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Original Article

Effect of hemodialysis combined with calcitriol on cardiac function and BNP in patients with hyperparathyroidism secondary to nephropathy

Jie Shen*, Xiaohua Feng*, Xiaoyan Li

*Nephrology, The First Affiliated Hospital of Hainan Medical College, Haikou 570000, Hainan, China. *Equal contributors.*

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Abstract: Objective: To explore the effect of hemodialysis plus calcitriol on cardiac function and BNP in patients with hyperparathyroidism secondary to nephropathy. Methods: In this retrospective study, a total of 80 patients with nephropathy secondary to hyperparathyroidism treated in our hemodialysis center from January 2018 to January 2020 were included. The patients were divided into a combination group (n=50) and a control group (n=30) according to treatment plan. Both groups were treated with hemodialysis, and the combination group was treated with additional calcitriol. The heart rate, heart functions such as left ventricular end-systolic volume (LVESV), left ventricular ejection fraction (LVEE), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), brain natriuretic peptide (BNP) level, blood calcium and phosphorus level, intact parathyroid hormone (iPTH) and alkaline phosphatase (ALP) level, total effective rate, and adverse reaction rate of the two groups were compared. Results: Compared to the control group, the heart rate, LVEE, LVEDD and LVESD, BNP level, blood calcium and phosphorus level, and the incidence of adverse reactions of the combination group were lower, while LVESV level, iPTH, and ALP levels, and the total effective rate were higher. Conclusion: Hemodialysis combined with calcitriol can better improve cardiac function and BNP level of patients than hemodialysis alone.

Keywords: Hemodialysis, calcitriol, hyperparathyroidism secondary to nephropathy, BNP

Introduction

Chronic kidney disease can easily trigger secondary hyperparathyroidism, which gradually deteriorates due to excessive parathyroid hormone produced by parathyroid glands [1]. This phenomenon starts from the early stage of chronic kidney disease, which can cause abnormal metabolism of fat and sugar, intractable itching, and anemia [2]. In addition, the increase in parathyroid hormone level will also lead to secondary bone diseases, fibrous osteitis, and other bone problems. This is the reason for the fact that patients with chronic kidney disease are prone to fracture [3]. In the late stage of the disease, secondary hyperparathyroidism tends to increase the mortality risk from cardiovascular disease [4]. The prevalence of secondary hyperparathyroidism in patients with kidney diseases is highly variable, depending on the definition of secondary hyperparathyroidism, the severity of kidney disease, phosphorus load, and vitamin D status [5]. The development and progression of chronic kidney disease will severely affect the maintenance of calcium and phosphorus metabolism, and then lead to secondary hyperparathyroidism [6, 7]. Therefore, for patients with hyperparathyroidism caused by kidney disease, it is necessary to adopt appropriate treatment.

Many current treatment methods, such as hemodialysis, have insufficient control over the levels of parathyroid hormone, phosphorus and calcium in patients. They increase risk of cardiovascular diseases, and may even lead to death [8]. In medical treatment, calcitriol is generally used to inhibit the synthesis and secretion of parathyroid hormone [9, 10]. Therefore, in medical treatment, especially hemodialysis, calcitriol is usually used as an auxiliary treatment to assist hemodialysis to

regulate parathyroid hormone [11]. In the clinical treatment of nephropathy secondary to hyperparathyroidism, hemodialysis combined with calcitriol is a commonly used method, but whether there is any effect on patients' cardiac function, BNP, and other indicators compared to treatment without calcitriol remains unclear [12].

Thus, the aim of this study was to analyze the effect of hemodialysis combined with calcitriol on cardiac function and BNP in patients with nephropathy secondary to hyperparathyroidism to provide a reference for the selection of clinical treatment.

Method

General data

Clinical data of eighty patients with nephrotic hyperparathyroidism who received routine hemodialysis in the hemodialysis center of the First Affiliated Hospital of Hainan Medical College from January 2018 to January 2020 were analyzed retrospectively. Among them, 30 patients treated with routine dialysis were assigned to the control group, and the other 50 patients treated with calcitriol in addition to routine dialysis were assigned to the combination group.

There was no difference in general data ($P > 0.05$). This research had been approved by the Ethics Committee of the First Affiliated Hospital of Hainan Medical College (L2018 (review) A33).

Inclusion criteria: Patients who met the diagnostic criteria of hyperparathyroidism in nephropathy with a serum total parathyroid hormone (IPTH) of >300 pg/mL; Patients with blood calcium ≤2.75 mmol/L and blood phosphorus ≤2.26 mmol/L; Patients with an age of 18-60; Patients who received conventional hemodialysis treatment for 3 months or more; Patients had no medication affecting bone metabolism prior to the current study; Patients with complete clinical data. Exclusion criteria: Patients with malignancy and severe malnutrition; Patients diagnosed with an inflammatory or infectious disease less than 3 months prior to the study; Patients who had surgical intervention, or with thyroid hyperplasia as an adenoma; Patients with cardiovascular disease; Patients who were resistant or allergic to calcitriolol.

Methods

Two groups of patients were treated with routine hemodialysis, 2-3 times a week for 4 h each time. The calcium concentration of dialysate was 1.5 mmol/L. The dietary intake of phosphorus should be controlled in both groups. On this basis, daily oral dose of calcium carbonate was 0.75-2.25 g depending on the condition of patients. In the combination group, calcitriol (trade name: intravenous calcijex, Abbott Laboratories Ltd, USA) was intravenously injected into the vessel at the end of each hemodialysis. According to the initial serum level of iPTH, the initial total dose of weekly irrigation was determined: 3 μg/week when IPTH was 300-600 pg/ml; 6 μg/week when IPTH was ≥600 pg/mL. At the beginning of treatment and at the 4th, 8th, 12th, and 16th week after treatment, the levels of blood calcium and phosphorus, alkaline phosphatase, and serum iPTH were measured. According to the level of iPTH and the situation of blood calcium and phosphorus, the dosage of calcitriol was adjusted, which was generally 1 μg per week to reduce the occurrence of complications. The target value of iPTH was 150-300 pg/mL, calcium was 2.10-2.50 mmol/L and phosphorus was 1.13-1.78 mmol/L in CKD5 stage, which were clinical observation endpoints. When the product of calcium (mg/dl) and phosphorus (mg/dl) (Ca × P) was more than 70 or blood calcium was more than 2.80 mmol/L, the calcitriol injection was stopped. Amount of improvement and remission rate of clinical symptoms of the two groups were observed and recorded.

Detection indicators

Heart rate: After admission, real-time detection of the heart rate (HR) was performed. HR of the two groups was compared when they were on admission and 14 days after treatment.

Cardiac function: The cardiac function of two groups of patients on admission and 14 days after treatment was tested. Color Doppler ultrasound HDI5000 (PHILIPS, USA), was used to examine the heart function of the patients in resting state. The left ventricular end systolic volume (LVESV), left ventricular ejection frac-

Table 1. General data

Classification	Combination group (n=50)	Control group (n=30)	t/X^2	P
Gender			0.030	0.862
Male	26 (52.00)	15 (50.00)		
Female	24 (48.00)	15 (50.00)		
Age (years)	54.4±4.1	56.0±4.0	1.702	0.093
Dialysis age (years)	4.29±0.35	4.43±0.42	1.606	0.112
Primary disease			0.566	0.904
Chronic glomerulonephritis	27 (54.00)	15 (50.00)		
Diabetic nephropathy	16 (32.00)	9 (30.00)		
Drug-induced renal damage	4 (8.00)	3 (10.00)		
Chronic renal interstitial nephritis	3 (6.00)	3 (10.00)		
Polycystic kidney				
High blood lipid			0.372	0.542
Yes	37 (74.00)	24 (80.00)		
No	13 (26.00)	6 (20.00)		
Hypertension			0.093	0.759
Yes	46 (92.00)	27 (90.00)		
No	4 (8.00)	3 (10.00)		

tion (LVEE), left ventricular end diastolic diameter (LVEDD) and left ventricular end systolic diameter (LVESD) were tested, and the ultrasonic data were recorded and compared.

Serological index: Peripheral blood was collected from patients at admission, 7 d and 14 d of treatment. The samples were left to stand for 30 min, centrifuged at 1500 g for 15 min, and the supernatant was collected for later analysis. Plasma brain natriuretic peptide (BNP) level was determined by fluorescence immunoluminescence with a fully automated biochemical analyzer (Beckman AU5800 fully automated biochemical analyzer), and immunoturbidimetric methods were adopted to determine blood calcium and phosphorus levels. Intact parathyroid hormone (iPTH) levels were measured using a Cobase 601 automated electrochemiluminescence immunoassay (Roche Diagnostics, Germany) with accompanying reagents.

