Controlled Release of Antibiotics and Bactericidal Effect of Thin Sol-Gel Film on Metallic Implant Devices

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Introduction: Management of infection in open fractures is challenging, especially, when internal fixation materials are used (1). Infection following joint arthroplasty is also a devastating complication with immense financial and psychological costs (2). A major limitation in the treatment of periprosthetic infection is lack of an effective local antibiotic delivery system

To address this problem, we propose to create antibiotic coatings on metallic fracture fixation or joint replacement devices. These coated prostheses can provide a continuous and predictable source of antibiotics that will prevent bacterial proliferation in the fracture vicinity or the hardware surface.

Herein we report on the modification of Ti alloy implant surfaces with a sol-gel film that permits immediate and controlled release of antibiotics with demonstrable bactericidal efficacy *in vitro* and *in vivo*.

Methods: *In vitro* release and film stability were studied by using Ti-6Al-4V plates. Tetraethylorthosilane (TEOS), deionized (DI) water, ethanol (Eth), and 1N HCl (DI:HCl:TEOS molar ratio=5:0.01:1, Eth/TEOS volume ratio=2) were mixed to form a sol. Vancomycin solution in DI was added to the sol. Coatings composed of one or several layers were deposited by dipping. The release and film stability were studied in PBS (pH 7.4) at 37^0C with daily solution exchange. Released vancomycin was measured spectrophotometrically at 280 nm. The film stability was determined by measuring the weight loss as a function of immersion time.

In vitro and in vivo bactericidal effects were determined by using Ti-alloy anodized Kirschner wires (Synthes, 1.25 mm), either uncoated or sol-gel coated with and without vancomycin. The coatings composed of 5 layers. Theoretical vancomycin concentration in these coatings was 21 µg/cm^2. Bactericidal activity *in vitro*: So-gel coated wires ± vancomycin (6 samples of each type) were incubated with 1x10^3 cfu of Staphylococcus aureus 24 hours at 37^0C: bacterial counts were determined by serial dilution followed by triplicate plating on agar plates. The incubated wires were stained with the Live/Dead Viability Kit and visualized with confocal laser microscopy. Wistar rats were used for the *in vivo* study. Sol-gel coated nails were inserted in the intramedullary canal of rat femora via the intercondylar grove in the knee. G28x11/2 needles were used to ream a hole. Prior to implantation of each nail, a suspension of S. aureus (150 µl of 10^4 cfu/ml) was injected into the canal. Sol-gel coated pins with and without vancomycin were inserted into the right side and into the left side, respectively. A total of 12 nails of each type were implanted into the animals. Three animals were sacrificed at 7, 14, 21 and 28 days and X-rayed.

Results/Discussion: The drug load, the initial release rate and the film stability increased with the number of applied layers. The rate of release and the total amount released also increased with increase of vancomycin load from 3 to 20%. As shown in Figure 1, coatings with 10% load, showed a steady release up to 2 weeks. Daily release of about 10 µg/ml for up to 1 week significantly exceeded the MCI of vancomycin against S.aureus (1.56-3.12 µg/ml). The close correlation between the release and degradation rates suggests that the prevailing mechanism of release is by film dissolution.

In vitro, the number of S aureus colonies on sol-gel/vancomycin coatings was reduced by three orders of magnitude in comparison to those on control samples. In addition, viable bacteria adhere and proliferate on uncoated wires, whereas the bacteria adhesion was prevented on the drug-containing coatings.

In vivo, vancomycin-containing coatings inhibited the infection development up to 4 weeks of implantation, whereas osteomyelitis was progressing on the control side (Fig. 3).

Conclusions: Thin and resorbable sol-gel films showed long-term controlled release of vancomycin. Outstanding bactericidal properties of sol-gel /vancomycin films on Ti-alloy intramedullary nails were demonstrated *in vitro and in vivo.* These results suggest that antibiotic-containing sol-gel films hold great promise for the prevention or treatment of bone infections.

References: 1. Eijer, H, Hauke, C, Arens, S., Printzen, G., Schlegel, U. and Perren, S. M. 2001.. *Injury.* **32**:S-B38-43. 2. Barrack, R. 1995 Clin Orthop. 319:209-214

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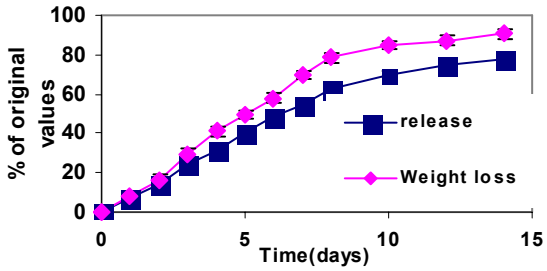

Figure 1. Cumulative vancomycin release and sol-gel film degradation (weight loss) expressed as % of the original values. The film composed of three layers and contained 10% of vancomycin by weight.

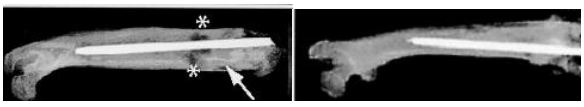

Figure 2. Sol-gel/Vancomycin coating (right) inhibits infection *in vivo*. After 4 weeks of implantation, infection on the control side (left) is evidenced by change in size, periosteal reaction (arrows), lytic lesions and bone abscesses (*), and extensive bone remodeling.