Dose-Dependent Enhancement of Spinal Fusion in Rats with Teriparatide [PTH (1-34)]

INTRODUCTION: Teriparatide [PTH (1-34)] is the amino-terminal fragment of parathyroid hormone which has anabolic effects on the skeleton and enhances bone healing. Previously, Teriparatide was shown to enhance spinal fusion in rats and rabbits. The present study characterized the dose-dependent and short-term efficacy of Teriparatide in inducing posterior-lateral spinal fusions in rats.

METHODS: All animal experiments were approved by the animal experimentation ethics committee, The Chinese University of Hong Kong. All rats had iliac crest surgery, and (0.5x0.5cm) trabecular bone grafts were taken. The vertebral column was exposed, and decortications were performed at the lumbar spine L5-L6 levels. The iliac crest autograft material was then implanted onto the L5 and L6 transverse processes of the same animal. Rats were randomly assigned into 3 groups of 10 per group. Treatment groups included saline vehicle controls (Vehicle); Teriparatide low dose of 4µg/kg/day (PTH4) and high dose of 23µg/kg/day (PTH23) subcutaneous injection in 0.5 ml volume for 4 weeks (5 days per week) from the 2nd day post-surgery. The L-5-6 spinal segments were harvested at week 4 post-surgery and assessments included x-ray radiography, μCT, manual palpation and histomorphometry. Analyses of excised L-3 vertebra, distal femora, the femoral diaphysis, proximal femora, and serum bone markers (PINP, osteocalcin) were also used to assess the systemic skeletal effects of Teriparatide.

RESULTS: According to the scoring system (“0”=no bone, “5”=definite fusion), the average radiographic score of L-5-6 fusion mass in Vehicle, PTH4 and PTH23 groups at 4 weeks post-surgery was 1.53, 2.87 and 4.11, respectively, with the PTH23 being significantly higher, relative to Vehicle controls (p<0.001) (Table 1). The average μCT score of L-5-6 fusion mass in Vehicle, PTH4, and PTH23 groups was 1.53, 2.40 and 3.74, respectively (p<0.001, PTH23 vs. Vehicle and PTH4) (Fig.1, Table 1). Manual palpation showed clinical fusion rate was 20%, 50% and 67.7% in Vehicle, PTH4, and PTH23 groups respectively. The bone mineralization apposition rate (mm/day) at the fusion site in Vehicle, PTH4, and PTH23 groups was 0.042±0.004, 0.093±0.009 and 0.246±0.009, respectively, which was significantly increased in a dose-dependent manner in the three groups (p<0.009) (Fig.2). Teriparatide significantly increased vertebral BMD (17% vs. 14%), BMC (11% vs. 28%) and trabecular area (4% vs.12%) in a dose-dependent manner relative to Vehicle (p<0.05, compared with PTH23 group). Teriparatide also significantly increased BMD and BMC of the distal femoral metaphyses (p<0.05). At 4 weeks post-surgery, no differences were found between the circulating PINP or intact osteocalcin levels.

Table 1. The score of radiography and 3D reconstructive images in three groups (Mean ± SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>Group A (Control)</th>
<th>Group B (Low PTH)</th>
<th>Group C (High PTH)</th>
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<tbody>
<tr>
<td>X-ray Score</td>
<td>1.53±0.92</td>
<td>2.87±1.62</td>
<td>4.11±0.69a</td>
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<tr>
<td>μCT Score</td>
<td>1.53±0.98</td>
<td>2.40±1.44</td>
<td>3.74±1.05a</td>
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</tbody>
</table>

DISCUSSION: Teriparatide at 23µg/kg/day for 4 weeks showed anabolic skeletal effects and significantly enhanced spinal fusion rate in rats, whereas Teriparatide at 4µg/kg/day had little effects. Higher doses of Teriparatide may be necessary to promote spinal fusion short-term, if these data are relevant to the clinical situation.

SIGNIFICANCE: Systemic use of Teriparatide [PTH (1-34)] at higher dose has significantly promoted spinal fusion in rats. Part of the underlying mechanisms was that high dose of PTH (1-34) has enhanced bone formation/mineralization.

REFERENCES: