

# World Journal of *Clinical Cases*

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## Contents

Thrice Monthly Volume 9 Number 33 November 26, 2021

### REVIEW

- 10052** Effects of alcohol consumption on viral hepatitis B and C  
*Xu HQ, Wang CG, Zhou Q, Gao YH*

### MINIREVIEWS

- 10064** Effects of anti-diabetic drugs on sarcopenia: Best treatment options for elderly patients with type 2 diabetes mellitus and sarcopenia  
*Ma XY, Chen FQ*

### ORIGINAL ARTICLE

#### Retrospective Cohort Study

- 10075** Utility of cooling patches to prevent hand-foot syndrome caused by pegylated liposomal doxorubicin in breast cancer patients  
*Zheng YF, Fu X, Wang XX, Sun XJ, He XD*

#### Retrospective Study

- 10088** Clinicopathological features of small T1 colorectal cancers  
*Takashina Y, Kudo SE, Ichimasa K, Kouyama Y, Mochizuki K, Akimoto Y, Maeda Y, Mori Y, Misawa M, Ogata N, Kudo T, Hisayuki T, Hayashi T, Wakamura K, Sawada N, Baba T, Ishida F, Yokoyama K, Daita M, Nemoto T, Miyachi H*
- 10098** Comparison of dental pulp periodontal therapy and conventional simple periodontal therapy as treatment modalities for severe periodontitis  
*Li L, Chen HJ, Lian Y, Wang T*
- 10106** Tripartite intensive intervention for prevention of rebleeding in elderly patients with hypertensive cerebral hemorrhage  
*Li CX, Li L, Zhang JF, Zhang QH, Jin XH, Cai GJ*
- 10116** Clinical and electroencephalogram characteristics and treatment outcomes in children with benign epilepsy and centrotemporal spikes  
*Chen RH, Li BF, Wen JH, Zhong CL, Ji MM*
- 10126** Endoscopic ultrasonography diagnosis of gastric glomus tumors  
*Bai B, Mao CS, Li Z, Kuang SL*
- 10134** Learning curves of robot-assisted pedicle screw fixations based on the cumulative sum test  
*Yu J, Zhang Q, Fan MX, Han XG, Liu B, Tian W*
- 10143** Value of GRACE and SYNTAX scores for predicting the prognosis of patients with non-ST elevation acute coronary syndrome  
*Wang XF, Zhao M, Liu F, Sun GR*

- 10151** Effectiveness of enhanced recovery after surgery in the perioperative management of patients with bone surgery in China

*Zhao LY, Liu XT, Zhao ZL, Gu R, Ni XM, Deng R, Li XY, Gao MJ, Zhu WN*

### Clinical Trials Study

- 10161** Association between plasma dipeptidyl peptidase-4 levels and cognitive function in perinatal pregnant women with gestational diabetes mellitus

*Sana SRGL, Li EY, Deng XJ, Guo L*

- 10172** Paricalcitol in hemodialysis patients with secondary hyperparathyroidism and its potential benefits

*Chen X, Zhao F, Pan WJ, Di JM, Xie WN, Yuan L, Liu Z*

### Observational Study

- 10180** Did the severe acute respiratory syndrome-coronavirus 2 pandemic cause an endemic *Clostridium difficile* infection?

*Cojocariu C, Girleanu I, Trifan A, Olteanu A, Muzica CM, Huiban L, Chiriac S, Singeap AM, Cuciureanu T, Sfarti C, Stanciu C*

- 10189** Effect of nursing intervention based on Maslow's hierarchy of needs in patients with coronary heart disease interventional surgery

*Xu JX, Wu LX, Jiang W, Fan GH*

- 10198** Impacts of statin and metformin on neuropathy in patients with type 2 diabetes mellitus: Korean Health Insurance data

*Min HK, Kim SH, Choi JH, Choi K, Kim HR, Lee SH*

### META-ANALYSIS

- 10208** Is endoscopic retrograde appendicitis therapy a better modality for acute uncomplicated appendicitis? A systematic review and meta-analysis

*Wang Y, Sun CY, Liu J, Chen Y, Bhan C, Tuason JPW, Misra S, Huang YT, Ma SD, Cheng XY, Zhou Q, Gu WC, Wu DD, Chen X*

- 10222** Prognostic value of ground glass opacity on computed tomography in pathological stage I pulmonary adenocarcinoma: A meta-analysis

*Pan XL, Liao ZL, Yao H, Yan WJ, Wen DY, Wang Y, Li ZL*

### CASE REPORT

- 10233** Atrial fibrillation and concomitant left subclavian, axillary and brachial artery embolism after fiberoptic bronchoscopy: A case report

*Yang CL, Zhou R, Jin ZX, Chen M, Zi BL, Li P, Zhou KH*

- 10238** Streptococcal toxic shock syndrome after hemorrhoidectomy: A case report

