USING HEAT GENERATED BY ALTERNATING MAGNETIC FIELD (AMF) TO ERADICATE PROSTHETIC JOINT ASSOCIATED BIOFILMS ON METAL IMPLANTS: EFFICACY & SAFETY IMPLICATIONS.

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Introduction

Prosthetic joint infection (PJI) is a significant complication of modern arthroplasty. Revision surgery is frequently required due to the formation of biofilm. The presence of biofilm makes non-surgical treatment difficult in part because traditional antibiotics are unable to penetrate this structure. Current treatment requires revision surgery alongside antibiotics which is not only expensive but also negatively affects the patient's life. We have developed a non-invasive way to eradicate biofilm from the outer surface of metal implants utilizing alternating magnetic fields (AMF). AMF creates focused surface heating on metallic implants and can be delivered in a fashion that spares significant heating of surrounding tissue.

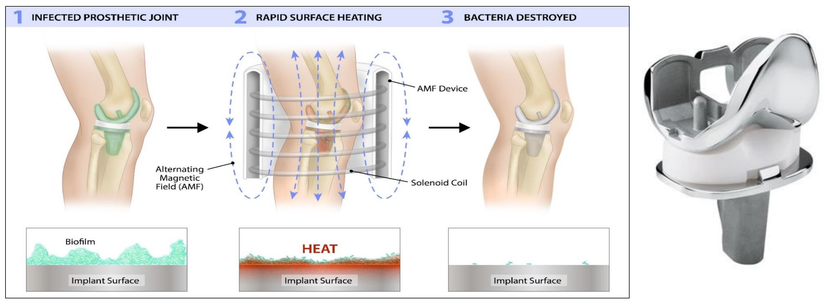

Figure 1: Targeting biofilm located on the surface of metallic implants with high-frequency alternating magnetic fields (AMF). This approach is completely non-invasive, focused on metal implants, and can be concentrated at the surface of implants, where biofilm resides. A typical prosthetic knee implant is shown on the right.

Objective

This study was to determine efficacy and safety of AMF when combined with traditional antibiotics in the mouse models of implant infection.

Materials and Methods

Response of biofilm to AMF Exposures

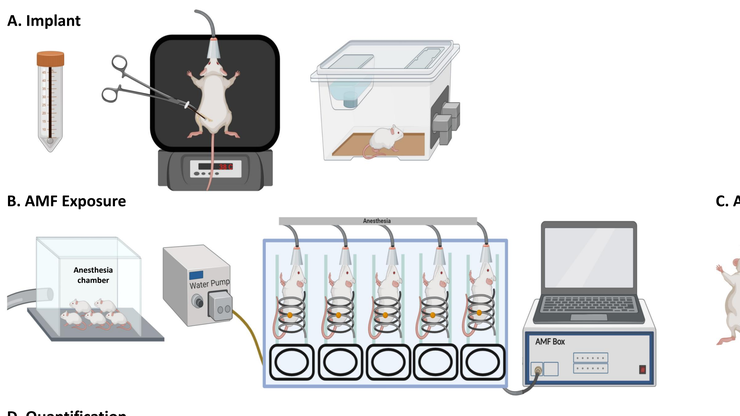

Figure 2: (A) Biofilms were grown individually on stainless steel balls that were implanted into the thigh muscle of mice. (B) Mice were placed in a custom solenoid coil for AMF treatments. AMF exposures generating a peak temperature of 75 or 65°C on the implant were delivered once a day for up to 4 days. (C) Antibiotics were administered via IP post AMF for 3 days (D) Stainless steel ball was harvested and quantified via CFU assay.

Treatment Groups

Gram negative: *Pseudomonas aeruginosa* (PAO1)
- Control
- AMF alone 75 °C & 65 °C
- Antibiotic alone (ciprofloxacin)
- Combination therapy (AMF + antibiotics)

Gram positive: *Staphylococcus aureus* (UAMS-1)
- Control
- AMF alone 75 °C & 65 °C
- Antibiotic alone (ceftriaxone)
- Combination therapy (AMF + antibiotics)

