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Comparison between recombinant human parathyroid hormone (1–34) and elcatonin in treatment of primary osteoporosis

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ABSTRACT

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Objective: To evaluate the efficacy and safety of rhPTH (1–34) *vs.* elcatonin. **Methods:** Sixty patients with primary OP were randomly divided into two groups according to the ratio of 3:1. rhPTH (1–34) group (PTH group) was treated with subcutaneous injection of rhPTH (1–34) 20 μ g daily for 18 months, and the elcatonin group (CT group) was treated with intramuscular injection of elcatonin 20 U weekly for 12 months. Bone mineral density (BMD) of the lumbar spine 2–4 (L_{2–4}) and femoral neck, serum calcium and phosphorus, urinary calcium, serum bone specific alkaline phosphatase (BSAP), and urinary c-terminal telopeptides of type I collagen/creatinine (uCTX–I/Cr) were tested at baseline, and 6, 12, and 18 months after treatment. **Results:** In PTH group, BMD of L_{2–4} at 6, 12, and 18 months, BMD of femoral neck at 18 month, BSAP at 6 and 12 months and uCTX–I/Cr at 6, 12 and 18 months were all significantly raised. In CT group, BMD of L_{2–4} at 12 month and that of femoral neck at 12 and 18 months were significantly elevated, while BSAP was significantly decreased at 12 and 18 months, and no significant difference on CTX–I/Cr was observed. When BMD growth and growth rate between two groups were compared, PTH group had better improvement in L_{2–4} BMD and growth rate than CT group at 6, 12, and 18 months. BMD growth and growth rate of femoral neck at 12 month and its growth at 18 month in CT group were higher than in PTH group, but there was no significant difference between two groups regarding the growth rates at 18 month. Besides, there were no significant differences regarding the rates of adverse reactions between two groups. **Conclusions:** rhPTH (1–34), is safe and effective in the treatment of primary OP. It is superior to elcatonin in improving vertebral BMD at onset time, growth rate and growth range, but inferior to elcatonin at BMD of femoral neck.

1. Introduction

With the development of social economy and extension of human lifespan, osteoporosis (OP) has become an important health problem in the elderly population. OP results from loss of the dynamic balance of bone formation and bone resorption that normally maintains bone mass stable

relatively[1]. Treatment for OP is primarily divided into two categories, anti-resorptive and anabolic (osteogenic) agents[2,3]. Elcatonin is a commonly-used drug for senile OP, primarily by inhibiting bone resorption and improving bone mineral density (BMD), but it is unable to maintain normal bone mass and bone strength[4]. Anabolic agents can make up for these deficiencies. Anabolic therapy can increase BMD and quality, while reducing the risk for osteoporotic fractures through stimulation of new bone growth. Teriparatide [rhPTH (1–34)], a recombinant human parathyroid hormone (rhPTH) analogue, maintains the major function of PTH hormone (84 amino acids) and has been an option for treating OP in a decade. Although the net effect of

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PTH in some circumstances like primary hyperparathyroidism could be catabolic^[4], small doses of intermittent application of parathyroid hormone (PTH) has a direct effect of inducing bone formation through stimulation of osteoblast activity and inhibition of apoptosis^[5,6]. It can increase the bone mass of patients and reduce the risk of fracture. Several studies in Europe and United States have confirmed that rhPTH (1–34) has remarkable benefits for elderly patients with OP^[7,8]. There are few clinical studies about this drug in Asian population^[9]. Hence, this study aimed to make further evaluation on the efficacy and safety of rhPTH (1–34) in improving BMD of primary OP and made a comparison with elcatonin, a traditional antiresorptive agent.

