Efficacy of Teriparatide in Patients with Hypoparathyroidism: A Prospective, Open-label Study

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Abstract

Context: Conventional treatment of hypoparathyroidism with calcium, Vitamin D analogs, and thiazide diuretics is often suboptimal, and these patients have poor quality of life. Teriparatide (parathyroid hormone 1–34 [PTH (1–34)]), an amide of PTH, is widely available for the use in osteoporosis; however, its use in hypoparathyroidism is limited. Aims: The aim of this study is to evaluate the efficacy of PTH (1–34) in the treatment of patients with hypoparathyroidism. Settings and Design: This was a prospective, open-label interventional study in a tertiary care hospital of Indian Armed Forces. Subjects and Methods: All patients with hypoparathyroidism presented to the endocrinology outpatient department were included and were exhibited injection PTH (1–34) 20 µg twice daily that was gradually reduced to 10 µg twice daily along with calcium, active Vitamin D (alfacalcidol), and hydrochlorothiazide. Oral calcium and alfalcacidol doses were also reduced to maintain serum calcium within normal range. The quality of life (QOL) score was calculated using RAND 36 QOL questionnaire at baseline and termination of the study. Statistical Analysis Used: Paired t-test was used to calculate pre- and post-treatment variables. Results: Eight patients (two males) were included in this study having mean age of 35.8 years. PTH (1–34) treatment led to the improvement in serum calcium (6.81–8.84 mg/dl), phosphorous (5.8–4.2 mg/dl), and 24 h urinary calcium excretion (416–203.6 mg). Parameters of QOL showed the improvement in overall QOL, physical performance, energy, and fatigue scores. No major adverse events were noted. Conclusions: Treatment of hypoparathyroidism with PTH (1–34) leads to improvement in calcium profile, reduction in hypercalciuria, and improvement in QOL, whereas it is safe and well tolerated.

Keywords: Hypoparathyroidism, quality of life, teriparatide

Introduction

Hypoparathyroidism is an uncommon disorder of calcium metabolism characterized by hypocalcemia, hyperphosphatemia, and reduced level of intact parathyroid hormone (iPTH).[1] Conventional treatment includes calcium and calcitriol which usually fails to control symptoms or correction of associated metabolic abnormalities optimally.[1,2] It often results in hypercalciuria that may cause nephrolithiasis or nephrocalcinosis and thiazide diuretics are added to control the same.[3]

Hypoparathyroidism is one of the endocrine disorders that are not treated with the deficient hormone. That is due to the fact that synthetic PTH was not available till recently; however, with the Food and Drug Administration approval of PTH (1–84), now, treatment with deficient hormone is feasible in this disorder. Nevertheless, it is still not widely available.

Teriparatide (PTH [1–34]) has been used extensively in the treatment of osteoporosis. It has been tried in patients with hypoparathyroidism,[4,5] however, it is not an accepted modality of treatment and is not commonly used in the management of primary hypoparathyroidism. Therefore, we undertook this study to assess the efficacy of PTH (1–34) in patients with primary hypoparathyroidism who were poorly controlled with conventional therapy.

Subjects and Methods

This was an open-label interventional study to assess the efficacy of PTH (1–34) in the management of hypoparathyroidism.
carried out in a tertiary care hospital of Indian Armed Forces that caters to patients from all over the country. It was carried out during February 1, 2014–January 31, 2016. All patients presented to the endocrinology outpatient department diagnosed with hyperparathyroidism between the ages 25 and 75 years were included in this study. Exclusion criteria were patients with pregnancy, history of malignancy, and those refusing consent.

At baseline, detailed history was obtained and patients were examined clinically. Laboratory parameters included calcium profile (serum calcium, phosphorous, alkaline phosphate, and albumin), 24 h urinary estimation of calcium, phosphorous, and creatinine, and hormonal evaluation (iPTH, 25 OH Vitamin D, and thyroid stimulating hormone [TSH]). Calcium profile was carried out in the central laboratory of the hospital, and hormonal profile was done in the endocrinology laboratory using fully automated IRMA SR300 machine.

A noncontrast computed tomography of the brain was carried out to rule out basal ganglia calcification, and ultrasonography of the abdomen was done and bone mineral density (BMD) estimation at three sites (spine, hip, and nondominant forearm) by DXA using Hologic ODR discovery machine. Slit-lamp examination was done at baseline to look for any cataract.

Patients were administered standard treatment with calcium carbonate 500 mg (1–2 tablets 4–6 times a day), alfacalcidol (0.25 mg once–four times a day), hydrochlorothiazide (25–50 mg/day), and tablet levothyroxine (in postsurgical patients with hypothyroidism). PTH (1–34) was added at a dose of 20 µg twice daily and was gradually reduced to 10 µg twice daily once the patient was stable and serum calcium values were within normal range. Oral calcium and alfacalcidol doses were also reduced to maintain serum calcium within normal range. Patients were followed up clinically at monthly interval for the first 3 months and at 3 monthly intervals thereafter. Calcium profile and hypercalcemia were checked every 3 monthly while TSH, 25 OH Vitamin D, iPTH, and BMD estimation were carried out at the time of termination of study or more frequently if indicated. For assessing changes in the quality of life (QOL), RAND 36 QOL questionnaire was filled at baseline and at the termination of the study. The statistical program for the Social Sciences (Release 10.01, PC Windows; SPSS Inc., Chicago, IL, USA) was used for the data analysis. Data were expressed as mean ± standard deviation (SD) until otherwise specified. Baseline and posttreatment data were compared using paired t-test. A P < 0.05 was regarded statistically significant.

