Clinical Trials Study

Paricalcitol in hemodialysis patients with secondary hyperparathyroidism and its potential benefits

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Abstract

BACKGROUND
Secondary hyperparathyroidism (SHPT) is a common complication in patients with end-stage renal disease and it is also common in hemodialysis patients. SHPT can increase bone fragility and calcification of blood vessels and soft tissues, which greatly increases the risk of death.

AIM
To discuss the outcome, safety and other potential benefits of paricalcitol injection in hemodialysis patients with SHPT.

METHODS
We recruited 40 patients who received hemodialysis at our hospital for chronic renal failure with SHPT between March and December 2019. They received paricalcitol injection for 24 wk (starting dose, 0.06–0.08 μg/kg), three times per week. They were followed up at the baseline (week 0), week 4, week 12 and week 24. The primary outcome indicator was the percentage of patients with a > 30% decrease in intact parathyroid hormone (iPTH) levels at week 24 compared with the baseline. The secondary outcome indicators included percentage decrease in iPTH levels at week 24, standard-reaching rate of iPTH (percentage of patients with iPTH down to 130–585 pg/mL), changes in serum levels of calcium (Ca), phosphate (P), Ca × P product, alkaline phosphatase (ALP), creatinine (Cre), hemoglobin (Hb), and C-reactive protein (CRP), and incidence of adverse events (AEs).

RESULTS
After 24 wk of treatment, iPTH levels decreased significantly (598.88 ± 381.29 pg/mL vs 888.84 ± 376.88 pg/mL, P < 0.05). More than 30% decrease of iPTH was found in 21 of 36 (58.33%) patients. The average decrease in iPTH levels was 32.16
INTRODUCTION

Secondary hyperparathyroidism (SHPT) is a common complication in patients with end-stage renal disease. Hyperphosphatemia, hypocalcemia and 1,25(OH)2D deficiency are considered important in the pathogenesis of SHPT[1]. SHPT is a component of chronic kidney disease-mineral and bone disorder, which is featured by increased fibroblast growth factor 23 and serum parathyroid hormone (PTH) concentrations, decreased 1,25(OH)2 vitamin D concentrations and abnormal serum phosphate (P) and calcium (Ca) concentrations[2-4]. SHPT can increase bone fragility and calcification of blood vessels and soft tissues. Patients with SHPT are at a higher risk for bone fractures and cardiovascular diseases, which, in turn, have a significant adverse impact on quality of life[5]. Clinically, nonselective vitamin D receptor activators (VDRAs) are the primary medication for SHPT, such as calcitriol and alfalcalcidol. It has been shown that the long-term use of VDRAs may enhance the intestinal absorption of Ca and phosphorus and tubular reabsorption, leading to an increase in serum levels of Ca and phosphorus and risk of vascular calcification[6]. Since paricalcitol, a selective VDRA, is available on the market, several studies have confirmed that paricalcitol can selectively act on the parathyroid glands, inhibiting parathormone secretion. Paricalcitol mildly affects intestinal Ca and phosphorus absorption. Paricalcitol is also effective for SHPT patients resistant to nonselective VDRAs[7-9]. This study investigated the outcomes, safety and potential benefits of paricalcitol injection in hemodialysis patients with SHPT.

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± 4.33%; the standard-reaching rate of iPTH levels was 66.67% (24/36); and ALP levels decreased significantly compared with the baseline (113.72 ± 41.73 IU/L vs 133.45 ± 56.86 IU/L) (t = 2.798, P < 0.05). There were no significant differences in the serum levels of calcium, Hb, Cre and CRP compared with the baseline (P > 0.05). After 24 wk of treatment, serum P levels decreased compared with the baseline (1.91 ± 0.40 mmol/L vs 2.16 ± 0.66 mmol/L) (t = 2.830, P < 0.05). Ca × P product decreased significantly compared with the baseline (56.38 ± 13.22 mg2/dL2 vs 63.97 ± 20.30 mg2/dL2) (t = 2.717, P < 0.05). No serious adverse events occurred.

