Combined Local And Systemic Antibiotic Treatment Effective Against Peri-implant Biofilm Infection With Staphylococcus aureus

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Introduction: Biofilm forming peri-implant infections are difficult to eradicate and often require explantation surgery. Although systemic antibiotics do not achieve concentrations high enough to kill bacteria in biofilms, locally applied antibiotics are capable of achieving such levels. In addition, cephalosporin antibiotics and aminoglycoside antibiotics are synergistic. We hypothesized that a combination of systemic ceftriaxone with high concentration local aminoglycoside antibiotics might be able to eliminate biofilm forming bacteria about such implants.

Methods: Experiment 1: Eighty-four chrome-cobalt/titanium/HDPE implants were inoculated with oxacillin sensitive, biofilm-forming Staphylococcus aureus and allowed to form biofilms. They were treated in vitro with (E1_Ctrl) saline as the negative control, (E1_Gnt) 2mg/mL gentamicin, (E1_Vnc) 2mg/mL vancomycin, (E1_Gnt-Rif) 2mg/mL gentamicin + 3µg/mL rifampin, or (E1_Vnc-Rif) 2mg/mL vancomycin + 3µg/mL rifampin for 2, 4, or 8 days then sonicated to release the biofilm and cultured. Data analysis comparing the control group (E1_Ctrl) with each treatment group was performed with Fisher Exact tests.

Experiment 2: Forty chrome-cobalt/titanium/HDPE implants with established S. aureus biofilms were cerclaged to rat femurs in vivo (Figure 1). After 48 hours, rats were treated (E2_Cef) with systemic ceftriaxone (16.6mg/kg/day) alone or (E2_Cef-Gnt) ceftriaxone combination with 0.4mL of locally injected gentamicin (2mg/mL), or (E2_Cef-Gnt-Rif) ceftriaxone in combination with 0.2mL local gentamicin (4mg/mL) and 0.2mL rifampin (14µg/mL), or (E2_Cef-Vnc) ceftriaxone in combination with 0.4mL of local vancomycin (2mg/mL) every 12 hours for 10 days. Quantitative cultures were performed 24 hours after the last dose. Data analysis comparing the systemic group (E2_Cef) to each treatment group was performed with the Mann-Whitney U test.

Results: Experiment 1: Implants treated in vitro with gentamicin alone were 100% culture negative after 48 hours (p = 0.005 compared to E1_Ctrl). The gentamicin-rifampin group was 83%, the vancomycin group was 67%, and the vancomycin-rifampin group was 50% culture negative at 48 hours (p = 0.048, 0.076, and 0.2, respectively; Figure 2). All treatments were 100% culture negative after 4 days treatment.

Experiment 2: Infection was eradicated in 0% of implants treated with systemic ceftriaxone alone (E2_Cef) and 100% of implants treated with a combination of systemic ceftriaxone and local gentamicin (E2_Cef-Gnt, p < 0.001). Systemic ceftriaxone with local gentamicin and rifampin (E2_Cef-Gnt-Rif, 80% eradicated) or with local vancomycin (E2_Cef-Vnc, 22% eradicated) were less effective though still
significantly better than systemic ceftriaxone alone (p = 0.001 and p = 0.016, respectively) (Figure 3 shows the mean numbers of colony forming units present in each group on quantitative culture).

**Discussion:** Experiment 1 demonstrated that 2mg/mL gentamicin was capable of curing an in vitro S. aureus infection within 48 hours, while 2mg/mL vancomycin required 4 days to reliably cure the same infection. Surprisingly, the addition of rifampin lowered the efficacy of the primary antibiotic. In Experiment 2, only a combination of systemic ceftriaxone and local gentamicin completely eradicated the infection in all implants, supporting Experiment 1’s in vitro results with in vivo data. We conclude that sterilization of peri-implant biofilm infection is possible with a combination of high concentration local gentamicin and systemic ceftriaxone with 10 days of twice daily dosing.

**Significance:** If our findings are supported by clinical trials, the combination of local gentamicin and systemic ceftriaxone could prove valuable in the treatment of peri-implant biofilm infections.
Figure 1. Implants were composed of a 5mm x 5mm x 2mm piece of high-density polyethylene (HDPE) and a 5mm piece of chrome cobalt (0.032” diameter) secured together with a 6.5mm piece of grade 2 titanium wire (0.025” diameter). The titanium wire was wrapped around the femur to secure the implant to the bone.

Experiment 1: percentage of infected implants after 48 hours of treatment

Figure 2. Percentage of implants still infected after antibiotic treatment in Experiment 1. * = significantly different from control (“No antibiotics”) (p < 0.0125).

Experiment 2: mean bacterial growth by treatment group

Figure 3. Mean CFUs from each of the three treatment groups and control (systemic only) group of Experiment 2. Results presented on a logarithmic scale. * = significantly different from control (“Systemic”) (p < 0.0167).

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