Sustained Release Lovastatin Applied One Week After Fracture Accelerates Healing in a Rat Model of Fracture Repair

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INTRODUCTION:

Statins are drugs widely prescribed to reduce cholesterol levels and the risk of cardiovascular events. In the last few years, many studies suggest that the use of hydroxy-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) is associated with increased bone mineral density (BMD) and a reduced risk of fractures in humans and animal models. The effect of statins is associated with increased expression of the bone morphogenetic protein-2 (BMP2) gene in bone cells (1).

A previous report in a nonhuman primate fibular osteotomy site, demonstrated that delayed treatment with BMP2, 1 or 2 weeks after surgery versus 3 hours, further accelerated healing (2). Lovastatin (LV) has been shown to be effective for fracture repair when injected locally immediately after fracture (3). The goal of this study was to determine if local administration of LV one week post-fracture could also accelerate fracture healing in a commonly used preclinical model of fracture repair.

METHODS:

A new sustained release LV formulation was developed where PLGA LV-loaded microparticles were tested in a rat model after a closed fracture following intramedullary pin fixation. A single dose of the drug was administered right after the fracture was created (day 0) or one week later (day 7).

All procedures performed in this study were approved by the Institutional Animal Care and Use Committee and conform to the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals.

Fracture healing was assessed by x-rays (weekly), biomechanical testing and uCT (4 weeks after fracture).

Radiographs were taken every two weeks using a Faxitron. After 4 weeks fractured bones were excised, soft tissue removed and bones were scanned at 32 μm resolution. Maximal force and stiffness were determined by three-point bending.

Data are expressed as the mean ± SEM. Statistical differences between groups were evaluated with one-way analysis of variance (ANOVA). When the analysis of variance performed over all groups was significantly different among the groups, statistical differences between two groups were subsequently analyzed using Tukey’s multiple comparison test. P values <0.05 were considered significant.

RESULTS

Fig 1. Radiographically, fractured femurs treated with LV at day 7 post-fracture showed enhanced repair at 4 weeks, compared to vehicle-treated animals. By week 4, almost complete healing of treated femurs was observed with very small callus present while large callus and incomplete bridging of cortical bone could clearly be seen in the vehicle treated animals.

Biomechanical testing: When LV treatment was administered at day 0, there was a dose-response increase in the structural strength reaching significance with the higher doses (Fig 2).

CONCLUSIONS

- These results show for the first time that one single injection of LV administered locally one week post-fracture is effective in accelerating fracture healing.
- More studies are necessary to confirm these results in other models of fracture healing.
- Sustained-release lovastatin formulation may prove to be very useful not only for fracture repair but for other diseases where BMP2 has proven to be effective.

REFERENCES