CONCLUSION

Paricalcitol was a safe and effective treatment for hemodialysis patients with SHPT. It decreased serum levels of iPTH, ALP and P and maintained stability of serum Ca levels.

Key Words: Paricalcitol; Hemodialysis; Secondary hyperparathyroidism; Drug efficacy; Drug safety

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Core Tip: In this study, 40 patients with chronic renal failure were treated with paricalcitol for 24 wk. It was found that paricalcitol can significantly reduce intact parathyroid hormone, alkaline phosphatase and serum phosphate levels, and maintain a relatively stable serum calcium level. Therefore, paricalcitol is effective and safe in the treatment of hemodialysis patients with secondary hyperparathyroidism.

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MATERIALS AND METHODS

Patients
We recruited 40 patients with chronic renal failure complicated by SHPT and receiving hemodialysis at our hospital between March and December 2019. There were 23 men and 17 women, with an average age of 49.10 ± 12.86 years. Inclusion criteria: (1) Age > 18 years; (2) Regular hemodialysis for ≥ 3 mo, three times per week, and hemodialysis continued during medication; (3) iPTH levels > 300 pg/mL; (4) Life expectancy > 6 mo; and (5) Good adherence to treatment. Exclusion criteria: (1) History of paricalcitol treatment before enrollment; (2) History of treatment with other active forms of vitamin D and its analogs (including calcitriol, alfacalcidol, doxercalciferol, fluoro-calcidol and maxacalcitol) and calcimimetics (cinacalcet); (3) Hypercalcemia or Ca × P product > 65 mg²/dL²; (4) Allergic to the investigational drug; (5) Serious heart disease, liver injury, active inflammatory disease, or malignancy; (6) Ready for kidney transplantation or parathyroidectomy; (7) Pregnant or lactating women; (8) Unwilling to take effective contraceptive measures; and (9) Participating in other studies in the same period. The present study was approved by the Ethics Review Committee of the hospital. All patients were enrolled on a voluntary basis and gave signed informed consent.

Methods
The investigational drug was paricalcitol injection (Zemplar®; Jiangsu Hengrui Medicine Co. Ltd., strength 1 mL: 5 μg) and stored at 30 °C. The starting dose of the paricalcitol injection was 0.06–0.08 μg/kg. Within 30 min before the end of the hemodialysis, paricalcitol injection was administered via the hemodialysis venous catheter (venous port) three times per week. The dose was adjusted according to the serum levels of iPTH, Ca and P, which were detected once every 2-4 wk. The specific dose adjustment criteria are shown in Table 1. If hypercalcemia occurred or the corrected Ca × P product was continuously above 65 mg²/dL², the dose should be reduced or discontinued until the above parameters returned to normal. After that, paricalcitol administration was resumed starting at a lower dose. The treatment lasted for 24 wk. Follow-up was conducted at the baseline and at weeks 4, 12 and 24. The patients were followed up on all designated days, with a window period of ± 4 d.

Observation indicators
Primary outcome indicator: Percentage of patients with > 30% decrease in iPTH levels at week 24 compared with the baseline. Secondary outcome indicators: Decrease in iPTH levels at week 24; standard-reaching rate of iPTH (percentage of patients with iPTH down to 130–585 pg/mL)[10]; changes in serum levels of Ca, P, Ca × P, alkaline phosphatase (ALP), creatinine (Cre), hemoglobin (Hb), and C-reactive protein (CRP); adverse events (AEs). The occurrence of any AEs during treatment was closely observed.

Statistical analysis
SPSS 19.0 software was used for data analysis. Measurement data (obeying normal distribution) were expressed as mean ± SD. Comparisons between the measurements at the baseline and at each time point of follow-up were conducted using the paired t test. Counts were described by cases (percentages) and subjected to Pearson’s χ² test. P < 0.05 indicated a significant difference.

RESULTS

Demographics and baseline features of the enrolled patients
A total of 40 patients were recruited, including 23 men and 17 women. Thirty-six patients finished all treatments planned, and four were lost to follow-up (Table 2).