**RESULTS**

A total of eight patients (two males) were included in this study, and their mean age ± SD was 35.8 ± 6.8 (range: 28–58) years. Three patients had postoperative while rest had idiopathic hypoparathyroidism. Median duration since diagnosis till inclusion into the study was 23 (4–168) months. Average of hospital admissions due to hypocalcemia-related illnesses before start of PTH (1–34) was 6.4 ± 3.9 (0–20) episodes. Mean duration of follow-up was 11.8 ± 2.17 (7–18) months.

Baseline and follow-up data of these patients are presented in Table 1. Parameters of QOL showed significant improvement in overall QOL, physical performance, energy, and fatigue scores. Changes in the parameters of QOL and BMD at the termination of study as compared to baseline are enumerated in Tables 2 and 3, respectively. A significant increase was seen in spinal BMD due to increase in BMD of L3 and L4 vertebrae. Only two patients required hospitalization due to recurrent carpopedal spasms (one patient missed the dose of PTH [1–34] for 3 days and other had tetany during menstrual cycle) during follow-up, no other major adverse events were noted, and the drug was well tolerated.

**DISCUSSION**

Our study demonstrates that treatment of primary hypoparathyroidism with PTH (1–34) for up to 18 months results in maintenance of normal calcium, values with concomitant reduction in oral calcium dose, and improvement in symptoms and QOL. It also leads to reduction of calciuria, is well tolerated and safe. To the best of our knowledge, our study is the first Indian report to demonstrate efficacy of PTH (1–34) in the treatment of hypoparathyroidism though earlier a review has been published.[7]

Corrected serum calcium increased significantly from baseline mean value of 6.81 ± 1.02 to 8.84 ± 0.63 mg/dl at the end of therapy. Published literature also shows similar normalization of serum calcium levels after administration of either PTH (1–34) or PTH (1–84).[1,2] PTH deficiency results in hypocalcemia due to reduced production of 1,25(OH)2 Vitamin D at kidneys that leads to reduced calcium absorption from the intestines and diminished calcium reabsorption at distal tubules occurring as a result of direct PTH action.[2] Mobilization of calcium from bones plays a minor role in the maintenance of eucalcemia in the setting of hypoparathyroidism that is also reduced in these patients. Administration of synthetic PTH (1–34) corrects these abnormalities and leads to correction of hypocalcemia.[4,5,8]

| Table 1: Baseline and follow-up parameters |
|------------------------------------------|
| Mean values | Baseline | Follow-up | P |
| Corrected serum calcium (mg/dl) | 6.81±1.02 | 8.84±0.63 | 0.002* |
| Serum phosphorus (mg/dl) | 5.82±0.61 | 4.26±0.42 | 0.009* |
| Serum alkaline phosphatase | 72.2±20.8 | 106.8±29.9 | 0.016* |
| 24 h urinary calcium (mg) | 416±329.2 | 203.6±64.5 | 0.211 |
| Daily calcium dose (mg) | 4000±707 | 1600±651.9 | 0.005* |
| Daily Vitamin D (alfacalcidol) dose (mcg) | 1.4±0.94 | 0.55±0.21 | 0.123 |
| Daily hydrochlorothiazide dose (mg) | 20±6.84 | 12.5±8.84 | 0.704 |
| RAND 36 QOL score | 258.9±85.06 | 203.6±64.5 | 0.008* |

*Significant P value. QOL: Quality of life
Another barrier in the treatment of hypocalcemia is dose of oral calcium that may be required to achieve normocalemia. Hence, goal of treatment of hypoparathyroidism may not be to maintain normocalcemia but to give calcium in such doses that provide symptomatic relief to the patient while serum calcium values remain undercorrected. Even with this goal, often large doses of oral calcium are needed that may lead to unacceptable hypercalciuria with its associated complications such as kidney stones and reduced renal function necessitating dose modification and addition of thiazide diuretics owing to their anticalciuric action. Addition of PTH (1–34) to conventional therapy was associated with significant reduction in mean daily calcium dose from 4 to 1.6 g in our study. This is in accordance with the published literature. We also noted reduction in 24 h urinary calcium excretion from mean value of 416–204 mg though it did not reach significant value. Small sample size and very high hypercalciuria (1463 mg) in one patient could have resulted in this finding. Serum phosphorous level also decreased significantly, a finding that is expected from mechanism of action of PTH and is well described.

