**Enhanced Bone Formation via Intermittent Release of Simvastatin**

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**Introduction**

Daily oral dosing or injections of the cholesterol lowering drug simvastatin have been reported to stimulate bone formation (*Science* 286:1946, 1999). Use of controlled release methods can provide local, intermittent concentrations while avoiding the need for daily treatments.

In previous studies, we developed a controlled release system based on blends of cellulose acetate phthalate (CAP) and Pluronic F-127 (PF-127) for intermittent release of small and large biomolecules. Cell culture experiments showed that intermittent exposure to simvastatin stimulated osteoblastic activity.

The purpose of this study was to investigate the ability of these devices to enhance new bone formation *in vivo*.

**Methods**

CAP/PF-127 microspheres (7:3 wt% blend ratio) were prepared by an acetone-oil-water (W/A/O/W) triple emulsion process. Implants were fabricated by pressure-sintering under acetone vapor using pre-sterilized with and without simvastatin incorporating microspheres. To provide directional release, the top and sides of devices were coated with 10% PLGA solution.

Two month old male Sprague-Dawley rats were used in this study. Blank (no drug controls) devices (n=7), intermittent release devices (n=9), and sustained release devices (n=8) were tested in a calvarial onlay model, in which devices were placed release side down directly on the bone and under the periosteum.

After 9 (n = 3), 18 (n = 1), and 28 (n = 20) days of implantation, calvaria and surrounding tissues were prepared for descriptive histology by light microscopy. Besides qualitative observations, the thickness of newly formed woven bone was measured.

**Results and Discussion**

At nine days following implantation, macroscopically visible differences in the amount of tissue were seen, with the sustained release devices having stimulated a greater response than control implants, and alternating release having elicited an even greater response than sustained release devices. Histologically, a fibrous layer was observed above the calvarium, and above that was a region of inflammation. Intimately apposed to the pre-existing lamellar bone of the calvarium was a layer of newly formed woven bone (Figure 1).

Figure 2 shows the thicknesses of newly formed woven bone layer for the three types of devices implanted. Intermittent release devices stimulated 133% greater woven bone thickness (187±40µm) compared to control devices (80±30µm) ($p<0.05$), and sustained release devices stimulated 77.5% greater woven bone thickness (142±56µm) compared to controls. Comparing the two release profiles, intermittent devices stimulated a 32.3% greater response than did the sustained release.

These results were similar to our previous *in vitro* studies, which showed that both intermittent and sustained exposure to simvastatin enhanced osteoblastic activities and that intermittent exposure stimulated greater bioactivity than constant treatment with simvastatin.

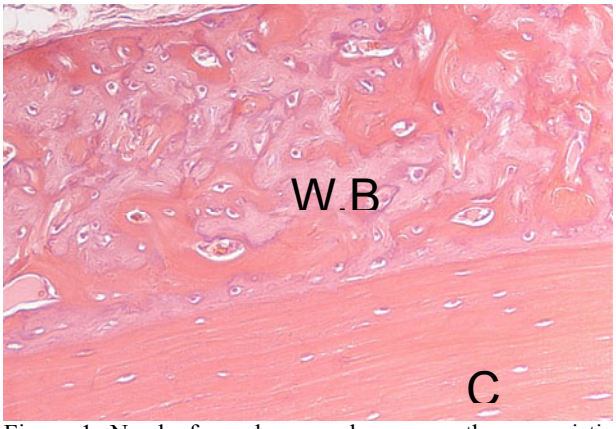


Figure 1. Newly formed woven bone over the pre-existing lamellar bone of the calvarium at four weeks after implantation (W.B: Woven Bone, C: Calvarium).

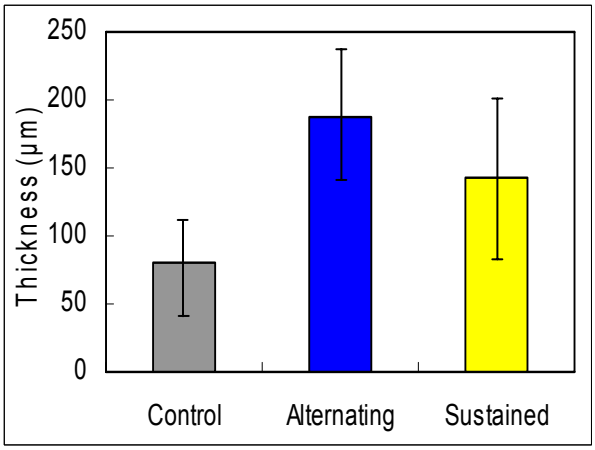


Figure 2. Thickness of newly formed woven bone layers after four weeks of implantation.

**Conclusions**

The CAP/PF-127 blend system is useful for creating different release profiles. Controlled release of simvastatin enhanced local bone formation *in vivo*, and intermittent release stimulated formation of the largest amount of new bone.

**Acknowledgment**

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