Changes in iPTH levels
The baseline iPTH level was 888.84 ± 376.88 pg/mL. After 24 wk of treatment, it decreased to 598.88 ± 381.29 pg/mL, and the average decrease was 32%, indicating a significant difference (t = 4.589, P < 0.05) (Figure 1A). After 24 wk of treatment, 21/36 patients (58.33%) had a > 30% decrease in iPTH levels. The standard-reaching rate of iPTH was 24/36 (66.67%).
Table 1 Dose adjustment criteria for paricalcitol injection

| iPTH level compared with baseline | Dose adjustment of paricalcitol |
|----------------------------------|---------------------------------|
| Not reaching the standard, unchanged or increased; or decreased by < 30% | Increase dose by 2-4 μg |
| When 150-300 pg/mL or iPTH down by ≥ 30% | Maintain original dose |
| When iPTH < 150 pg/mL or serum Ca > 11.0 mg/dL or Ca × P product > 70 mg²/dL² | Decrease dose by 2-4 μg |

Ca: Calcium; iPTH: Intact parathyroid hormone; P: Phosphate.

Table 2 Demographics and baseline features of 40 patients

| Variable                               | Patients     |
|----------------------------------------|--------------|
| Age in yr                              | 49.10 ± 12.86|
| Sex                                    |              |
| Male                                   | 23 (57.5%)   |
| Female                                 | 17 (42.5%)   |
| Duration in mo of dialysis             | 55.20 ± 29.32|
| Weekly dose of paricalcitol in g/wk    | 12.38 ± 2.77 |
| iPTH in pg/mL                          | 888.84 ± 376.88|
| ALP in IU/L                            | 133.45 ± 56.86|
| Blood P in mmol/L                      | 2.16 ± 0.66  |
| Blood Ca in mmol/L                     | 2.38 ± 0.16  |
| Ca × P product in mg²/dL²              | 63.97 ± 20.30|
| Hb in g/L                              | 114.82 ± 20.45|
| Cre in mol/L                           | 807.43 ± 254.64|
| CRP in mg/L                            | 8.60 ± 16.76 |

Ca: Calcium; Cre: Creatinine; CRP: C-reactive protein; Hb: Hemoglobin; iPTH: Intact parathyroid hormone; P: Phosphate.

Changes in ALP levels
After 24 wk of treatment, ALP levels decreased significantly compared with the baseline (113.72 ± 41.73 IU/L vs 133.45 ± 56.86 IU/L) (t = 2.401, P < 0.05) (Figure 1B).

Changes in serum Ca and P levels and Ca × P product
During treatment, serum Ca levels remained stable. At week 12, the serum Ca level increased to 2.45 ± 0.19 mmol/L, but was still within the normal range (2.1–2.5 mmol/L). At week 24, the serum Ca level (2.39 ± 0.20 mmol/L) was not significantly different from that at the baseline (2.38 ± 0.16 mmol/L) (t = 0.242, P > 0.05). At week 24, the serum P level (1.91 ± 0.40 mmol/L) was not significantly different from that at the baseline (2.16 ± 0.66 mmol/L) (t = 2.830, P < 0.05). At week 24, Ca × P product (56.38 ± 13.22 mg²/dL) was not significantly different from that at the baseline (63.97 ± 20.30 mg²/dL) (t = 2.717, P < 0.05) (Figure 1C and D).

Changes in Hb, Cre and CRP levels
At each time point of follow-up, there were no significant differences in Hb and CRP levels compared with the baseline (P > 0.05). At weeks 4 and 24, the Cre level was not significantly different from that at the baseline (P > 0.05). However, there was a significant difference in Cre levels at week 12 compared with the baseline (P < 0.05) (Table 3).