Total effective rate: The clinical effects were compared with the following criteria: (1) the clinical symptoms, such as intractable itching and anemia, were improved, which was recorded as markedly effective; the clinical symptoms, such as intractable itching and anemia, were relieved, which was recorded as effective; the clinical symptoms of patients, such as intractable itching and anemia, were not improved, which was recorded as ineffective. Clinical total effective rate = markedly effective rate + effective rate.

Incidence of adverse reactions: Adverse reactions, including nausea and vomiting, abdominal pain and myalgia, during treatment were recorded, and the incidence of adverse reactions was compared between the two groups.

Statistical methods

The data collected were analyzed by SPSS 20.00 software, and the images were visualized by GraphPad Prism 8 software. The counted data were expressed as % and comparisons were made using the chi-square test. Measured data were expressed as the mean ± standard deviation. The independent sample t-test was used for inter-group comparison, and paired t-test was used for intra-group comparison. $P<0.05$ was considered a significant difference.

Results

General data

There was no difference in gender, age, dialysis age, primary disease, hypertension or hyperlipidemia between the two groups (all $P>0.05$) (**Table 1**).

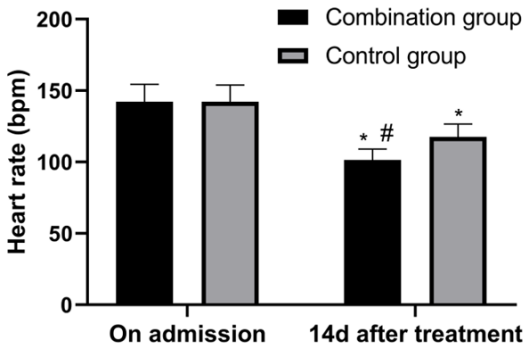

Figure 1. Heart rate of patients in both groups. Note: * means compared to on admission, P<0.05; # means compared to the control group, P<0.05.

HR of patients in the combination group were lower than those in the control group

The HR levels of the two groups changed after treatment, and those in the combination group were lower than those of the control group (P<0.05) (**Figure 1**).

Recovery of cardiac function in the combination group was better than in the control group

LVEE, LVEDD, LVESV, and LVESD in both groups changed significantly after treatment LVEE of the combination group was significantly higher than that of the control group, and LVEDD, LVESV and LVESD in the combination group were significantly lower. This indicated that the cardiac function recovery of the combination group was better than that of the control group (P<0.05) (**Figure 2**).

BNP level of the combination group was lower than that of the control group

BNP changed significantly after treatment, with notably lower level in the combination group than the control group (P<0.05) (**Table 2**).

Blood calcium and phosphorus levels in the combination group were higher than in the control group

The blood calcium and phosphorus levels of both groups changed after treatment, and those in the combination group were higher than those of the control group (both P<0.05) (**Figure 3**).

iPTH and ALP levels of patients in the combination group were lower than those of the control group

iPTH and ALP in the two groups changed significantly after treatment, and those in the combination group were lower than those in the control group (both P<0.05) (**Figure 4**).

Total effective rate of patients in the combination group was higher than that in the control group

The combination group had a higher total effective rate than the control group, indicating better clinical efficacy (P<0.05) (**Table 3**).

Incidence of adverse reactions in the combination group was lower than that in the control group

The incidence of adverse reactions in the combination group was lower than that in the control group, which indicated higher safety (P<0.05) (**Table 4**).

Discussion

Secondary hyperparathyroidism, as a frequent complication of kidney disease, can easily affect patients undergoing hemodialysis. This complication, together with the primary disease, will cause serious harm to the cardiovascular system of patients and seriously affects their lives [13-15]. Therefore, hemodialysis should be implemented in combination with drugs such as calcitriol [16, 17]. In this section, we will discuss the effect of this combination therapy on secondary hyperparathyroidism from different aspects, such as blood calcium, blood phosphorus, iPTH, ALP, and BNP levels and cardiovascular function.

