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Original Research

Effect of calcitriol combined with sevelamer carbonate on serum parathyroid hormone in patients with chronic renal failure

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Abstract: This study aimed to observe and analyze the effect of calcitriol combined with sevelamer carbonate on serum parathyroid hormone in patients with chronic renal failure. This study included 180 patients who had been treated for chronic renal failure in our hospital were enrolled as research objects. The patients were randomly divided into two groups: a research group and a control group, each containing 90 cases. The research group was treated with calcitriol combined with sevelamer carbonate, and the control group was treated with calcitriol alone. The therapeutic effects of the two groups were observed and analyzed by SPSS 21. Comparing the levels of blood indexes (Ca, Cr, P, ALP, iPTH, TC, TG, LDL-C, HDL-C) of the two groups showed no significant difference between the two groups, P <0.05. Our results have the effect of different treatment regimens, the improvement effect of various blood indicators in the research group was significantly better than the control group, p<0.05. We concluded that the combined therapy of calcitriol and sevelamer carbonate in chronic renal failure patients can significantly improve the therapeutic effect, and at the same time actively improve the serum parathyroid hormone level, which is a treatment model that can be popularized and applied.

Key words: Calcitriol; Sevelamer carbonate; Chronic renal failure; Serum parathyroid hormone.

Introduction

Chronic renal failure (CRF) is a clinical syndrome characterized by chronic progressive renal parenchymal damage caused by various causes, obvious renal atrophy, inability to maintain basic functions, metabolic product retention, imbalance of water, electrolyte, acid and base balance, and systemic involvement (1,2). The main causes of renal failure in patients include primary glomerulonephritis, chronic pyelonephritis, hypertensive arteriolosclerosis, diabetic nephropathy, secondary glomerulonephritis, tubular interstitial lesions, hereditary kidney diseases, and long-term use of antipyretic analgesics and exposure to heavy metals (3).

Chronic renal failure in patients presents with uremia, uremia is not an independent disease, but it is a symptom of kidney damage and progressive deterioration. When renal diseases develop to the end stage and renal failure, the renal function is up to 10% ~ 15% of normal renal function, which caused a series of clinical symptoms (like uremia, etc. (4–6).

Secondary hyperparathyroidism (SHPT) (Figure 1) is one of the serious complications of chronic renal failure (Figure 2), which can involve multiple systems such as nerve, circulation, hematopoietic and immune systems, and seriously affect the quality of life and prognosis of patients. The treatment principle is to reduce blood phosphorus (P), adjust the reasonable application of blood calcium (Ca), 1, 25-dihydroxyvitamin D_3 [1, 25(OH) 2 D_3], and surgical treatment (7–9).

This study observed and analyzed the effect of calci-

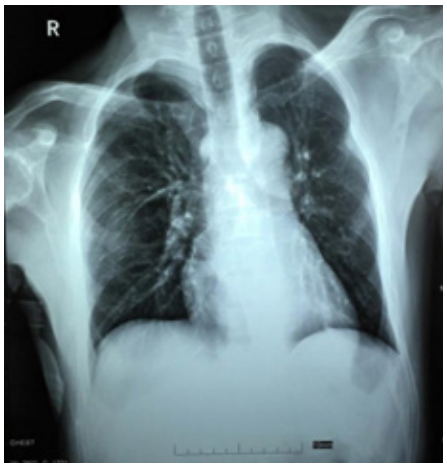

Figure 1. AP supine chest X-ray in Secondary hyperparathyroidism, showing calcification zones in both sides of lung.

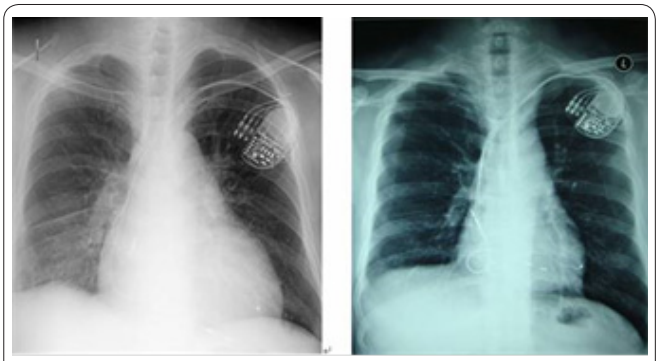

Figure 2. Chronic renal failure AP supine chest X-ray showing right basal opacity.

triol combined with sevelamer carbonate on serum parathyroid hormone levels in patients with chronic renal failure.

Materials and Methods

General data

In this study, 180 patients who had been diagnosed with chronic renal failure from January 2016 to January 2018 were enrolled as research objects.

Inclusion and exclusion criteria

All selected patients met the standards of Harrison's internal medicine 7th edition, and their serum iPTH concentration was between 33-55pmol/L. The examination image selected patients were familiar with the example patient's graph shown in Figure 3. All patients had the right to know everything about this study and signed the formal informed consent. Patients with primary hyperparathyroidism, abnormal liver function, myeloma nephropathy and idiopathic hypercalcemia were excluded from selected patients.

The patients were randomly divided into a research group and a control group, each containing 90 patients. There were 50 males and 40 females in the research group, with an average age of (65.42±0.19) years old. The primary diseases involved nephrotic syndrome (22 cases), chronic glomerulonephritis (30 cases), hypertensive renal damage (18 cases), and diabetic nephropathy (20 cases). There were 48 males and 42 females in the control group, with an average age of (63.85±0.22) years old. The primary diseases involved nephrotic syndrome (25 cases), chronic glomerulonephritis (28 cases), hypertensive renal damage (17 cases), and diabetic nephropathy (20 cases). There was no significant difference in general data between two groups before applying different treatment modes, $p>0.05$. The study was conducted with the approval of the hospital ethics association.

Patients in both the research group and the control group were treated with bicarbonate dialysate. The Ca ion concentration in the dialysate was 1.5mmol/L, and the dialysis duration was 1 to 4 hours each time. In the process of dialysis treatment, patients should be provided with a scientific and reasonable diet plan, and be instructed to eat a low-salt, low-fat, low-phosphorus and high-quality protein diet. Meanwhile, corresponding treatments for blood pressure, hypoglycemic and calcium supplementation should be carried out, and symptomatic treatment plans for improving acidosis should be launched.

On the basis of the above routine treatment, patients in the control group were treated with calcitriol, that is, instructing patients to take oral administration of calcitriol in fasting state in the morning (Shanghai Roche Pharmaceutical Co., Ltd., SFDA approval number: J20050021), with a dose of 0.5 μg each time, once a day. In the research group, patients were treated with calcitriol combined with sevelamer carbonate, in which the treatment of calcitriol was the same as that of the control group. The oral dose of sevelamer carbonate (Genzyme Generals, USA) was 800mg each time, and the drug was administered three times a day. Patients in both groups were treated for six consecutive months.