2. Materials and methods

2.1. Patients

Sixty patients with primary OP were recruited in Sichuan Provincial People's Hospital from March, 2008 to January, 2009. Inclusion criteria were as follows: (1) OP was diagnosed according to WHO diagnostic criteria^[10], with one of the following: a) BMD T-score of lumbar spine 2–4 (L_{2-4}) or of femoral neck is less than -2.5 SD; b) One place of L_{2-4} was compressed deformation, and T-score less than -1.05 D; (2) The females at the age of 50–79 had more than 3 years of menopause, and males were at the age of 60–79. Exclusion criteria included: (1) any non-primary OP bone disease and other metabolic bone diseases; (2) liver and kidney dysfunction; (3) patients with severe cardiac, hematological, psycho, and nervous system diseases; (4) cancer and other serious progressive disease; (5) patients treated with anti-OP drugs of bisphosphonate in recent 6 months; (6) patients took drugs that affected bone metabolism in recent 1 month. All patients signed the informed consent form voluntarily. Among 60 patients, and 53 cases could be evaluated and 7 quitted because of adverse reactions during treatment. All participants signed informed consent before enrollment into the study according to Declaration of Helsinki, and the study was approved by the ethics committee.

2.2. Methods

According to visiting order, the patients were randomly assigned to two groups: PTH group and CT group according to the ratio of 3:1. PTH group (45 cases) received subcutaneous injection of rhPTH (1–34) (Shanghai United Cell Biotechnology Co., Ltd production), 20 μ g once daily,

and continuously for 18 months. CT group (15 cases) received intramuscular injection of elcatonin (Asahi Kasei Corporation production), 20 U once a week, 12 months of continuous treatment. During treatment, both groups received Caltrate D 600 mg, once daily, which contained 1 500 mg of calcium carbonate (providing 600 mg of calcium) and 125 IU of vitamin D3 (Wyeth Pharmaceutical Co., Ltd) for 18 months continuously. Drugs that could affect bone metabolism were banned, such as bisphosphonates, glucocorticoids, sex hormones, bone-strengthening tablet.

2.3. BMD, bone turnover and biochemical markers measurements

BMD in L_{2-4} and femoral neck were measured by dual energy X-ray absorptiometry using densitometers from GE Lunar Corp (DPX-MD, USA). Serum calcium and phosphorus were determined by ALYMPUSAU5400/AU2700 automatic biochemical analyzer. Urinary calcium was tested by VITROS250 automatic dry-type chemistry analyzer. Bone specific alkaline phosphatase (BSAP, Immunodiagnostic System Ltd, USA) and urinary c-terminal telopeptides of type I collagen/creatinine (uCTX-I/Cr, Nordic Bioscience Diagnostics a/s, Denmark) were use as bone formation and bone resorption marker, respectively. BSAP and uCTX-I were measured by enzyme-linked immunosorbent assay (SEAC Company, Italy), the coefficient of variation within batch $<5\%$, between batch $<8\%$. Urine CTX-I was corrected by urine creatinine, with correction formula: $uCTX-I/Cr (\mu g/mmolCr) = \text{measured urine CTX-I } (\mu g/L) / \text{urine creatinine (mmol/L)}$. During observation, the patients were followed up once every 2 months, 9 times in total. BMD, biochemical and bone metabolism markers mentioned above were measured again when the followed-up was conducted at 6, 12 and 18 months. Additionally, adverse reactions were recorded. The above-mentioned indexes were all compared before and after treatment.

2.4. Statistical analysis

Descriptive statistics of the study subjects were summarized with means \pm standard deviation (SD) for continuous variables, number and percentages for categorical items. The normality of the distribution of the study sample was assessed by Kolmogorov–Smirnov test. Student's t test was used for the group differences of continuous items and Pearson's χ^2 test for categorical items at baseline. Independent-sample t test was used to compare BMD and serum biochemical markers from baseline to endpoint between two treatment groups. The paired t test was used to

assess the changes from baseline to endpoint within each treatment group. The adverse reactions experienced by subjects in the study were analyzed using Pearson's χ^2 test. All statistical tests were two sided, with an α level of 0.05. Statistical analysis was performed by SPSS 17.0.

3. Results

3.1. Demographics of patients

Following successful screening, a total of 60 patients with primary OP were enrolled in the current study and randomly assigned to two groups as the intent-to-treat (ITT) population. The demographics of patients were summarized in Table 1. There were no statistically significant differences between both groups. Additionally, 25 of the overall patients (41.7%) suffered from fracture prior to the treatment. During the study period, 5 patients in PTH group (11.1%) and 2 in CT group (13.3%) discontinued intervention due to withdrawal of consent. Finally, a total of 53 patients completed the entire study protocol (Figure 1).

