Electrical Stimulation as an Adjunct to Antibiotic Treatment During Periprosthetic Joint Infection

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Introduction: The current gold standard for treating periprosthetic joint infections (PJI) remains a two-staged revision. This treatment method involves multiple operations and removal of an implant that may be well fixed. In addition, depending on the spacer utilized, the patient is left biomechanically deficient until placement of the revised implant. The limitations of a two-staged revision arthroplasty necessitate alternative methods for treating periprosthetic joint infection. We have previously shown that application of cathodic voltage-controlled electrical stimulation to titanium implants is effective a treating PJI both in vitro and in vivo1. In this study we evaluated the antimicrobial effects of cathodic voltage-controlled electrical stimulation in combination with antibiotic therapy in a rodent PJI model.

Methods: Prior to the start of the study, approval from our Institutional Animal Care and Use Committee (IACUC) was obtained. Thirty-two adult male Long-Evans rats had a custom made, commercially pure, sterile titanium implant surgically placed into the right shoulder via a ventral peri-axillary approach. The implant was placed through the central aspect of the humeral head and extended approximately 5-7 mm past the lateral aspect of the humeral shaft. At the time of implantation, 1x10^5 colony-forming units (CFU) of a clinical strain of a known biofilm forming methicillin resistant Staphylococcal aureus (NRS70) was injected into the joint and implant drill hole just prior to rotator cuff and deep tissue closure. The rats were maintained for 7 days postoperatively to develop localized PJI. The thirty-two rats were subsequently randomly assigned to four treatment groups: electrical stimulation alone (ES), antibiotic alone (ABX), electrical stimulation with antibiotics (ABX-ES), or no treatment controls (CONT). In the ES group on postoperative day (POD) seven, electrical contact was made to the lateral extension of the titanium implant (working electrode) via a skin incision. In addition, a sterile platinum wire (counter electrode) and a sterile Ag/AgCl disc (reference electrode) were placed subcutaneously at separate sites that were adjacent to the incision used to access the lateral extension of the titanium implant. This standard three-electrode configuration was connected to an external potentiostat to apply -1.8V vs. Ag/AgCl to the titanium implant for 1 hour. Following the electrical stimulation, the counter electrode, reference electrode, and contact to the implant were removed, all incisions sutured, and the animals were returned to their cages. In the ABX group, on POD six the animals began receiving twice daily, subcutaneous injections of vancomycin (150mg/kg). On POD seven, skin incisions were made to allow access to the lateral aspect of the implant and placement of the counter and reference electrodes. However, there was no stimulation applied in this sham surgery and the incisions were subsequently closed and the animals continued to receive vancomycin therapy until POD fourteen. In the ABX-ES group, the animals began vancomycin treatment on POD six, received the one-hour electrical stimulation at -1.8V on POD seven, and continued vancomycin treatment until POD
fourteen. The CONT group received the sham surgery on POD seven and returned to their cage until POD fourteen.

On POD fourteen all animals were euthanized and the implants, humeral heads, and synovial fluid were harvested and sonicated for five minutes in 0.1% saponin to release adherent bacteria before being serially diluted and plated for enumeration of CFU/mL. Peripheral blood samples were also cultured for bacteria on standard agar plates. Following enumeration of CFU, the implants from the ES and CONT groups were subjected to a three-point bending test to evaluate the potential influence of hydrogen embrittlement during the electrical stimulation. The CFU and bending yield strength data were compared across groups with the Kruskal-Wallis non-parametric tests, followed by serial Mann-Whitney tests with a Bonferroni correction (p<0.05/4).

**Results:** Electrical stimulation combined with vancomycin decreased bacterial burden on the implant by 99.8% when compared to the CONT group and by 96% when compared to the ABX group. Specifically, implant associated CFU enumerated from the ABX-ES (3702 ± 6279) group were significantly less than those from the CONT (1.3e6 ± 2.8e6, p<.0001), ES (1.4e6 ± 2.0e6, p=.002), and ABX (5.8e4 ± 5.7e4, p<.0001) groups (Figure 1). Bone CFU enumerated from the ABX-ES (63 ± 102) group were significantly less than those from the CONT (2.8e5 ± 4.8e5, p<.0001), and ES (2.6e4 ± 2.5e4, p=.0001) groups. The ABX (434 ± 630) group also had significantly lower CFU counts as compared to the CONT (2.8e5 ± 4.8e5, p<.0001) and ES (2.6e4 ± 2.5e4, p=.0004) groups (Figure 2). Synovial fluid CFU enumerated from the ABX-ES group (46 ± 118) were significantly lower than the CONT group (3.3e4 ± 6.0e4, p=.0008) and ES group (4.5e4 ± 1.2e5, p=.01). Synovial fluid CFU enumerated from the ABX group (68 ± 92) were significantly lower than the CONT (3.3e4 ± 6.0e4, p=.007) but not the ES group (4.5e4 ± 1.2e5, p=.28). All peripheral blood cultures remained negative. Average yield load to failure of stimulated and non-stimulated implants were not significantly different (122.9N ± 5.5N vs. 127.4N ± 4.9N, respectively, p=.28).

**Discussion:** We have previously shown significant reduction in the biofilm associated bacterial burden on a titanium implant immediately following the one-hour application of cathodic voltage-controlled electrical stimulation.1 The current study showed that a one-time application of cathodic voltage-controlled electrical stimulation at -1.8V alone does not sustain the decrease in bacterial burden beyond time zero. However, combining the electrical stimulation with vancomycin therapy was successful in sustaining a greater than 99% reduction in implant and bone tissue bacterial burden. The yield strength data obtained from the three-point bending test indicated that the electrical stimulation does not significantly alter the mechanical properties of the implant. Future work will be focused on optimization of the antibiotic therapy and timing of electrical stimulation.

**Significance:** Cathodic voltage-controlled electrical stimulation is an effective treatment for PJI resulting in a 99.8% reduction in implant bacterial burden when combined with vancomycin therapy. This treatment provides a rationale for the possibility of component retention during PJI, and warrants further investigation.
Figure 2
Bone Bacterial Burden

![Bar graph showing CFUs/mL for different groups: CONT, ES, ABX, ABX-ES.]

Figure 3

![Images depicting various bone samples labeled A to F.]

Legend:
- *: Significant difference
- #: Significant difference
- \(\infty\): No significant difference
Figure 1

Implant Bacterial Burden

CFUs/mL

CONT    ES    ABX    ABX-ES

ORS 2015 Annual Meeting
Poster No: 1049