We found that, compared to the control group, patients in the combination group had better recovery of related cardiac function, and the HR also decreased rapidly. Impaired renal function will easily lead to increased parathyroid hormone level and calcification of blood vessels, especially cardiovascular, thus affecting the heart structure of patients. Studies have shown that abnormal internal structure of the heart can lead to impaired function, such as ventricular diastolic or systolic dysfunction,

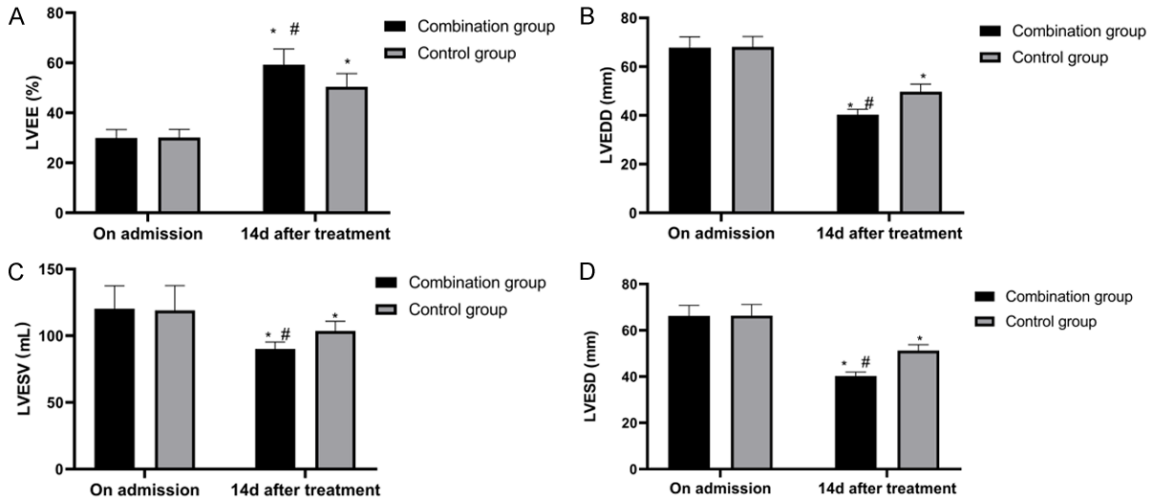

Figure 2. Heart function of two groups of patients: (A) The LVEE level of two groups of patients changed after treatment. (B) The level of LVEDD in the combination group changed. (C) The LVESV level of both groups changed. (D) The LVESD level of both groups changed after treatment. Note: * means compared to on admission, P<0.05; # means compared to the control group, P<0.05. Left ventricular end-systolic volume (LVESV), left ventricular ejection fraction (LVEE), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD).

Table 2. BNP levels of patients in both groups (pg/mL)

Classification	Combination group (n=50)	Control group (n=30)	t	P
On admission	125.43±29.66	126.21±31.22	0.111	0.911
Fourteen days after treatment	92.21±19.57	110.45±22.14	3.841	<0.001
t	6.412	2.255		
P	<0.001	0.028		

Note: brain natriuretic peptide (BNP).

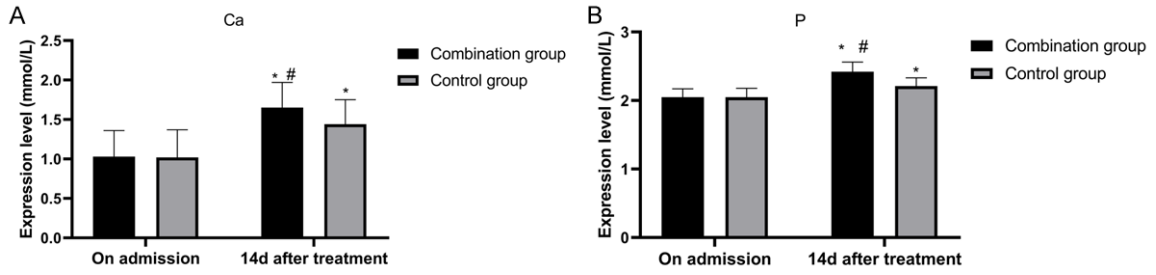

Figure 3. Blood calcium and phosphorus of two groups of patients: (A) The blood calcium level of two groups of patients changed after treatment. (B) The blood phosphorus level of the two groups changed. Note: * means compared top on admission, P<0.05; # means compared to the control group, P<0.05.

