Erythromycin-Doped Nanofiber Coating Enhances Osseointegration and Inhibits Staphylococcus Aureus Induced Osteolysis

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Statement of Purpose:
Failure of osseointegration and periprosthetic joint infection (PJI) are the two main reasons of implant failure and osteolysis after total joint replacement (TJR). Strategies aimed at reducing the risks of defective osseointegration and PJI are likely to improve the success of TJR and increase implant longevity. Implants with nanofiber (NF) coating represent an alternative approach as a local drug eluting device to enhance implant osseointegration and prevent PJI. The purpose of this study was to investigate the therapeutic efficacies of erythromycin (EM)-loaded coaxial PLGA/PCL-PVA NF coating in a rat S. aureus-infected tibia implantation model.
Methods: The details of coaxial NF coating methods were as we described before[1, 2]. NF coating with EM at the dose of 100 ug (EM100) and 1000 ug (EM1000) per ml were prepared. NF without EM (EM0) was included as positive control. A total of 56 SD rats were used and divided into 4 groups (n=8 for each group and each time point, except the negative control, **Table 1**).

Table 1. Rat Group Designations.

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n	Description
8	Ti pin (NF, No S. aureus)
16	Ti pin (NF/no EM (EM0)
16	Ti pin (NF/EM 100µg/ml)
16	Ti pin (NF/EM 1000µg/ml)

A titanium pin (1.0-mm x 8 mm) was placed flush into the tibia through the intercondylar notch. S. aureus (SA) was introduced by both direct injection of 10 µl broth (1×10^4 CFU) into the medullary cavity and single dip of Ti pins into a similar solution prior to insertion. Rats were sacrificed at 8 and 16 weeks after surgery, respectively. The outcome measurements include µCT based quantitative osteolysis evaluation at 8 and 16 weeks (**Fig. 1)** and the histology of hard tissue sections collected at 16 weeks, (**Figure 3**).

Results: As shown in **Figure 2**, EM-NF coating (EM100 and EM1000) reduced the osteolysis both at 8 week and 16 weeks, compared to EM0 control, respectively. The effective infection control by EM-NFs (EM100 and EM1000) was further confirmed by hard tissue section analysis. The Bone implant contact (BIC) and bone area fraction Occupancy (BAFO) within 200 µm of the surface of the implanted pins were used to evaluate the osseointegration and new bone formation around the implants (Fig. 3). At 16 weeks, the BIC (%) of EM 100 (35.08%) was higher than that of negative control (3.43%) and EM0 (0%), respectively. The BAFO of EM100 (0.63 mm^2) was higher than that of negative control (0.390 mm^2) and EM0(0.0 mm^2). The BAFO of EM 100 was also higher than that of EM1000 (0.3mm^2).

Conclusion: There appeared to be much less osteolysis observed with EM100 and EM1000 NF coatings at 16 weeks, as compared to EM0 positive control, p=0.08 and p=0.1, respectively. Data from hard tissue histology demonstrated that the osseointegration and periprosthetic new bone formation was enhanced by EM-NFs, especially EM100, as compared to EM0 and negative control. We further demonstrated that EM100 was better than EM1000 in enhancing periprosthetic new bone formation (BAFO) and osseointegration (BIC). We propose that both EM100 and EM1000 are both effective in infection control and NF coating with high dose of EM loading (EM1000) might have inferior impacts on new bone formation. Data generated from this pilot study may provide new implant surface fabrication strategies aimed at reducing the risks of defective osseointegration and PJI.

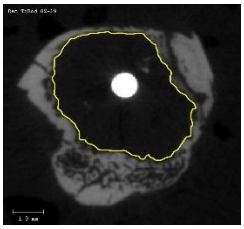

Fig. 1. Representative CT image of EM0 sample at 16 weeks. The osteolysis area around the Ti pin was selected and quantified using built in software.

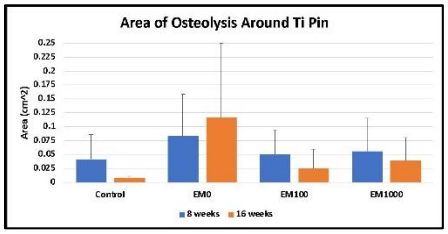

Fig. 2. Comparison of osteolysis among groups at both 8 and 16 weeks, Avg and STDV.

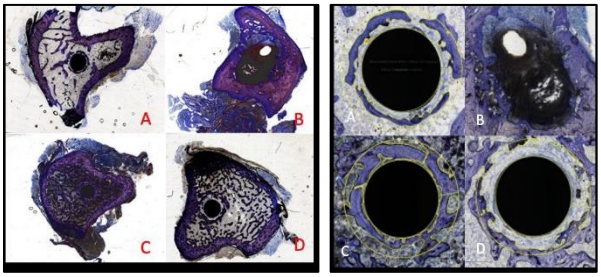

Fig. 3. Representative images of hard tissue sections collected at 16 weeks: A) negative control); B) EM0, C) EM100, and D) EM1000. Left A-D (red) lower power (X4) gross histology images. Right A-D (white) higher power for BIC and BAFO measurements, inner yellow line used to calculate BIC, outer yellow line is 200 µm from the implant and used to calculate BAFO.

Resources:

1. Song W. Doxycycline-loaded coaxial nanofiber coating of titanium implants. *Biomed Mater*. 2017;12(4):045008.
2. Chen L. Sustained release of strontium (Sr2+) from PCL/PLGA coaxial nanofibers enhances osteoblastic differentiation. *Journal of Biomaterials Applications*. 2019;34(4):533-545.