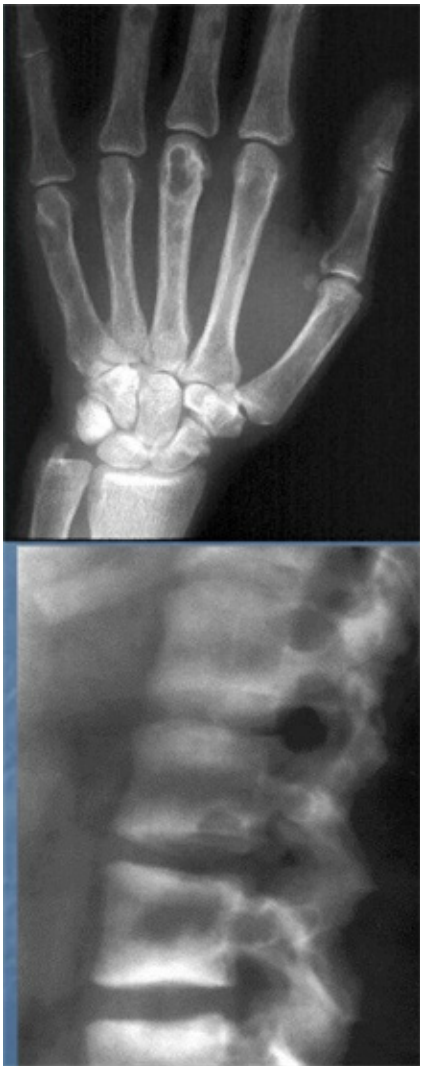

Figure 3. Symptoms of renal osteodystrophy seen as smooth hypodense lesions in bones.

Calcitriol is mainly used in chronic renal failure patients, especially to treat the renal osteodystrophy Postoperative caused by parathyroid dysfunction in hemodialysis patients. This drug also plays a role in the transport of phosphorus in the intestines, kidneys and bones, so the amount of phosphorus binding agent must be adjusted according to the blood phosphorus concentration (normal blood phosphorus concentration: 2-5mg/100mL or 0.6-1.6mg molecule /L). Sevelamer carbonate is a metal or calcium-free polymer that can't be absorbed by the GI tract. It carries multiple amine groups, connected by a single carbon atom to the polymer skeleton. These amine groups are partially protonated in the intestine and bind to phosphoric acid molecules by ion exchange and hydrogen bonding. By binding to phosphorus in the gastrointestinal tract, Sevelamer carbonate reduces the concentration of phosphorus in the blood and its absorption. Its molecular formula is (C3H7N·C3H5ClO)x·xCH2O3, and its molecular weight is 211.6436. The main indications are the control of serum inorganic phosphorus and calcium content in patients with chronic renal failure (7).

Observational indexes

The levels of phosphorus (P), iPTH, alkaline phosphatase (ALP), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-

C), cholesterol (TC), triglyceride (TG), serum creatinine (Cr) and other indicators in the two groups were observed and compared.

Statistical method

Statistical analysis software SPSS21.0 was used to process data. The measurement data were expressed by mean ± average ($\bar{x}$ ± s), with a t-test conducted for intergroup comparison. Enumeration data were expressed by natural (n) and percentage (%), with X^2 used for intergroup comparison. The intergroup difference is of statistical value when $P < 0.05$.

Results

Comparison of levels of ALP, TC, TG, LDL-C and HDL-C before and after treatment in the two groups

As shown in Table 1, there was no significant difference in levels of ALP, TC, TG, LDL-C and HDL-C between the two groups before treatment, $p>0.05$. After the implementation of different treatment modes, the improvement effect of the research group was more ideal compared with the control group, $p<0.05$.

Comparison of iPTH, Cr, P and Ca levels before and after treatment between the two groups

As shown in Table 2, there was no significant difference in iPTH, Cr, P and Ca levels between the two groups before treatment, $P >0.05$. After treatment, the improvement effect of various indicators in the research group was significantly better than that in the control group, $p<0.05$.

Discussion

Chronic renal failure (CRF) is a kidney damaging disease caused by many factors, which can be accompanied by multi-system damage. It is one of the most important and life-threatening diseases and its prevalence is increasing in developed and developing countries. Diabetes and hypertension are the most common causes of this disease. In recent years, the prevalence of chronic kidney disease has also increased (1). Hemodialysis is an important method for the treatment of this disease, but secondary hyperparathyroidism is one of the serious complications of long-term dialysis in patients with chronic renal failure, which can lead to Ca and P metabolic disorders and increase the disability rate or mortality rate of patients (8–10). Chronic kidney disease has many side effects, and hyperphosphatemia is one of the most common side effects, due to decreased glomerular filtration rate (GFR). the history of hyperphosphatemia alone or in combination with hypercalcemia is associated with increased mortality in dialysis patients. In addition, hyperphosphatemia causes significant morbidity for chronic renal failure patients with Ca and P metabolic disorders, the phenomenon of increasing iPTH concentration will generally occur, leading to injury of target organs and even death (10).