AEs
During paricalcitol treatment, the Hb level was decreased in two cases (5.56%), and a transient elevation of serum P was found in one case (2.78%). After dose adjustment,
Table 3 Changes in hemoglobin, creatinine and C-reactive protein levels over time

| Time     | Hb in g/L   | t     | P value | Cre in mol/L  | t     | P value | CRP in mg/L | t     | P value |
|----------|-------------|-------|---------|---------------|-------|---------|-------------|-------|---------|
| Baseline | 114.82 ± 20.45 |       |         | 807.43 ± 254.64 |       |         | 8.60 ± 16.76 |       |         |
| Week 4   | 109.69 ± 19.78 | 1.530 | 0.131   | 749.67 ± 398.06 | 1.062 | 0.292   | 7.13 ± 10.71 | 0.642 | 0.523   |
| Week 12  | 111.47 ± 21.11 | 0.967 | 0.337   | 586.40 ± 358.51 | 4.326 | 0.000   | 7.72 ± 4.98 | 0.486 | 0.629   |
| Week 24  | 116.21 ± 23.50 | 0.380 | 0.705   | 803.27 ± 192.31 | 0.112 | 0.911   | 8.23 ± 14.82 | 0.206 | 0.838   |

Hb: Hemoglobin; Cre: Creatinine; CRP: C-reactive protein.

Figure 1 Changes in the biochemical index level over time. *P < 0.05, **P < 0.01 vs baseline. A: Intact parathyroid hormone level; B: Alkaline phosphatase level; C: Serum calcium and phosphate levels; D: Serum calcium × phosphate product. iPTH: Intact parathyroid hormone; ALP: Alkaline phosphatase; Ca: Calcium; P: Phosphate.

all of these cases returned to normal.

**DISCUSSION**

The hemodialysis patients enrolled in this study also had SHPT and were treated with paricalcitol at a median starting dose of 0.06–0.08 µg/kg. iPTH levels decreased from 888.84 ± 376.88 to 598.88 ± 381.29 pg/mL after treatment. Twenty-one of 36 (58.33%) patients had a > 30% decrease in iPTH. The standard-reaching rate of iPTH (percentage of patients with iPTH levels down to 130–585 pg/mL) was 66.67% (24/36 patients). Koc et al.[11] reported that after 6 mo of treatment, iPTH levels decreased from 518.9 to 264.0 pg/mL. There were 63.0% of patients with a > 30% decrease in iPTH levels. Olaizola et al.[12] reported that after 6 mo of paricalcitol treatment in hemodialysis patients with SHPT, 17 of 19 (89.47%) patients had a > 30% decrease in iPTH levels. Twelve of 19 (63.16%) patients had iPTH levels down to 150–300 pg/mL. The effect of paricalcitol on iPTH levels was most significant in the first 4 wk. After that, iPTH levels changed less noticeably. This confirmed the efficacy of paricalcitol in inhibiting iPTH, which was coupled to progressive weakening of its inhibitory effect on iPTH over time. Therefore, excessive inhibition of iPTH caused by paricalcitol was
prevented, which means that paricalcitol is safer than calcitriol.

Active vitamin D can stimulate intestinal Ca and P absorption by activating the intestinal VDRs, thereby contributing to hypercalcemia. Nonselective VDRAs, such as alfalcacidol and calcitriol, have no significantly different affinity for VDRs in intestinal mucosal cells and parathyroid cells. Paricalcitol is a highly selective VDRA with a higher affinity for VDRs in parathyroid cells than for those in intestinal mucosal cells. As intestinal Ca transport is weakened, the incidence of hypercalcemia decreases. Serum Ca and P levels in patients were detected in the present study. In the first 12 wk of paricalcitol treatment, there was a transient mild increase in average serum Ca levels. This has been reported in other studies[13] and may be considered a response in the adaptive period. Such a finding might have also been attributed to the diet of individual patients at the initial stage. Serum Ca levels stabilized after introduction of a Ca-restricted diet and the dose of paricalcitol was reduced. The Ca × P product decreased throughout the treatment period. After 24 wk of treatment, there were significant differences in serum P levels and Ca × P product compared with the baseline. These results indicated that paricalcitol reduced the risk of hyperphosphatemia. Li et al[14] reported no significant differences in the serum Ca and P levels and Ca × P product in hemodialysis patients with SHPT before and after paricalcitol treatment. Their findings disagree with ours, probably due to the differences in treatment duration.

