Effects of Cinacalcet and Parathyroidectomy on Blood Pressure in Maintenance Hemodialysis Patients with Secondary Hyperparathyroidism

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Introduction. Secondary hyperparathyroidism may cause an increase in blood pressure among maintenance hemodialysis (MHD) patients. The objective of this study were to observe the effects of different treatment modalities of hyperparathyroidism on blood pressure among MHD patients with secondary hyperparathyroidism.
Methods. This retrospective cohort study was conducted on 69 patients divided into three groups, based on the therapeutic strategies (parathyroidectomy, n = 22; cinacalcet, n = 14; calcitriol, n = 33). Changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) from pre- to post-treatment visits at 1st, 3rd, 6th, and 12th month were analyzed by mixed-effects repeated-measures model. Serum levels of the renin-angiotensin system (RAS) mediators (renin and aldosterone), endothelin, and echocardiography were compared before and after one year of treatment within the three groups.
Results. Changes in blood pressure were significantly different among the three groups (SBP: *P* for group < 0.05; DBP: *P* for group < .05; both *P* for group × time interaction < .05). SBP and DBP showed a significant downward trend in the surgery group (*P* for change in SB*P* < .05, *P* for change in DB*P* < .001, adjusted mean change of SB*P* = -12.16 (-19.70 to -4.62) mmHg and of DB*P* = -6.82 (-10.58 to -3.06) mmHg in the surgery group on the 12th month). Diastolic BP showed a significant upward trend in the cinacalcet group (*P* for change in DB*P* < .05, adjusted mean change of DB*P* = 6.03 (2.08 to 9.98) mmHg in cinacalcet group in the 12th month). No significant change in BP was observed in the calcitriol group. The levels of serum RAS mediators, endothelin, or cardiac ultrasonography didn't change and almost remained consistent during the treatment course.
Conclusion. Blood pressure decreased significantly over a year in patients with parathyroidectomy, while DBP increased significantly over time by cinacalcet treatment.

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INTRODUCTION

Secondary hyperparathyroidism (SHPT) in end-stage kidney disease (ESKD) patients is associated with calcium and phosphorus metabolism disorders, resulting in arterial calcification and increased risk of death.[1,2] With deeper understanding of the pathogenesis of the disorder, medical treatment for SHPT has made a great progress.[3] In addition

to the classical treatment with active vitamin D, cinacalcet activates the calcium-sensing receptor (CaR) on parathyroid cells. Following attachment to the transmembrane region of the receptor, it induces a conformational change that increases the receptor's sensitivity to Ca^{2+} and suppresses the secretion of parathyroid hormone (PTH). Cinacalcet is being increasingly used to treat SHPT in uremic patients.[4] However, as suggested by the kidney disease: improving global outcomes (KDIGO) guidelines, parathyroidectomy is the mainstay for patients with refractory hyperparathyroidism, resistant to other treatments.[5-7]

Abnormal blood pressure is associated with a high level of PTH. Surgical subtotal parathyroidectomy decreases systolic blood pressure in ESKD patients.[8,9] Parathyroidectomy has also been reported to decrease the blood pressure in kidney transplant recipients.[10] Cinacalcet has been shown to reduce systolic and diastolic blood pressures in several clinical trials, including the EVOLVE trial.[11,12] Interestingly, activation of CaR increases the mean arterial pressure (MAP) in uremic and non-uremic rats, despite acute reduction in serum Ca^{2+}.[13, 14] The mechanism responsible for this paradoxical increase in blood pressure in the presence of reduced extracellular Ca^{2+} reduction is not clear.

The functional consequence of CaR stimulation exerted by cinacalcet and its effects on hemodynamic status is not yet well understood. In addition, the effects of different treatments in maintenance hemodialysis (MHD) patients with SHPT are not fully elucidated. In this longitudinal cohort , we evaluated the effects of different therapeutic methods of SHPT on blood pressure during the first year of treatment in a group of maintenance hemodialysis (MHD) patients.

MATERIALS AND METHODS

Participants

Retrospectively, 69 out of 126 MHD patients with SHPT who had been dialyzed for at least one year in hemodialysis center of Huashan Hospital, Shanghai, China from January 2015 to December 2018 were selected and studied according to different treatment modalities for SHPT. The patients were retrospectively divided into parathyroidectomy + forearm parathyroid transplantation group (n = 22), cinacalcet treatment group (n = 14), and calcitriol treatment group (n = 33). Fifty-seven patients were excluded due to unavailability of data for diagnosis of mineral bone disease (MBD) parameters, blood pressure recordings, the volume of ultrafiltration during dialysis sessions, single-pool Kt/V (spKt/V), or treatment duration less than one year. Patients who underwent parathyroidectomy, were usually those who had failed to respond to medical therapy, including calcitriol and cinacalcet. These patients did not receive calcitriol or cinacalcet because of lower levels of PTH in the first year after parathyroidectomy. Instead, they only received 4.5 to18 grams of calcium carbonate per day to prevent hypocalcemia. In the cinacalcet group, patients only received 25to 50 mg of cinacalcet per day. In the calcitriol group, patients were only prescribed calcitriol 0.25 to 0.5 ug every night or 1 to 2 ug thrice a week to reduce PTH levels. The Ethics Committee on Human Research at Huashan Hospital, examined and approved the study (ID number: 369). A written informed consent was provided by all patients.