The results of our study showed that patients treated with calcitriol showed good improvement in iPTH and P levels, indicating the therapeutic effect of calcitriol.

The results of various studies such as the study by Massey et al., (11) Llach et al., (12) As well as Forero et al., (13) have shown that Calcitriol is an important metabolic active product of vitamin D3, which does not need to be activated by liver and kidney hydroxylation, and has a fast onset speed. It can promote the absorption of calcium in the intestinal tract, effectively regulate bone calcification, reduce hyperplasia of parathyroid gland cells, and improve the clinical symptoms of patients which was consistent with the results of our study.

The results of our study showed that calcitriol can make P level higher than normal during Ca level adjustment in patients, so phosphate-lowering therapy should be combined which was consistent with the results of Kim et al., (14) Baker et al., (15) and Teng et al (16).

Sevelamer carbonate belongs to the non-aluminum and non-calcium phosphate binder. The active ingredient is polyacrylamine hydrochloride, which has strong hydrophilicity and can bind with phosphate through ion exchange and hydrogen bonding, effectively reducing the level of blood phosphorus. In addition, sevelamer carbonate has a larger particle diameter, which is not easy to be absorbed by the gastrointestinal tract and excreted with feces, so it will not produce serious systemic side effects (17–19). The results of this study showed that there were no significant differences in the levels of various blood indexes (Ca, Cr, P, ALP, iPTH, TC, TG, LDL-C, HDL-C) between the two groups, $P <0.05$. After different treatment regimens, the improvement effect of blood indicators in the research group had significant advantages over the control group, which is consistent with the relevant research results like Di Iorio et al.,

Table 1. Comparison of levels of ALP, TC, TG, LDL-C and HDL-C before and after treatment in the two groups ($\bar{x}$ ±s).

Group	Time	ALP (U/L)	TC (mmol/L)	TG (mmol/L)	LDL-C (mmol/L)	HDL-C (mmol/L)
Research group	Before treatment	160.02±30.19	4.40±1.21	1.33±0.90	2.31±0.94	1.76±0.04
	After treatment	122.57±12.49	4.23±0.94	1.46±0.58	2.98±0.36	1.80±0.26
Control group	Before treatment	165.11±30.38	4.43±1.90	1.32±0.88	2.16±0.62	1.70±0.03
	After treatment	140.73±29.06	5.39±1.28	1.40±0.84	2.70±0.95	1.96±0.20

Table 2. Comparison of iPTH, Cr, P and Ca levels before and after treatment between the two groups ($\bar{x}$ ±s).

Group	Time	iPTH (pmol/L)	Cr (μmol/L)	P (mmol/L)	Ca (mmol/L)
Research group	Before treatment	46.59±9.06	835.40±100.93	1.88±0.90	2.02±0.85
	After treatment	32.70±8.51	723.08±118.97	1.24±0.42	2.26±0.80
Control group	Before treatment	45.70±9.30	843.46±107.97	1.90±0.27	2.00±0.62
	After treatment	40.75±9.02	780.46±102.48	1.56±0.37	2.10±0.34

(20) M Izumi et al., (21) Medow et al (22).

Many CKD and dialysis patients require the administration of phosphate binders to maintain normal serum phosphorus levels, and it is therefore recommended that CKD patients who have high phosphorus serum levels despite dietary phosphorus limitation use these drugs (23). A few studies have looked at the effects of these drugs in CKD patients and dialysis; In a randomized study, comparing the effect of phosphate binders and placebo on the prognosis of 148 patients, which had 20-45 ml/min of GFR, the use of these drugs caused the serum levels of phosphorus to decrease further in 3, 6 and 9 months after administration compared to the placebo group. Also, the results of that study show that the use of phosphate binders stabilizes serum levels of parathyroid hormone (PTH), while its level in the placebo group had increased (24). In study of Cannata Andía et al. the benefits of these drugs were noted. The study showed that the use of phosphate binders reduced the mortality rate from cardiovascular disease by about 22 percent. And a 29% reduction in mortality from all causes (25). Although these studies have emphasized the benefits of phosphate binders, some studies have noted the side effects of these drugs, especially those linked to calcium, and have suggested that their use may have side effects like vascular calcification of CKD patients (24).

