Doxycycline-Loaded Coaxial Nanofiber Coating Enhances Osseointegration and Inhibits Infection

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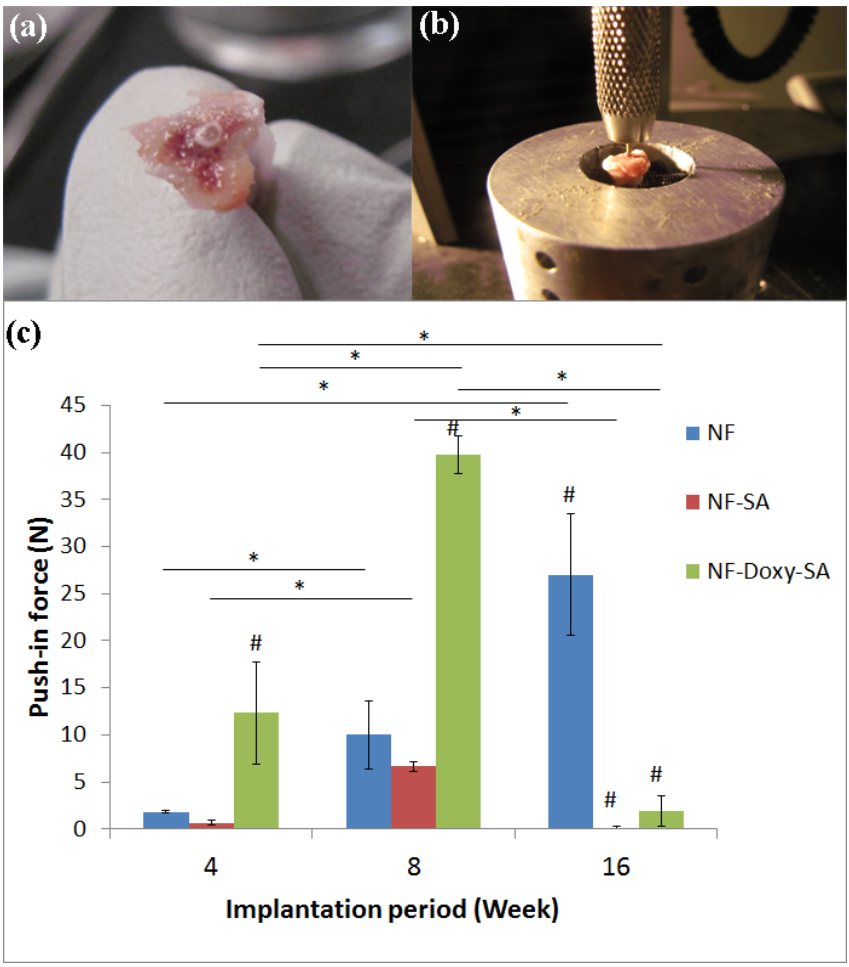
Purpose: Few studies have focused on developing an implant surface nanofiber (NF) coating to prevent infection and enhance osseointegration by local drug release. We presented our preliminary work on coaxial doxycycline (Doxy)-doped polycaprolactone/polyvinyl alcohol (PCL/PVA) NFs that could be directly deposited on titanium (Ti) implant surface during electrospinning at a previous OTA meeting. We found that an NF coating provided sustained antibiotics release, that the bonding strength of NFs to the Ti surface was strong, and no delamination and/or disruption of NF coating was found in ex vivo porcine bone push-in and pullout tests.The aim of this continuing study was to determine the therapeutic efficacy of Doxy-doped PCL/PVA NF coating using a Staphylococcus aureus-infected rat tibia implantation model.

Methods: A Ti pin with coaxial PCL (sheath)/PVA (core) NF coating with Doxy loading (200 μg/mL) was prepared by electrospinning. A total of 72 rats were divided into three groups: (1) control, NF coating; (2) NF coating + S. aureus infection (NF-SA); and (3) Doxy-NF coating + S.aureus infection (Doxy-NF-SA). Rats were sacrificed at 4, 8, and 16 weeks after surgery. Each group included 24 rats (8 rats for each time point). The osseointegration and the inhibition of bacterial growth were evaluated by microbiologic testing, histology, mechanical push-in test, and micro-CT.

Results: We demonstrated that Doxy-doped NF coating effectively inhibited bacterial infection and enhanced osseointegration in this infected (S. aureus) rat tibia implantation model. Doxy released from NF coating inhibited bacterial growth for up to 8 weeks in vivo. The maximal pushin force of Doxy-NF-SA group (38 N) was much higher than that of NF-SA group (6.5 N) 8 weeks after implantation ($P < 0.05$); enhanced osseointegration was further confirmed by quantitative micro-CT. For the NF (control) group, a gradual increase of bone volume around the Ti pin surface was observed up to 16 weeks. Progressive bone loss around the Ti pin was observed in the NF-SA group, forming a visible gap between Ti and the surrounding bone matrix. The incorporation of Doxy (Doxy-NF-SA) successfully prevented bacterial infection and enhanced osseointegration as manifested by continued increase of new bone formation around the Ti pin up to 8 weeks. Finally, the status of osseointegration was carefully evaluated by quantitative histological analysis. More new bone formation was found in the Doxy-NF-SA group than that of the NF-SA group at the 4-week time point. A significant inflammatory tissue response observed in the NF-SA group was not seen in the NF-Doxy-SA group. At the 8-week time point, the local bacterial growth and tissue response are visible in the NF-SA group, which cannot be observed in the NF-Doxy-SA group.

See pages 49 - 106 for financial disclosure information.

Push-in test



Representative image of harvested rat tibia with Ti pin. (b)The photo of push-in test setup. (c) Rat tibia implanted Ti-pin push-in test result. Rat tibias were harvested from different time points (4, 8, 16 weeks). n= 8. $p^{*}< 0.05$ represents significant difference between different time points within group. $p^{\#}< 0.05$ represents significant difference between different groups within the same time point.

Conclusion: Many strategies have been used to prevent implant infection by either implant surface fabrication or incorporation of antibiotics into/onto the implant devices. A desired implant coating system should deliver antibiotics well above their minimum inhibitory concentration for at least 6 weeks for the treatment of implant infection. In this study, we demonstrated that Doxy was released from the NF coating and stimulated implant osseointegration and inhibited bacterial growth for up to 8 weeks in a rat tibia implantation model. These findings may provide a new implant surface fabrication strategy aimed at reducing the risk of poor osseointegration and/or implant infection, especially in the face of a contaminated trauma situation.