Results

Electromagnetic and thermal simulation on coil and tissue with metal implant

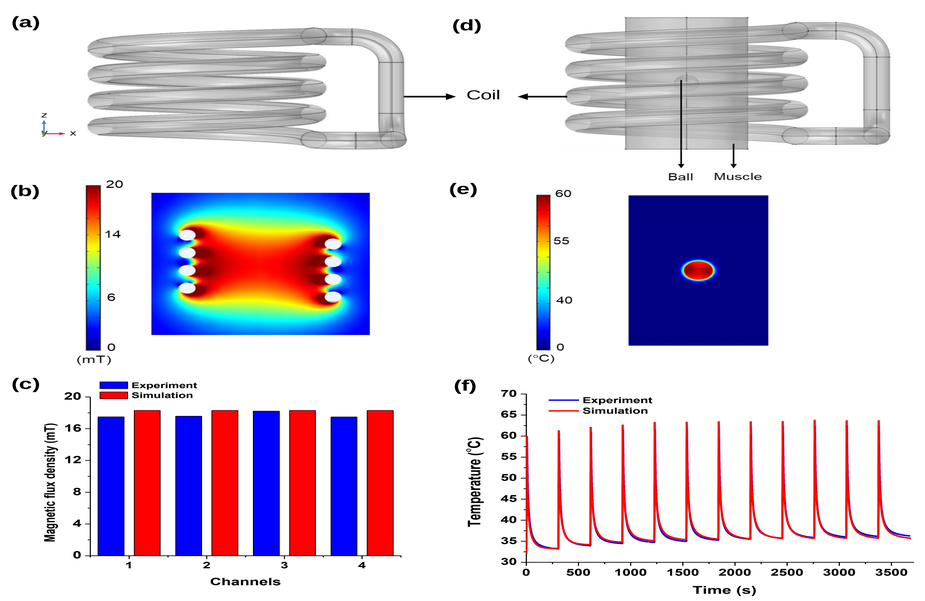

Figure 3: Electromagnetic and thermal simulation on coil and tissue with metal implant (a) 3D physical model of coil (b) magnetic field distribution along the cross section of the coil (c) comparison of magnetic field with experiment and simulation (d) 3D physical model of the coil with metal implant and surrounding muscle tissue (e) temperature distribution along the cross section of metal implant and surrounding muscle tissue (f) comparison of experimental and simulated temperature rise and cool down for pulsed heating.

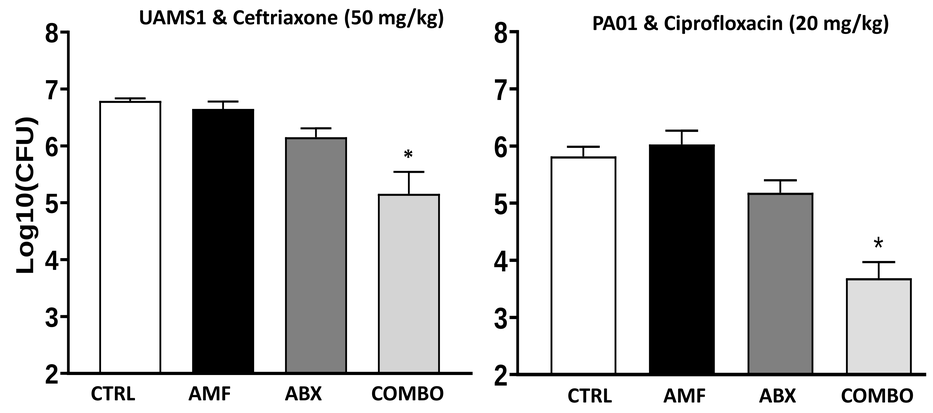

Figure 4: Intermittent AMF (75℃) and antibiotics remove biofilm. The graphs depict the CFU on an infected ball 4 days after daily treatment with AMF, antibiotics, or the combination. The CFU for sham-treated animals is shown for comparison. For both *S. aureus* (UAMS1) and *P. aeruginosa* (PA01), the combination treatment was significantly more effective ($p<0.01$) than the individual treatments.

