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ABSTRACT OF DISSERTATION

Title	The Effectiveness of Human Parathyroid Hormone and Low-Intensity Pulsed Ultrasound on the Fracture Healing in Osteoporotic Bones [骨粗鬆症病態下での骨折創傷治癒に対する副甲状腺ホルモンと低出力超音波の影響]
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Introduction

Preventing osteoporotic fracture is one of the most important goals in the treatment for osteoporosis. Nevertheless, the management of fractures caused by osteoporosis is also crucial. Parathyroid hormone (PTH) is the first anabolic drug approved for the treatment of osteoporosis and a number of animal studies suggest that PTH could be beneficial in the treatment of fractures in normal animal models. Furthermore, investigation about the ideal time and administration timing of PTH for fracture healing after ovariectomized (OVX) in rats should be addressed. Although PTH treatment for osteoporosis is indicated for up to 24 months in humans, its continual use, cost and the unpleasantness of daily subcutaneous injections, have become a concern. Thus, discovering the least possible duration of PTH treatment in combination with other non-invasive treatment, such as low-intensity pulsed ultrasound, is essential.

Materials and Methods

Thirty-two, three-month-old, weighing 220-260 g, female Sprague-Dawley rats were purchased from Nihon SLC Co., (Shizuoka, Japan). To obtain reliable model of osteoporosis, OVX were performed to the animals, and lumbar vertebrae of each animals were scanned. After 12-week post OVX, the lumbar vertebrae were rescanned to confirm the changes in microarchitectures and all of the animals were underwent surgery to produce bilateral mid-diaphyseal fractures of proximal tibiae. Then, experimental animals were randomly divided to 4 groups (n=8 for each): control group as placebo, PTH group, LIPUS group, and combined group. PTH group had PTH administration at a dose of 30 μg/kg/day for 3 days/week for 6 weeks. LIPUS group received treatment for 20 minutes per day, 5 days per week until 6 weeks whereas rats in the combined group received both PTH

administration and LIPUS exposure for 6 weeks. Radiology and qualitative analysis of the fractured tibiae were detected by micro-CT. Five weeks after the fracture, the tibia were harvested to permit histological assessments and at week 6, for mechanical properties of the fracture callus.

Results

From micro-CT results, BMD and trabecular bone integrity of the PTH and combined groups showed significantly higher value than control group at weeks 4-6 post fracture. Representative longitudinal radiography showed that the callus formation were detected within 2 weeks, and enlarged in size during the following 1-2 weeks. The fracture healing score and mean callus area also indicated that the combined group revealed better healing processes than the individual treatment groups. Mechanical testing was significantly higher in LIPUS, PTH and combined groups than in control group.

Discussion and conclusion

This study investigated the individual and combined effects of PTH and LIPUS on osteoporotic fracture healing. Our results from micro-CT, weekly radiographic assessments, histology and mechanical test indicated LIPUS treated group had greater healing responses than control group. Meanwhile, PTH group showed similar callus formation, faster callus bridging and more rapid replacement of fracture line by osseous tissues than LIPUS group. Even though the effects observed with LIPUS were relatively lower compared with to systemic administration of PTH, this implies that LIPUS alone could not achieve satisfactory healing of osteoporotic bone. Furthermore, the combined group was with better healing processes than individual PTH and LIPUS groups and revealed a higher ratio of increment in BV/TV value compared to PTH group during weeks 3-6. Although the combined therapy of PTH and LIPUS has no additive effects on osteoporotic fracture healing, both PTH and LIPUS enhanced osteoporotic fracture healing and the favourable of PTH effect might not be diminished by the LIPUS exposure to the fracture sites. In summary, this study found PTH and LIPUS leads to accelerated fracture healing and enhanced bone mineral density as well as bone microarchitectural parameters at the fracture sites compared to the individual treatment. These findings suggest that the combined treatment of PTH and LIPUS might be applicable in the treatment of osteoporotic fracture healing.