Conventional therapy with calcium and Vitamin D analogs is often associated with wide fluctuations in serum calcium level. Patients with hypoparathyroidism complain fluctuations in energy levels, low mood, fatigue, and overall well-being. PTH (1–34) causes improvement in serum calcium levels through various mechanisms as cited above and reduces fluctuations in its levels. In fact, twice daily injections are better than once daily and PTH (1–34) administered through infusion pump gives more stable calcium level control as compared to twice daily injections. Our patients also had similar symptoms at baseline owing to hypocalcemia and probably fluctuating serum calcium levels or pleiotropic effect of PTH itself. Our study showed improvement in various parameters of QOL at the end of study as compared to baseline in the parameters of general health, energy level, and fatigue and physical functioning. Similarly, therapy with PTH (1–84) has also been shown to be associated with improvement in QOL though improvement in QOL score has not been described earlier with teriparatide.

BMD showed quantitative improvement in bone mineral content (BMC) in spinal BMD owing to its improvement in L3 and L4 spine while no change was noted in hip or forearm. This finding is in contrast to no change in BMC observed in some studies and can be ascribed to anabolic effect of PTH (1–34) on bone. However, this aspect of treatment has not been explored in the existing literature and needs further studies.

During the period, two patients got admitted to hospital one for panic attack and another for tetany that got precipitated during the study period.

Table 2: Quality of life parameters: Baseline versus follow-up

| Parameter | Baseline | Follow-up | P   |
|-----------|----------|-----------|-----|
| RAND 36 QOL score (maximum - 800) | 258.9±85.06 (135-369) | 602.7±91.87 (470-686) | 0.008* |
| PF | 51±20.4 (15-65) | 87±13.51 (70-100) | 0.007* |
| PH | 0 | 55±51.23 (0-100) | 0.074 |
| EP | 20±44.7 (0-100) | 80±44.72 (0-100) | 0.070 |
| E/F | 13.8±10.6 (0-25) | 80±9.35 (65-90) | 0.0008* |
| EW | 57.6±16.1 (40-80) | 87.2±13.08 (68-100) | 0.06 |
| SF | 37.5±17.7 (12.5-62.5) | 64.34.69 (12.5-100) | 0.17 |
| PN | 67±28.2 (22.5-100) | 89.5±7.98 (77.5-100) | 0.15 |
| GH | 12±9.1 (0-25) | 59±29.45 (30-95) | 0.03* |

*Significant P value. PF: Physical functioning, PH: Limitation due to physical health, EP: Limitation due to emotional health, EF: Energy/fatigue, EW: Emotional well-being, SF: Social functioning, PN: Pain, GH: General health, SD: Standard deviation, QOL: Quality of life

Table 3: Bone mineral density: Baseline versus follow-up

| Site          | Baseline mean (g/cm²) | Follow-up mean (g/cm²) | Percentage change | P   |
|---------------|-----------------------|------------------------|------------------|-----|
| L1            | 1.002±0.13            | 1.06±0.12              | 5.76±8.77        | 0.23 |
| L2            | 1.043±0.11            | 1.12±0.08              | 7.94±7.08        | 0.06 |
| L3            | 1.099±0.14            | 1.16±0.13              | 5.87±4.43        | 0.02* |
| L4            | 1.05±0.15             | 1.14±0.14              | 8.58±3.54        | 0.003* |
| Total L1-L4   | 1.052±0.13            | 1.12±0.12              | 7.07±5.42        | 0.03* |
| Femur neck    | 0.91±0.06             | 0.91±0.06              | −0.07±2.34       | 0.90 |
| Total hip     | 1.074±0.10            | 1.03±0.12              | −4.58±6.01       | 0.18 |
| Distal radius | 0.690±0.05            | 0.72±0.07              | 3.92±2.82        | 0.14 |

*Significant P value. BMD: Bone mineral density
after omission of PTH (1–34) for 2 days that resolved quickly to calcium infusion and restarting PTH (1–34). We found no major adverse events during the study similar to published literature. In fact, safety profile for the use of PTH (1–34) in hypoparathyroidism has been established for 3 years duration. However, we did not use it for a period more than approved use for osteoporosis. Furthermore, due to limitation of its use for 2 years as per the current safety guidelines owing to lack of safety data, it is recommended that PTH (1–34) be used in patients with difficult to control disease on conventional therapy.

The strength of our study is its prospective design and evaluation of parameters of QOL and its limitations include small sample size and nonevaluation of bone turnover markers.

**Conclusions**

To conclude, our study shows that treatment of hypoparathyroidism with PTH (1–34) leads to improvement in calcium profile, reduction in hypercalciuria, and improvement in QOL, whereas it is safe and well tolerated. At present, PTH (1–34) is approved for treatment of osteoporosis and is widely available. It may be an effective in the treatment of patients having difficult to control disease or unacceptable hypercalciuria. However, further larger studies are required to establish its use in the treatment of hypoparathyroidism.

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**Conflicts of interest**

There are no conflicts of interest.

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