*Lee CY, Lee YJ, Chen CC, Kuo LJ*

- 10244** Subsequent placenta accreta after previous mifepristone-induced abortion: A case report

*Zhao P, Zhao Y, He J, Bai XX, Chen J*

- 10249** Autosomal dominant tubulointerstitial kidney disease with a novel heterozygous missense mutation in the uromodulin gene: A case report  
*Zhang LL, Lin JR, Zhu TT, Liu Q, Zhang DM, Gan LW, Li Y, Ou ST*
- 10257** Novel KDM6A mutation in a Chinese infant with Kabuki syndrome: A case report  
*Guo HX, Li BW, Hu M, Si SY, Feng K*
- 10265** Pancreatic cancer with synchronous liver and colon metastases: A case report  
*Dong YM, Sun HN, Sun DC, Deng MH, Peng YG, Zhu YY*
- 10273** Veno-venous-extracorporeal membrane oxygenation treatment for severe capillary leakage syndrome: A case report  
*Nong WX, Lv QJ, Lu YS*
- 10279** Anticoagulant treatment for pulmonary embolism in patient with cerebral hemorrhage secondary to mechanical thrombectomy: A case report  
*Chen XT, Zhang Q, Zhou CQ, Han YF, Cao QQ*
- 10286** Complete restoration of congenital conductive hearing loss by staged surgery: A case report  
*Yoo JS, Lee CM, Yang YN, Lee EJ*
- 10293** Blastic plasmacytoid dendritic cell neoplasm with skin and bone marrow involvement: Report of three cases  
*Guo JH, Zhang HW, Wang L, Bai W, Wang JF*
- 10300** Extracranial multiorgan metastasis from primary glioblastoma: A case report  
*Luan XZ, Wang HR, Xiang W, Li SJ, He H, Chen LG, Wang JM, Zhou J*
- 10308** Transverse myelitis after infection with varicella zoster virus in patient with normal immunity: A case report  
*Yun D, Cho SY, Ju W, Seo EH*
- 10315** Duodenal ulcer caused by coil wiggle after digital subtraction angiography-guided embolization: A case report  
*Xu S, Yang SX, Xue ZX, Xu CL, Cai ZZ, Xu CZ*
- 10323** Crab lice infestation in unilateral eyelashes and adjacent eyelids: A case report  
*Tang W, Li QQ*
- 10328** Local random flaps for cervical circumferential defect or tracheoesophageal fistula reconstruction after failed gastric pull-up: Two case reports  
*Zhang Y, Liu Y, Sun Y, Xu M, Wang XL*
- 10337** Incurable and refractory spinal cystic echinococcosis: A case report  
*Zhang T, Ma LH, Liu H, Li SK*
- 10345** Individualized treatment of breast cancer with chronic renal failure: A case report and review of literature  
*Cai JH, Zheng JH, Lin XQ, Lin WX, Zou J, Chen YK, Li ZY, Chen YX*

- 10355** Persistent fibrinogen deficiency after snake bite: A case report  
*Xu MH, Li J, Han L, Chen C*
- 10362** Successful prolonged cardiopulmonary resuscitation after intraoperative cardiac arrest due to povidone-iodine allergy: A case report  
*Xiang BB, Yao YT, Jiao SL*
- 10369** Clinical algorithm for preventing missed diagnoses of occult cervical spine instability after acute trauma: A case report  
*Zhu C, Yang HL, Im GH, Liu LM, Zhou CG, Song YM*
- 10374** Carbon ion radiotherapy for synchronous choroidal melanoma and lung cancer: A case report  
*Zhang YS, Hu TC, Ye YC, Han JH, Li XJ, Zhang YH, Chen WZ, Chai HY, Pan X, Wang X, Yang YL*
- 10382** Heart failure as an adverse effect of infliximab for Crohn's disease: A case report and review of the literature  
*Grillo TG, Almeida LR, Beraldo RF, Marcondes MB, Queiróz DAR, da Silva DL, Quera R, Baima JP, Saad-Hossne R, Sasaki LY*

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## 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 ( $598.88 \pm 381.29$  pg/mL vs  $888.84 \pm 376.88$  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



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$\pm 4.33\%$ ; the standard-reaching rate of iPTH levels was 66.67% (24/36); and ALP levels decreased significantly compared with the baseline ( $113.72 \pm 41.73$  IU/L *vs*  $133.45 \pm 56.86$  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 ( $1.91 \pm 0.40$  mmol/L *vs*  $2.16 \pm 0.66$  mmol/L) ( $t = 2.830$ ,  $P < 0.05$ ).  $\text{Ca} \times \text{P}$  product decreased significantly compared with the baseline ( $56.38 \pm 13.22$   $\text{mg}^2/\text{dL}^2$  *vs*  $63.97 \pm 20.30$   $\text{mg}^2/\text{dL}^2$ ) ( $t = 2.717$ ,  $P < 0.05$ ). 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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## INTRODUCTION