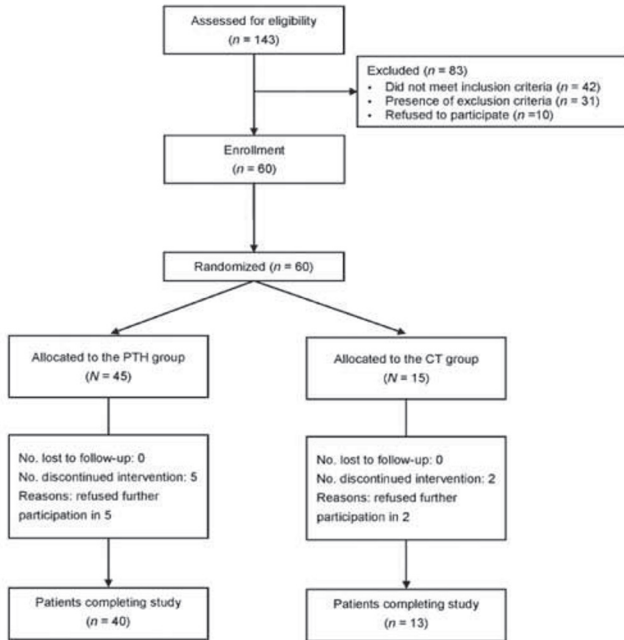


Figure 1. Changes of L_{2-4} and femoral neck (FN) BMD before and after treatment at 6, 12 and 18 months.

3.2. Changes in BMD at the L_{2-4} and FN

Compared with treatment before, L_{2-4} BMD in PTH group had a significant increase at 6, 12 and 18 months. In CT group, L_{2-4} BMD was increased significantly at 12 month, and showed higher values than treatment before, but the

difference was not significant (Figure 2A). The femoral neck BMD was significantly increased in PTH group at 18 month, while in CT group at 12 and 18 months (Figure 2B).

3.3. Changes of biochemical markers before and after treatment

In PTH group, the serum calcium levels were increased significantly at 6 and 12 months, but returned to normal at 18 month compared with treatment before. In CT group, the serum calcium showed no significant difference (Figure 3A). In PTH group, the serum phosphorus levels were increased significantly at 6, 12 and 18 months. No significant differences were observed in CT group (Figure 3B). Regarding the urinary calcium level, no significant differences were observed before and after treatment (Figure 3C).

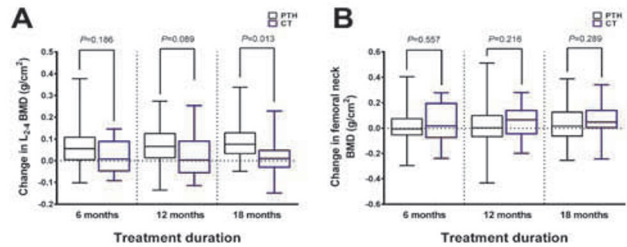


Figure 2. Changes of biochemical markers before and after treatment at 6, 12 and 18 months.

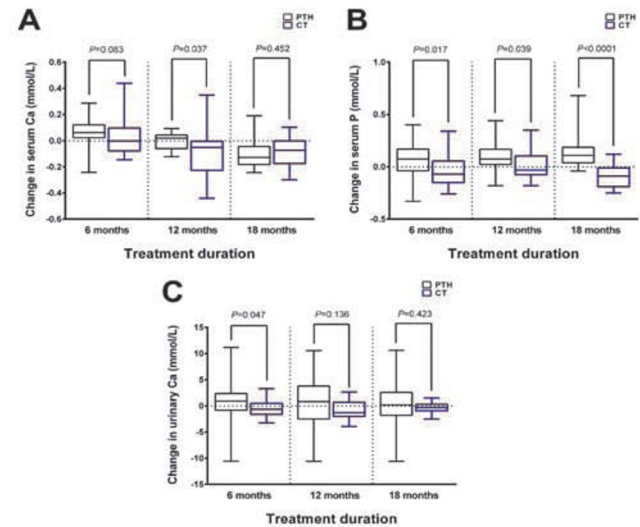


Figure 3. Changes of bone markers before and after treatment at 6, 12 and 18 months.

