purpose: Microbial contamination of implanted devices remains a significant complication in orthopedic medicine. While antimicrobial surface technologies have revolutionized a variety of medical devices, an efficacious antimicrobial coating for orthopaedic devices has remained elusive. To address this challenge we have developed a strongly adherent, biocompatible rifampin- and minocycline-containing coating for orthopaedic implants. Herein, we evaluate the efficacy of coated external fixation pins through several in vitro assays and in an animal model of pin-track infection.

Methods: The in vitro performance of coated Kirschner wires (K-wires) was evaluated by performing repeat zone of inhibition (ZOI) studies and measuring antimicrobial elution kinetics. For the in vivo evaluation of the technology, K-wires with and without the antimicrobial-containing coating were implanted bilaterally into the tibial metaphysis of New Zealand White rabbits. The surrounding soft tissue was surgically closed and the K-wire skin interface was inoculated with a suspension of 1×10^7 colony forming units (cfu) of *Staphylococcus aureus*. After 7 days, the animals (n = 8) were euthanized and the severity of infection was evaluated through the enumeration of adherent cfu on the surface of the K-wires. Additionally, pin loosening and local inflammation was evaluated semi-quantitatively. The size of the K-wires and location of placement were chosen to mimic the human clinical use of 5.0-mm half pins. No systemic antibiotics were administered in order to represent a worst-case scenario for microbial virulence.

Results: In vitro testing demonstrated that the antimicrobial-containing coating produced sizeable plate-to-plate ZOIs for 42 days and continuously released the antimicrobial agents in quantities above pathogenic MICs (minimum inhibitory concentrations) for at least 70 days. The coating completely inhibited biofilm formation on the surface of the K-wires in vivo (limit of detection = 3.7×10^1 cfu/cm^2), while the non-coated K-wires were colonized with $3.0 \times 10^6 \pm 1.5 \times 10^5$ cfu/cm^2, a 4.9 log reduction ($P < 0.0001$). Clinical microbiology confirmed that the bacteria recovered on the control implants were the strain of *S. aureus* employed in the testing. The coated K-wires also maintained significantly higher anchoring strength ($P = 0.017$) and displayed significantly reduced local tissue inflammation ($P = 0.001$) compared to the controls. Furthermore, animals implanted with coated devices lost significantly less weight during the study (4.9% vs. 12.9%, $P = 0.007$) and were significantly less likely to develop a fever (6.3% vs. 43.8% of study days, $P = 0.017$) than animals implanted with control devices.

Conclusion: As microbial contamination of implants continues to present serious complications in orthopaedic medicine, new technologies are urgently needed to address this challenge. The described rifampin- and minocycline-containing coating has demonstrated excellent in vitro and in vivo activity. These results, coupled with the previously reported biocompatibility and strong coating adhesion, makes this technology an exciting prospect for clinical development.

See pages 99 - 147 for financial disclosure information.