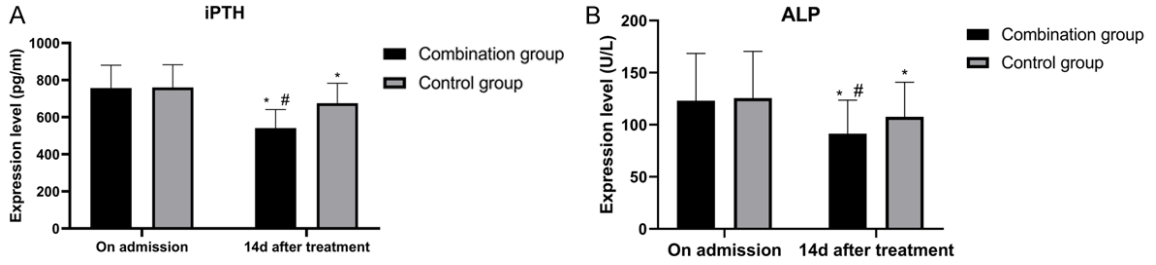

Figure 4. iPTH and ALP of two groups of patients: (A) There were significant changes in iPTH levels after treatment in both groups. (B) After treatment, the ALP level of the two groups changed. Note: * means compared to on admission, P<0.05; # means compared to the control group, P<0.05. Blood calcium and phosphorus level, intact parathyroid hormone (iPTH), and alkaline phosphatase (ALP) level.

Table 3. Total effective rate of both groups of patients

Classification	Combination group (n=50)	Control group (n=30)	X^2	P
Markedly effective	31 (62.00)	12 (40.00)	-	-
Effective	16 (32.00)	9 (30.00)	-	-
Ineffective	3 (6.00)	9 (30.00)	-	-
Total effective rate (%)	47 (94.00)	21 (70.00)	8.471	0.004

Table 4. Incidence of adverse reactions in both groups

Classification	Combination group (n=50)	Control group (n=30)	X^2	P
Nausea and vomiting	1 (2.00)	3 (10.00)	-	-
Abdominal pain	0 (0.00)	1 (3.33)	-	-
Myalgia	1 (2.00)	2 (6.67)	-	-
Incidence of adverse reactions (%)	2 (4.00)	6 (20.00)	5.333	0.021

resulting in pathophysiologic changes to the heart [18-21]. The results of this experiment verified that calcitriol combined with hemodialysis can evidently improve the ventricular function of patients. At the same time, other symptoms of patients in the combination group also recovered better, the total effective rate was higher, and the probability of adverse reactions was lower. McCabe [22] et al. found that calcitriol can better improve the pathologic indexes of patients with secondary hyperparathyroidism. Chen et al. [23] found that after calcitriol was applied, the pathological indexes were improved, and the incidence of postoperative adverse reactions was lower, which was similar to the results of this study. Therefore, calcitriol-assisted hemodialysis can solve a series of problems caused by hemodialysis, so that patients can recover from secondary hyperparathyroidism more effectively and safely.

The increase of parathyroid hormone level caused by secondary hyperparathyroidism will interfere with serum calcium, phosphorus, and ALP levels. Recently, some studies have shown that if the serum calcium and phosphorus levels of patients with kidney disease decrease, it may be the result of cardiovascular calcification, which will increase the risk of cardiovascular disease mortality [24]. Research has proven that calcitriol can effectively reduce serum iPTH and ALP in hemodialysis patients [25]. Calcitriol can inhibit essential proteins of arterial calcification, and also stimulate and inhibit the production of mineral proteins [26]. iPTH and ALP in the combination group decreased more obviously, while the levels of calcium and phosphorus in blood increased. This proved that calcitriol could inhibit the level of parathyroid hormone in secondary hyperparathyroidism. At the same time, BNP has a great influence on ventricular function [27]. In this experiment, the BNP level in the combination group decreased, indicating that calcitriol could improve ventricular function better. Combined with these experimental results, we conclude that calcitriol can reduce cardiovascular calcification of patients by inhibiting the level of parathyroid hormone, which makes the BNP level of patients lower and the cardiac function recover better. However, in this study, we did not explore the deeper molecular mechanism of the disease and the relationship between BNP and parathyroid hormone. We will further investigate these in future research. Besides, we will investigate the compliance and satisfaction of each patient after treatment, so as to improve our treatment methods.

To sum up, hemodialysis combined with calcitriol can better improve patients' heart function and reduce the BNP level.

Disclosure of conflict of interest

None.

Address correspondence to: Xiaoyan Li, Nephrology, The First Affiliated Hospital of Hainan Medical College, No. 31, Longhua Road, Haikou 570000, Hainan, China. Tel: +86-13976631649; E-mail: lfss-ciccc@163.com

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