3.4. Changes of bone metabolism markers before and after treatment

Compared with treatment before, BSAP levels were

increased significantly in PTH group at 6 and 12 months, while decreased significantly in CT group at 12 and 18 months. There were significant differences between two groups regarding BSAP levels respectively at 6, 12 and 18 months (Figure 4A). Compared with treatment before, uCTX– I /Cr levels were increased significantly in PTH group at 6, 12 and 18 months, but no significant differences were observed in CT group. Significant differences were showed between two groups regarding uCTX– I /Cr levels respectively at 6, 12 and 18 months (Figure 4B).

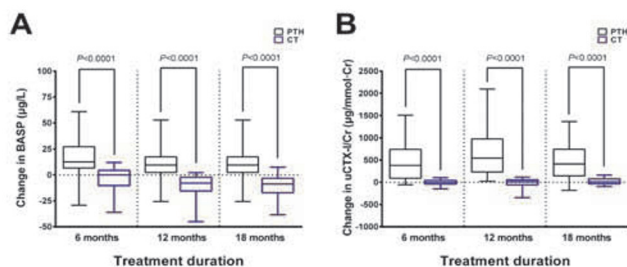


Figure 4. Changes of bone metabolism markers before and after treatment at 6, 12 and 18 months.

3.5. Comparison on BMD growth and its growth rate between two groups

Compared with CT group, PTH group had a higher growth in L_{2-4} BMD, even a rapid growth rate at 6, 12 and 18 months.

Regarding the femoral neck BMD, no significant differences on growth and growth rate were observed at 6 month between these two groups. BMD growth and growth rate of femoral neck at 12 month and its growth at 18 month in CT group were higher than in PTH group, but there was no significant difference between two groups regarding the growth rates at 18 month.

3.6. Adverse reaction

The incidence of drug-related adverse reactions was 35.6% (16/45) in PTH group, in which 5 cases quitted, while 33.3% (5/15) in CT group, in which 1 case quitted. There was no significant difference between two groups with regard to the incidence of adverse reactions ($P>0.05$). No severe drug-related adverse reactions occurred in both groups. The main adverse reactions in PTH group were dizziness (11.1%), fatigue (2.2%), pruritus at the injection site (8.9%), rash (8.9%) and transient hypercalcemia (28.9%), while those in CT group included dizziness (13.3%), fatigue (13.3%) and elevated transaminases (6.7%). The patients were not given any special treatment for adverse reactions. Two cases suffered from new fractures throughout the follow-up process in PTH group, respectively T-12 vertebra compression fracture and occipital linear fracture, while 1 from new fracture of right fibular head linear fracture in CT group. Compared with the

Table 1

Baseline characteristics of patients enrolled in the current study.

Characteristic ^a	PTH group (n=45)	CT group (n=15)	P value
Gender (male/female)	4/41	1/14	1.000
Age (years)	65.1 ± 7.6	65.5 ± 8.7	0.865
Course of disease (years)	7.0 ± 4.4	7.2 ± 5.1	0.884
Fracture prior to the treatment (n, %)	–	–	0.782
None	25 (55.6)	10 (66.7)	–
One body site	17 (37.8)	4 (26.7)	–
Two body sites	2 (4.4)	1 (6.7)	–
Three or more body sites	1 (2.2)	0 (0)	–
L_{2-4} BMD (g/cm^2)	0.764 ± 0.088	0.787 ± 0.090	0.387
Femoral neck BMD (g/cm^2)	0.719 ± 0.145	0.673 ± 0.143	0.290
Serum Ca (mmol/L)	2.52 ± 0.15	2.55 ± 0.19	0.533
Serum P (mmol/L)	1.08 ± 0.17	1.16 ± 0.18	0.125
Urinary Ca (mmol/L)	3.39 ± 1.56	3.28 ± 1.44	0.811
BSAP ($\mu g/L$)	27.16 ± 10.88	25.04 ± 10.69	0.514
uCTX– I /Cr ($\mu g/mmol-Cr$)	253.71 ± 145.83	204.69 ± 163.09	0.364

Note: ^a Data were presented as means ± SD unless stated otherwise. PTH, recombinant human parathyroid hormone (1–34); CT, elcatonin; L_{2-4} , the lumbar spine 2–4; uCTX– I /Cr, urinary c-terminal telopeptides of type I collagen/creatinine.

incidence of new fracture between two groups, there was no significant difference ($P>0.05$).