Phosphate binders are divided into two main types, calcium and non-calcium. Calcium-containing binders include calcium carbonate and calcium acetate, and the major non-calcium binders are Sevelamer, all of which appear to be effective in reducing serum phosphates (25).

In future studies, it is recommended that inflammatory factors such as CRP and ESR be used alongside other variables. Homogeneous groups of patients can also be considered in terms of background and laboratory variables and the level of hemoglobin and hematocrit in these patients can be examined. In people with chronic kidney disease, check for serum phosphorus levels and related items such as calcium, and 25-vitamin D hydroxy. The results of these tests vary depending on the severity of kidney failure.

In conclusion, the combination of calcitriol and sevelamer carbonate can achieve good results in the treatment of chronic renal failure patients, which can positively improve the iPTH concentration, calcium and phosphorus levels, and have relatively high drug safety. Animal experiments show that it can effectively reduce blood phosphorus, and rarely cause hypercalcemia and increase of calcium-phosphorus product. Clinical studies show that it has a good prevention and treatment effect on hyperphosphatemia, with few side effects, which is a treatment model that can be popularized and applied. It should be noting that in the clinical treatment process, active vitamin D should be applied correctly, and it is particularly important to strictly grasp the drug indications to reduce adverse drug reactions. Active vitamin D is an important substance for the body to regulate iPTH secretion and prevent parathyroid hyperplasia. Since the sample size of this study is small, the larger sample size studies are needed.

Conflicts of interest

None.

References

1. Zhang CQ, Zhang HX. Clinical observation of hyperphosphatemia in hemodialysis patients treated with carbonated sveramme combined with low calcium dialysate. J of Qiqihar Med Colg 2017; 38(23): 2772-2774.

2. Xu ZB, Zhao J, Jia XM, Du YL. Effect of calcitriol on silicosis fibrosis in rats and its mechanism. J of Envir and Occup Med 2018; 35(03): 272-276.

3. Martín–Llahí M, Guevara M, Torre A, Fagundes C, Restuccia T, Gilabert R, Solá E, Pereira G, Marinelli M, Pavesi M, Fernández J. Prognostic importance of the cause of renal failure in patients with cirrhosis. Gastroenterology. 2011; 140(2):488-96.

4. He XX, Liu J, Zhan YL, Wang J, Chu B. Effect of calcitriol injection combined with high-flux hemodialysis in the treatment of chronic renal failure with secondary hyperparathyroidism. Contemp Med Sympos 2018; 16(12): 168-170.

5. Diggle PJ, Sousa I, Asar Ö. Real-time monitoring of progression towards renal failure in primary care patients. Biostatistics 2018; (63): 231-236.

6. Nagaraja P, Thangavelu A, Nair H, Kumwenda M. Successful living related kidney transplantation for end-stage renal failure caused by orellanine syndrome. QJM: An Internat J Med 2015; (85): 120-125.

7. Duan SY. Clinical observation of low calcium dialysate combined with active vitamin D and sveramol hydrochloride in the treatment of secondary hyperparathyroidism in hemodialysis patients. Chin J Modr Drug Aplic 2016; 10(14): 27-28.

8. Chen XF, Lu JR, Wang XH, Hu J, Chen J, Liao L, Han HY, Zhang CF, Li WF. Clinical observation of sveramol hydrochloride combined with hemodialysis filtration in the treatment of renal bone disease. Chin J Clin Res 2015; 28(08):1036-103.

9. Lüscher TF. Heart failure and comorbidities: renal failure, diabetes, atrial fibrillation, and inflammation. Europ Heart J 2017; (23): 102-104.

10.Marchetto L, Sordino D, De Bernardo G, Trevisanuto D. Postnatal acute renal failure after fetal exposure to angiotensin receptor blockers. BMJ Cas Report 2015; (08): 88-94.