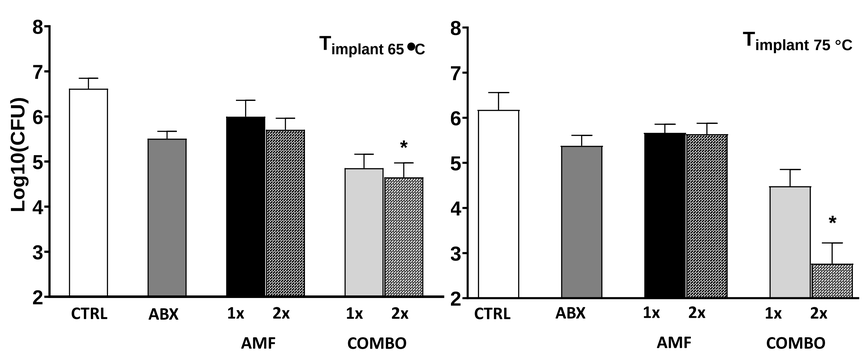

Figure 5: AMF Treatments delivered Once (1x) & Twice(2x) a day with P. *aeruginosa* Infection:
PAO1 biofilms implanted in the mice, AMF exposures occurred every 12 hours – twice a day for peak temperature of 75° C (a) & 65 °C (b) . 65 °C twice a day treatments show negligible change in values when heated once a day versus twice a day in both AMF alone and in the combination of AMF (65 C) and antibiotic (ciprofloxacin 20mg/kg). However, when heated at 80 °C, a significant difference can be observed when the combination of AMF and antibiotics was delivered once versus twice a day.

Histopathological analysis

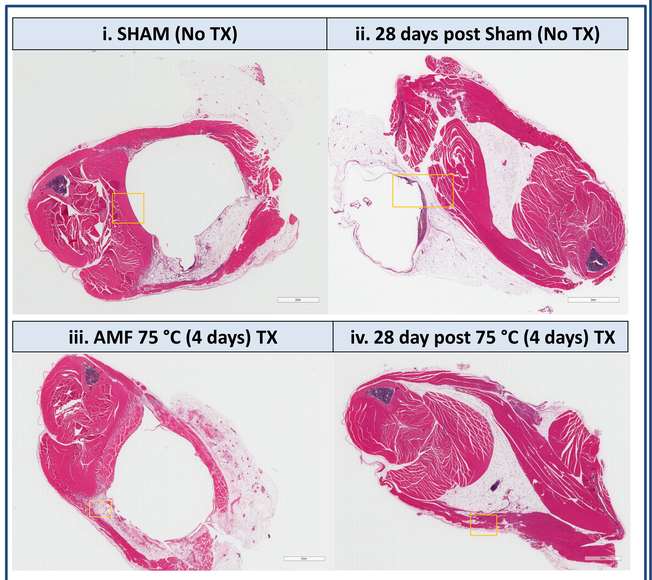

Figure 6: Non infected Implants histology:

(i) There is minimal myofiber necrosis and attendant inflammatory reaction around the implant site. (ii) 28 day post sham shows no signs of inflammation. (iii) Significant myofiber necrosis is seen surrounding the implant site; associated inflammatory infiltrate, composed of mixed acute and chronic inflammatory cells, surrounds the area of myofiber necrosis. (iv) Small peripheral area in the muscle where fibrosis is observed showing almost complete healing. No thermal damage observed after 28 days post treatment.

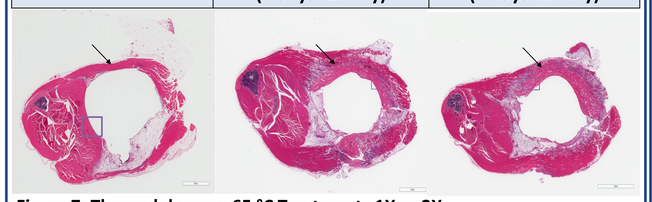

Figure 7: Thermal damage 65 °C Treatments 1X vs 2X

(i) In the no treatment group, little necrosis of the muscle tissue around the implant; mild concomitant inflammatory cell infiltrate seen in the muscle with the thermal damage of (81 +/- 10 microns (µm) at the 12 o clock marked region. (ii) There is chronic inflammation in once a day 65 °C treatment, (mostly macrophages) infiltrates the necrotic muscle and fibroadipose tissue that surrounded the implant site with (747 +/- 7 µm) damage marked at 12 o clock position. (iii) Necrosis with twice a day (Q12h) treatment, muscle and fibroapidose tissue has necrosis identified around the implant site, all with inflammatory infiltrate, with noted area of damage (1118 +/- 23 µm) at the same region.

Conclusion

- These *in vivo* studies confirm that AMF exposures combined with antibiotics are bactericidal biofilm on metal surfaces.
- Thermal damage in the surrounding tissue depicts that AMF exposures are safe with little damage to surrounding tissue.
- AMF combined with antibiotics leads to enhanced reduction of biofilm on metallic implants *in vivo*.

Next Steps

- Characterize biofilm eradication with higher-power AMF exposures in weight bearing model (Sheep).
- Investigate the dynamics of AMF-biofilm interaction at a microscopic level
- Conduct further synergy studies with other bacterial strains & antibiotics