Effects of Intermittent Low-Dose Parathyroid Hormone Treatment on Rapid Mandibular Distraction Osteogenesis in Rabbits

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Purpose: To determine whether low-dose recombinant human parathyroid hormone (rhPTH) would have a beneficial effect on regenerate healing and surrounding bone in a rabbit model of rapid mandibular distraction osteogenesis (DO).

Materials and Methods: Twenty-eight rabbits underwent unilateral mandibular lengthening at a rapid rate of 2 mm per day for 5 days. From the first day of DO, the experimental group received daily subcutaneous injections of rhPTH 10 μg/kg for 30 days and the control group received the same volume of saline (n = 14 in each group). At 6 weeks after completion of DO, the distracted callus was examined by micro-computed tomography (micro-CT), histology, and the 3-point bending test. Moreover, bone mineral density of the anterior pin region was evaluated by dual-energy x-ray absorptiometry.

Results: Under rapid distraction, poor bone healing was observed in the distracted callus from the control group. In contrast, more mature and abundant bone formation was found in the distracted callus from the experimental group by histologic and micro-CT examinations. Quantitatively, the PTH-treated animals had superior parameters in bone volume fraction, trabecular number, and trabecular thickness and mechanical properties compared with controls ($P < .05$). Bone mineral density of the anterior pin region was greater in the experimental than in the control group ($P < .05$).

Conclusion: Low-dose intermittent rhPTH administration not only enhance new bone formation but also can prevent fixator-related osteoporosis of surrounding segments after rapid mandibular DO in rabbits.

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Distraction osteogenesis (DO) has become an accepted surgical procedure for the treatment of many congenital and acquired maxillofacial deformities and deficiencies. Nevertheless, prolonged duration of treatment and possible fibrous union or nonunion hamper its further clinical application. Moreover, fixator-related stress-shielding osteopenia remains problematic. Because the fixator takes much of the load during the lengthening and the patient might not be fully mobile, osteoporosis develops in the bone adjacent to the site of lengthening, especially around pin sites.[1,2] Osteoporosis, which is characterized by decreased bone mass and deterioration of bone microarchitecture, leads to enhanced bone fragility and a consequent increase in fracture risk. Occurrence of fracture in the regenerate or surrounding regions after removal of the fixator has been reported as up to 38%.[3,4] This is a devastating complication after such a complex and lengthy procedure.

Numerous physical means and interventional methods have been explored to improve the distraction regenerate, including local application of growth factors, transplantation of osteoblast cell lines, local gene therapy, low-level laser therapy, and electronic and ultrasonic stimulation.[5-7] However, not only have these studies met with mixed results, but most have failed to consider the integrity of the entire bone in the fixator, concentrating solely on the regenerate. As of yet, none of these approaches have been used in clinical practice. Therefore, to explore an effective method to promote new bone formation and decrease stress-shielding osteoporosis in DO, even under poor osteogenic conditions, has important clinical relevance.

Interventional methods are not very appealing, because of limited accessibility of the distraction site, fear of interference with the normal sequence of events attributable to injury, inability to retain a constant stimulatory action on the regenerate, and increased risk of infection.[8] The systemic administration of an exogenous substance to accelerate the phenomenon of DO is an intriguing prospect.

Parathyroid hormone (PTH) is the only therapy approved by the US Food and Drug Administration for stimulating bone formation in patients with osteoporosis and has been shown to reverse loss of bone mineral density (BMD) and prevent fractures in clinical trials.[9] Animal studies also have shown that systemic intermittent administration of PTH promotes osteogenesis in normal and impaired fracture healing and enhances implant anchorage in low-density bone.[10,11]

However, knowledge on the effects of intermittent PTH treatment on the regenerate and surrounding bone during mandibular DO is very limited. Although previous animal studies have documented the enhancement of DO treated with relatively high doses of PTH (range, 30 to 60 μg/kg per day),[12,13] these doses are superior to the clinical doses used in osteoporosis. The purpose of this experiment was to investigate the effects of intermittent PTH administration at a lower dose on the regenerate and adjacent pin areas in a rapidly distracted rabbit mandible. In this study, the regenerate callus was assessed by histology, microcomputed tomography (micro-CT), and the 3-point bending test. BMD in the regions anterior to the regenerate were evaluated by dual-energy x-ray absorptiometry (DXA) to test distraction device-associated osteopenia at the pin site.

Materials and Methods

ANIMALS

The protocol for animal experiments was approved by the animal ethics committee of the Hospital of Stomatology, Sichuan University (Chengdu, China). Twenty-eight skeletally mature (2.0 to 3.0 kg) male New Zealand White rabbits were used in this study. Anesthesia for all experimental procedures was achieved by intravenous administration of pentobarbital (15 mg/mL) and diazepam (2.5 mg/mL).

DO AND TREATMENT PROTOCOL

After a 3-cm longitudinal incision was made along the inferior border of the right mandible, the platysma and the periosteum were reflected from the mandible laterally. A vertical mandibular osteotomy was performed just between the mental foramen and the first premolar using a fissure bur under constant saline irrigation. Then, a custom-made distractor was adapted along the plane perpendicular to the osteotomy line.[14] Then, the wound was closed in layers. The rabbits were randomly divided into 2 groups of 14 rabbits each.

After a latency period of 5 days, distraction was initiated at a rate of 1 mm every 12 hours for 5 days (2 mm per day). From the first day of the distraction period, the experimental group received a daily subcutaneous injection of recombinant human PTH (rhPTH; 1-34; Bachem, Bubendorf, Switzerland) at a dosage of 10 μg/kg of body weight for 30 days, and the control group received the same volume of saline during the same period. At 6 weeks after the completion of distraction, all animals were euthanized with an overdose of pentobarbital (150 mg/kg) and the distracted mandibles were harvested.

DXA EXAMINATION

The mandible samples were scanned with DXA (Lunar iDXA, GE Healthcare, Chicago, IL) using the small animal mode. The BMD of region of interest was