Local Application of Zoledronic Acid incorporated in a Poly(D,L-Lactide) Coated Implant Accelerates Fracture Healing in Rats
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Introduction: Zoledronic acid (ZOL), a nitrogen containing bisphosphonate, has been shown in vitro to inhibit osteoclastic activity and to regulate cell proliferation, differentiation and gene expression in osteoblasts (Greiner et al. 2006; Greiner et al. 2007). Because of its impact on bone cells there might be a possible benefit in treatment of fractures by local application of this potent substance. A local application from a biodegradable Poly(D,L-Lactide) (PDLLA) coating of osteosynthetic implants might lead to a stimulating effect on fracture healing. Aim of the study was to analyze the effect of locally applied ZOL from a PDLLA coating of intramedullary implants on fracture healing.

Materials and Methods: Standardized midshaft fractures of the right tibia of 5-month-old rats were stabilized either with uncoated, PDLLA-coated or ZOL-coated implants (10 μg, 2% w/w). To evaluate systemic side effects throughout the investigation blood serum analysis, body weight and body temperature were taken. X-ray examinations were taken at directly after the operation, 28, 42 and 84 days postoperatively. Bridging and mean calusa area in fracture hight were determined. Tibiae were dissected 42 and 84 days after fracture. Biomechanical testing was performed and torsional stiffness and maximum load was determined. All data were expressed as mean +/- standard deviation. A Kruskal-Wallis test and Mann-Whitney U test were performed, p < 0.05 was considered statistically significant.

Results: X-rays demonstrated 42 days after fracture at least unilateral fracture consolidation in all groups (Figure 1 a-c). There was a significant increase in radiological bridging after 42 days in the ZOL-coated group in comparison to the uncoated group (p=0.004) and to the PDLLA group (p=0.037). Analysis of mean radiographic calusa areas after 42 days revealed significantly increased calusa area in fracture height in the ZOL treated group (0.175 cm² ± 0.03) in comparison to the uncoated group (0.124 cm² ± 0.02) (Mann - Whitney U Test: p<0.001) and the PDLLA group (0.139 cm² ± 0.02) (p=0.002). Biomechanical testing revealed a significantly higher maximum load and torsional stiffness in the group treated with ZOL in comparison to the controls (Figure 2a,b). The torsional stiffness 84 days after fracture of the ZOL treated group remained significantly higher than the controls whereas the maximum load of the control groups reached the results of the ZOL coated group (data not shown). There were no measurable systemic side effects of the locally applied ZOL (data not shown).

Discussion: The present study demonstrates the influence of ZOL incorporated in an osteosynthetic implant coating on achievement of biomechanical stability in fracture healing in rats. ZOL was applied locally using an implant coating which is already in clinical use (Schmidmaier et al. 2006). There were no measurable systemic side effects of the locally applied ZOL (data not shown). Moreover the radiographic evaluation showed significantly improved bridging of the ZOL coated group already after 42 days in comparison to the controls. Analysis of mean callus area in fracture height showed significantly higher values in the ZOL coated group in comparison to the controls after 42 and 84 days. Biomechanical testing showed significantly increased stability of mid-tibial fractures after treatment with ZOL incorporated in the PDLLA coating. However, there are still numerous questions about bone remodelling and the influence of bisphosphonates in fracture healing to be answered. Analysis of release kinetics and histomorphological evaluation of the callus should be done further on.