The number and activity of osteoclasts usually increase in SHPT patients due to an excessively high iPTH level. Besides, bone transport and destruction are promoted, resulting in ALP elevation. In the present study, the ALP level decreased significantly after 24 wk of paricalcitol treatment compared with the baseline among the hemodialysis patients with SHPT, indicating that paricalcitol potentially corrects the SHPT-induced changes in bone histomorphology, which might be related to its inhibitory effect on bone metabolism. Some researchers believe that elevation of ALP is associated with a higher incidence of cardiovascular diseases in patients with chronic kidney disease. It is also one of the major reasons for the high mortality of hemodialysis patients[15]. A decrease in ALP levels indicates that hemodialysis patients with SHPT may benefit from paricalcitol treatment.

The microinflammatory state in hemodialysis patients may be closely related to such complications as anemia and cardiovascular disease in hemodialysis patients. Some studies have shown that paricalcitol is not only effective for SHPT complicating hemodialysis but also benefits patients by regulating bone metabolism, participating in anti-inflammatory and antioxidative stress activities, and improving anemia[16]. Cre is the most common indicator of kidney function, and Hb is an important indicator of anemia. CRP not only indicates the inflammatory state but also participates in cardiovascular injury. It has been found that during paricalcitol treatment, Hb and CRP levels at different time points are not significantly different from those at the baseline. In our study, at week 12, the Cre level was markedly reduced compared with the baseline. Later, the Cre level began to increase. These changes suggested that paricalcitol had no evident effect on kidney function indicators and inflammatory factors while reducing iPTH levels. The fact that the Cre level first decreased and then increased might be explained by the abnormal kidney function in hemodialysis patients. Paricalcitol may reduce the release of inflammatory factors such as CRP[17]. It is reported that paricalcitol has no significant impact on the inflammatory factors in hemodialysis patients with SHPT[18], which agrees with our findings.

**CONCLUSION**

In conclusion, paricalcitol significantly decreased serum levels of iPTH, ALP and P in hemodialysis patients with SHPT. In contrast, serum Ca, Hb, Cre and CRP levels remained stable. However, our study had a small sample size without a control group. In future, multicenter studies with a larger sample size will be performed to provide evidence for the clinical use of paricalcitol.

**ARTICLE HIGHLIGHTS**

*Research background*

Secondary hyperparathyroidism (SHPT) is a common complication in patients with end-stage renal disease. SHPT is a component of chronic kidney disease-mineral and
bone disorder, which is featured by increased fibroblast growth factor 23 and serum parathyroid hormone concentrations, decreased 1,25(OH)2 vitamin D concentrations and abnormal serum phosphate and calcium concentrations.

**Research motivation**
The long-term use of vitamin D receptor activators (VDRAs) may enhance the intestinal absorption of calcium and phosphorus and tubular reabsorption, leading to an increase in serum levels of calcium and phosphorus and risk of vascular calcification. But Paricalcitol mildly affects intestinal calcium and phosphorus absorption. Paricalcitol may be better than VDRAs in this aspect.

**Research objectives**
This study aimed to discuss the outcome, safety and other potential benefits of paricalcitol injection in hemodialysis patients with SHPT.

**Research methods**
Total 40 patients who received hemodialysis for chronic renal failure with SHPT received paricalcitol injection for 24 wk, three times per week. The primary outcome indicator was the percentage of patients with a > 30% decrease in intact parathyroid hormone (iPTH) levels at week 24 compared with the baseline.

**Research results**
After 24 wk of treatment, iPTH levels decreased significantly. More than 30% decrease of iPTH was found in 21 of 36 (58.33%) patients. The average decrease in iPTH levels was 32.16 ± 4.33%; the standard-reaching rate of iPTH levels was 66.67% (24/36); and alkaline phosphatase levels decreased significantly compared with the baseline. There were no significant differences in the serum levels of calcium, hemoglobin, creatinine and C-reactive protein compared with the baseline.

**Research conclusions**
This study suggested that the paricalcitol was a safe and effective treatment for hemodialysis patients with SHPT.

**Research perspectives**
Multicenter studies with a larger sample size will be performed to provide evidence for the clinical use of paricalcitol.

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