11.Massry SG, Coburn JW, Popovtzer MM, Shinaberger JH, Maxwell MH, Kleeman CR. Secondary hyperparathyroidism in chronic renal failure: The clinical spectrum in uremia, during hemodialysis, and after renal transplantation. Archives of internal medicine. 1969.

12.Llach F. Secondary hyperparathyroidism in renal failure: the trade-off hypothesis revisited. Am J Kidney Dis 1995 May 1;25(5):663-79.

13.Llach F, Forero FV. Secondary hyperparathyroidism in chronic renal failure: pathogenic and clinical aspects. Am J Kidney Dis 2001; 38(5): S20-33.

14.Kim HW, Park CW, Shin YS, Kim YS, Shin SJ, Kim YS, Choi EJ, Chang YS, Bang BK. Calcitriol regresses cardiac hypertrophy and QT dispersion in secondary hyperparathyroidism on hemodialysis. Nephro Clinic Pract 2006; 102(1):c21-9.

15.Baker LR, Muir JW, Sharman VL, Abrams SM, Greenwood RN, Cattell WR, Goodwin FJ, Marsh FP, Adami S, Hately W. Controlled trial of calcitriol in hemodialysis patients. Clinic Nephro. 1986;26(4):185-91.

16.Teng M, Wolf M, Lowrie E, Ofsthun N, Lazarus JM, Thadhani R. Survival of patients undergoing hemodialysis with paricalcitol or calcitriol therapy. NEJM. 2003; 349(5):446-56.

17.Toussaint ND, Damasiewicz MJ.Do the benefits of using calcitriol and other vitamin D receptor activators in patients with chronic kidney disease outweigh the harms? Nephro (Carlton). 2017; 22 Suppl 2:51-56. doi: 10.1111/nep.13026.

18.Negri AL, Brandenburg VM. Calcitriol resistance in hemodialysis patients with secondary hyperparathyroidism. Int Urol Nephrol. 2014 Jun;46(6):1145-51. doi: 10.1007/s11255-013-0637-2. Epub 2014 Jan 3.

19.Negrea L.Active Vitamin D in Chronic Kidney Disease: Getting Right Back Where We Started from? Kidney Dis (Basel). 2019 Mar;5(2):59-68. doi: 10.1159/000495138. Epub 2018 Dec 19.

20.Di Iorio B, Molony D, Bell C, Cucciniello E, Bellizzi V, Russo D, Bellasi A, INDEPENDENT Study Investigators. Sevelamer versus calcium carbonate in incident hemodialysis patients: results of an open-label 24-month randomized clinical trial. Am J Kidney Dis 2013 Oct 1;62(4):771-8.

21.Izumi M, Morita S, Nishian Y, Miyamoto T, Kasumoto H, Oue M, Hori K, Kitamura R, Yamamoto S, Nakanishi T. Switching from Calcium Carbonate to Sevelamer Hydrochloride Has Suppressive Effects on the Progression of Aortic Calcificationin Hemodialysis Patients: Assessment Using Plain Chest X-Ray Films. Renal Failure 2008 Jan 1;30(10):952-8.

22.Medow JE, Sanghvi SR, Hofmann RM. Use of high-flow continuous renal replacement therapy with citrate anticoagulation to control intracranial pressure by maintaining hypernatremia in a patient with acute brain injury and renal failure. Clinic Med Res 2015; 13(2):89-93.

23.Friedman EA. An introduction to phosphate binders for the treatment of hyperphosphatemia in patients with chronic kidney disease. Kidney Int Suppl 2005; (96): S2.

24.Block GA, Wheeler DC, Persky MS, Kestenbaum B, Ketteler M, Spiegel DM. Effects of phosphate binders in moderate CKD. J Am Soc Nephrol 2012; 23(8): 1407.

25.Cannata-Andía JB, Fernández-Martín JL, Locatelli F, London G, Gorriz JL, Floege J. Use of phosphate-binding agents is associated with a lower risk of mortality. Kidney Int 2013; 84(5): 998.