Secondary hyperparathyroidism (SHPT) is a common complication in patients with end-stage renal disease. Hyperphosphatemia, hypocalcemia and  $1,25(\text{OH})_2\text{D}$  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  $1,25(\text{OH})_2$  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 alfacalcidol. 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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## 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  $49.10 \pm 12.86$  years. Inclusion criteria: (1) Age > 18 years; (2) Regular hemodialysis for  $\geq 3$  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  $\text{Ca} \times \text{P}$  product >  $65 \text{ mg}^2/\text{dL}^2$ ; (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  $\text{Ca} \times \text{P}$  product was continuously above  $65 \text{ mg}^2/\text{dL}^2$ , 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  $\pm 4$  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,  $\text{Ca} \times \text{P}$ , 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  $\pm$  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  $\chi^2$  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  $888.84 \pm 376.88$  pg/mL. After 24 wk of treatment, it decreased to  $598.88 \pm 381.29$  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/mL or Ca × P product > 70 mg <sup>2</sup> /dL <sup>2</sup>	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 mg <sup>2</sup> /dL <sup>2</sup>	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 mg<sup>2</sup>/dL<sup>2</sup>) was not significantly different from that at the baseline (63.97 ± 20.30 mg<sup>2</sup>/dL<sup>2</sup>) ( $t = 2.717$ ,  $P < 0.05$ ) (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).

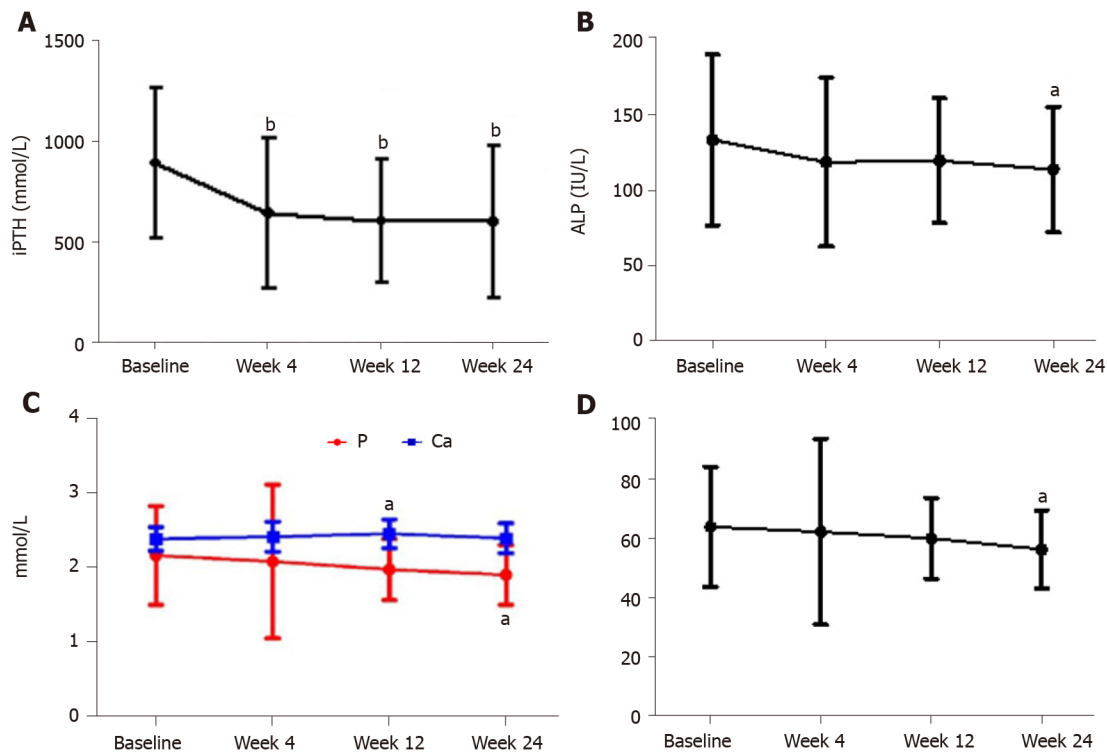
### AEs

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	<i>t</i>	<i>P</i> value	Cre in mol/L	<i>t</i>	<i>P</i> value	CRP in mg/L	<i>t</i>	<i>P</i> 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. <sup>a</sup>*P* < 0.05, <sup>b</sup>*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 alfacalcidol 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  $\times$  P product decreased throughout the treatment period. After 24 wk of treatment, there were significant differences in serum P levels and Ca  $\times$  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  $\times$  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)<sub>2</sub> 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  $32.16 \pm 4.33\%$ ; 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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