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Basic Science

Intermittent administration of teriparatide enhances graft bone healing and accelerates spinal fusion in rats with glucocorticoid-induced osteoporosis

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Abstract

BACKGROUND CONTEXT: There has been no study regarding the effect of intermittent administration of teriparatide (TPTD [recombinant human parathyroid hormone (1-34)]) on spinal fusion in patients with glucocorticoid-induced osteoporosis (GIOP).

PURPOSE: To elucidate the effect of intermittent administration of TPTD on spinal fusion in rats with GIOP.

STUDY DESIGN: An experimental animal study of rats under continuous glucocorticoid (GC) exposure undergoing spinal fusion surgery and administration of TPTD or saline.

METHODS: Male 8-week-old rats (n=18) were administered 5 mg/kg methylprednisolone (MP) for 12 weeks. After 6 weeks of MP administration, the rats underwent posterolateral spinal fusion (L4–L5) with iliac crest autograft. Then, five times a week, they were given either saline or 40 μg/kg TPTD for 6 weeks. The following assessments were performed: time-course bone microstructural analysis of the fusion mass and adjacent vertebrae (L6), with in vivo microcomputed tomography (μCT); fusion assessment, with manual palpation testing and three-dimensional CT images; and bone histomorphometrical analysis of the fusion mass.

RESULTS: In the TPTD group, values for bone volume and other bone microstructural parameters at the fusion mass increased and peaked 4 weeks after surgery, and these values were significantly greater than those for the control (CNT) group at 4 and 6 weeks after surgery. Fusion assessment showed that fusion rate was higher in the TPTD group than in the CNT group (CNT group: 56%, TPTD group: 89%). Bone histomorphometry revealed that values for bone formation parameters were significantly higher in the TPTD group than in the CNT group.

CONCLUSIONS: Under continuous GC exposure in a rat model of spinal fusion, intermittent TPTD administration accelerated bone modeling and remodeling predominantly by stimulating bone formation at the fusion mass and increasing the fusion rate. Intermittent TPTD administration also improved bone microarchitecture of adjacent vertebrae.

Keywords: Teriparatide; Glucocorticoid-induced osteoporosis; Bone graft; Bone remodeling; Spinal fusion; Adjacent vertebrae

FDA device/drug status: Approved: Teriparatide, Methylprednisolone.

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Introduction

Glucocorticoids (GCs) are potent antiinflammatory and immunosuppressive agents widely used for the treatment of diseases such as asthma, chronic lung disease, rheumatoid arthritis and other connective tissue diseases, inflammatory bowel disease, and neuromuscular disease. However, clinical and experimental data have shown that prolonged GC exposure leads to trabecular bone loss and osteoporosis [1,2]. Prolonged exposure to GCs has the primary effect on decreasing bone formation because of the inhibition of the differentiation, activity, and life span of osteoblasts and osteocytes [3,4]. In one study, bone biopsies from those who received GCs showed a greater reduction in bone formation at the cellar and tissue levels compared with those with postmenopausal osteoporosis [5].

Spinal fusion surgery is one of the standard treatments for degenerative and traumatic spine diseases. In performing it, surgeons generally use bone grafting to restore mechanical stability to the affected spinal segment by bridging bone between the vertebrae, and successful bony union at unstable spine segments leads to pain relief and neurologic recovery [6–9]. Many authors have reported that spinal fusion in patients with osteoporosis carries a high incidence of surgical complications such as adjacent vertebral fractures of the surgical site or spinal instrumentation failure [10,11]. In particular, delayed union or pseudarthrosis of grafting bone, instrumentation failure, and adjacent vertebral fractures after surgery create more serious problems in performing spinal fusion surgery for patients with glucocorticoid-induced osteoporosis (GIOP) [12]. Depending on the pathophysiology of GIOP, pharmacological agents that stimulate bone formation and accelerate bone remodeling may hold the promise of resolving these problems.

Intermittent administration of parathyroid hormone (PTH) has a potent stimulatory effect on bone remodeling [13,14]. It has been reported that intermittent administration of teriparatide (TPTD or recombinant human PTH [1-34]) increases the cortical and cancellous bone mass, improves the microarchitecture of bone, and reduces the risk of osteoporotic vertebral fractures. Teriparatide has been widely used for the treatment of postmenopausal women and men with severe osteoporosis [15–17]. In addition, several randomized controlled clinical trials have shown the effectiveness of TPTD for treating GIOP, which was superior to that of antiresorptive bisphosphonates [18–20].

Teriparatide induces the maturation of circulating osteoblast precursors and differentiation of lining osteoblasts, stimulates the preexisting osteoblasts to form new bone, and reduces osteoblast and osteocyte apoptosis [21–23]. Teriparatide has potential as the ideal agent for resolving many problems regarding spinal fusion surgery in patients with GIOP, but there have been no studies on the effect of intermittent TPTD administration in spinal fusion in animals and patients with severe osteoporosis, such as GIOP. Thus, we conducted a study to elucidate whether intermittent TPTD administration stimulates graft bone healing in spinal fusion in GIOP in a rat model.

Methods

Animals

We purchased 8-week-old male Sprague-Dawley rats (n=21; mass, 260–285 g; purchased from SLC Japan, Hamamatsu, Japan). All rats were acclimated to an animal room at a controlled temperature (23°C±1°C) and humidity (45%–65%) and were housed in cages under specific pathogen-free conditions with a 12-hour light-dark cycle (light on, 0800–2000 hours). They were housed in cages under specific pathogen-free conditions with free access to water and standard laboratory feed (Oriental Yeast, Tokyo, Japan). Their housing and care and our experimental protocol were approved by the Animal Experimental Committee of Osaka University.

Chemicals and reagent

Methylprednisolone (MP) was purchased from Sigma-Aldrich (Tokyo, Japan) and dissolved in saline to 5 mg/kg. A powdered form of TPTD acetate (Asahi Kasei, Tokyo, Japan) was dissolved in saline to 40 μg/kg. For use in fluorescence labeling, calcein was purchased from Dojinwako (Tokyo, Japan).

Experiment design

Three rats were subcutaneously injected with saline per week for 6 weeks before surgery and were euthanized with an overdose of anesthetic agents as a baseline group. The other 18 rats were subcutaneously injected with MP five times per week at a dose of 5 mg/kg/d for 6 weeks before surgery. The dose of MP and dosing periods were determined on the basis of methods reported by Hulley et al. [24]. After 6 weeks of MP administration, rats were randomized into two groups before surgery; rats in the control group (CNT group; n=9) were given subcutaneous injections of 0.9% saline five times per week for 6 weeks and rats in the TPTD group (n=9) were given subcutaneous injections of 40 μg/kg/d of TPTD five times per week for 6 weeks. The dose of TPTD was determined according to the method used by Abe et al. [25]. After grouping, all rats were underwent posterolateral spinal fusion (L4–L5) with iliac crest autograft. Saline or TPTD injection started just after the surgery and continued for 6 weeks until the animals were euthanized, and MP administration also continued for 6 weeks until the animals were euthanized. All rats were weighed weekly, and the doses of MP and TPTD were adjusted accordingly. At 6 weeks after surgery, all rats were euthanized with an overdose of anesthetic agents.