4. Discussion

PTH secreted by the parathyroid participates in the regulation of calcium and phosphorus metabolism. It increases bone formation by several mechanisms: (1) regulate bone growth by mediating the proliferation and differentiation of osteoblasts^[11]; (2) activate the signaling pathway of anti-apoptosis rapidly so as to inhibit apoptosis of osteoblasts^[12]; (3) stimulate osteoblasts to produce local regulatory factors, such as insulin-like growth factor 1 (IGF-1) and transforming growth factor that promote osteogenesis^[13]; (4) intermittent PTH is associated with sustained stimulation of receptor activator of nuclear factor Kappa B ligand^[14]. A current concept on its mechanism is related to what has been termed “anabolic window”, which is defined as a period when bone formation is greater than bone resorption. The basis for the anabolic window is due to its ability to stimulate bone formation and block bone resorption^[15]. With increasing importance of biological balance of bone formation/resorption in bone homeostasis, rhPTH has become a research hotspot in the treatment of OP^[16–18].

In the current study, we compared the effects of rhPTH (1–34) with elcatonin. Continuous administration of elcatonin more than one year increased the incidence of pituitary tumors^[19], so we limited the duration of elcatonin administration to 12 months in this trial. BSAP and CTX-I were chosen as markers for evaluating bone turnover, because BSAP produced by osteoblasts reflected the activity of osteoblast and bone formation, and CTX-I, a degradation product of bone collagen, reflected bone resorption. Our data showed that both rhPTH (1–34) and elcatonin could significantly increase vertebral BMD and femoral neck BMD. The different action mechanism of both anti-OP agents can be appreciated by the levels of BSAP and uCTX-I/Cr: (1) BSAP was significantly elevated in PTH group, suggesting that rhPTH (1–34) improves BMD by promoting bone formation. On the contrary, BSAP in CT group was significantly decreased; (2) uCTX-I/Cr was increased during rhPTH (1–34) treatment, suggesting that it simultaneously increases bone resorption when stimulating bone formation, which further stimulates and promotes bone formation. This finding is consistent with those of previous studies. Intermittent low dose of PTH may maximize the effect of bone formation and minimize the effect of bone

absorption^[20–22]. The temporal changes in BSAP and uCTX-I/Cr levels showed that there was a “synthetic window” when the bone formation was significantly greater than bone resorption, leading to the largest osteogenic effect: in PTH group, BSAP reached its peak at 6 month, and uCTX-I/Cr reached the peak at 12 month. However, the vertebral and BMD femoral neck (especially L_{2–4} BMD) progressively increased. rhPTH (1–34) showed better results compared with elcatonin in improving vertebral BMD. Regarding the femoral neck BMD, as compared with rhPTH (1–34), elcatonin was able to maintain its effect for additional 6 months after the 12-month treatment. However, at 18 months, no significant difference was observed between both groups regarding the growth rate of femoral neck BMD. Hence, this study reveals that a small dose of rhPTH (1–34) has an anabolic effect, and this effect is better for cancellous bone, which is consistent with prior studies^[4].

In this study, hypercalcemia was observed in 28.9% of patients in PTH group, relatively higher than previously reported data^[23]. Nevertheless, it neither required any medical treatment nor led to discontinuation. With exception of the study by Li *et al*^[24], most studies were limited to 12 months. In this study, the limitation included: (1) The sample size was small; (2) The courses of treatment in these two groups were not entirely consistent. Hence, the conclusion may not be necessarily suitable for majority of patients with OP, which may explain the difference on PTH on BMD effects of femoral neck. Currently, the longest treatment period of OP with rhPTH (1–34) is limited to 18 months in Europe^[25]. However, a growing interest is how to maintain its effect on BMD growth and fracture prevention after treatment^[26,27]. We speculate that a sequential combination can be considered (perhaps rhPTH (1–34) followed by elcatonin) due to their different action mechanisms and respective advantages. Hence, the results in this study provide a supporting evidence for rhPTH (1–34) safe administration for up to 18 months to treat primary OP in Asian population.

Conflict of interest statement

We declare that we have no conflict of interest.

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