Clinical Parameters

Information on demographic and laboratory variables were obtained from database of our dialysis center. Systolic and diastolic blood pressure (SBP and DBP) before each dialysis session were recorded. Ultrafiltration volume of each dialysis session was also recorded. To minimize measurement variability, an averaged blood pressure and ultrafiltration levels were calculated form 12 or 13 hemodialysis sessions for one month before treatment for SHPT and at the 1st, 3rd, 6th and 12th months after treatment. Antihypertensive medications were also recorded as binary variables during the one-year period, because only 9 of them were using antihypertensive medications.

Laboratory Parameters

Pre-dialysis blood samples were obtained on the midweek dialysis day for routine laboratory assessment by standard techniques. MBD parameters were measured at least once a month after initiating the treatment of SHPT, and then every three month or anytime as needed. Other laboratory variables were measured at least every three months. The serum levels of angiotensin I, angiotensin II, aldosterone, renin, and endothelin

were measured using ELISA method (Beijing North Institute of biological Technology, Beijing, China), according to the manufacturer's protocol before the treatment and at the 12th month after the treatment of hyperparathyroidism. The spKt/V delivered by hemodialysis was estimated by the second-generation Daugirdas equation.[15] The normalized protein catabolic rate (nPCR) was calculated as described by Termorshuizen *et al*. and normalized to standard body weight (total-body water/0.58).[16] The total body water was determined by Watson's formula.[17]

Echocardiography

Transthoracic echocardiography was performed in the patients resting at the left lateral decubitus position by 2 professional cardiologists using a Siemens Sequoia 512 ultrasound machine and a 3V2C transthoracic transducer (Siemens Medical Systems, Mountain View, CA, USA), one day after the dialysis treatment. Complete two-dimensional, color, pulsed and continuous-wave doppler examinations were performed according to the standard techniques(18). Parasternal long-axis views were used to M-Mode measurements of LA size, LV end-diastolic interventricular septal (IVST) and posterior wall thickness (PWT), and LV end-diastolic (LVDd) and end-systolic dimensions (LVDs). LV mass (LVM) was calculated using the regression equation as described by Devereux *et al*, i.e. $LVM = 1.04 \times ((IVST + PWT + LVDd)^3 - LVDd^3) - 13.6$, and was corrected for body surface area.[19,20] LV fractional shortening (LVFS) was calculated as (LVDd – LVDs) / LVDd. LV ejection fraction (LVEF) was calculated by the modified biplane Simpson rule and expressed as percentage. All echocardiographic measurements used in the analysis were averaged from 3 heart beats.[21, 22]

Statistical Analysis

Comparisons of continuous and categorical variables among treatment groups were evaluated by Kruskal Wallis test and χ^2 test, both at the baseline (one month before treatment) and at the 12th month after treatment. The paired t-test and signed rank test were used to compare the values of means in baseline and 12th month after treatment evaluations, within each group. We calculated delta SBP and delta DBP by averaged blood pressure at each monthly visit minus averaged baseline value to describe the changes of blood pressures during the one-year follow up. Delta ultrafiltration was calculated in the same manner. Then, changes from baseline to each post-baseline visit for delta SBP and DBP were analyzed by Maximum-likelihood, Mixed-Effects Repeated-Measures model (MMRM) with terms of treatment, visit, treatment× visit interaction, gender, and antihypertensive medication used as fixed categorical effects, and with age, vintage, dry weight at the baseline, delta averaged ultrafiltration, spKt/V, PTH, and serum calcium at each visit as continuous covariates. Means and 95% confidence intervals from the MMRM were presented throughout. Also, MMRM tests for differences of delta blood pressure across visits in each group, tests for interaction of treatment and visit, and tests for the difference of delta blood pressure between the pairwise groups at each visit were presented.

Two-sided *P* values less than .05 were considered statistically significant. Statistical analyses were performed using Stata version 14.0 (Stata Corp, College Station, Texas 77845 USA).

RESULTS

Characteristics of Patients at Baseline and After 1-year Treatment

The baseline characteristics of 69 MHD patients are shown in Table 1. The patients in the surgery group were younger, while patients of the cinacalcet group had lower dry weight and DBP. Patients in the surgery and the cinacalcet groups had higher levels of serum intact PTH, phosphorus and alkaline phosphatase.

At 12th month after treatment, the levels of PTH decreased significantly in the surgery and cinacalcet groups, but not in the calcitriol group. Levels of serum alkaline phosphatase, calcium and phosphorus in the surgery group also decreased significantly compared to levels before treatment ($P_{\text{within-group}} < .001$). Besides, the levels of serum intact PTH and calcium at 12th month after the treatment were significantly lower in the surgery group than those of the cinacalcet and calcitriol groups ($P_{\text{among groups}} < .05$) (Table 2). Patients of the cinacalcet group had less ultrafiltration ($P < 005$) and lower nPCR ($P < .05$) compared to the other two groups. During the one-year treatment, one patient in the surgery group underwent left-arm aneurysm repair operation and one in the calcitriol

Table 1. Baseline Characteristics of 69 Hemodialysis Patients Stratified by Therapies for Secondary Hyperparathyroidism

Characteristics	Surgery (n = 22)	Cinacalcet (n = 14)	Calcitriol (n = 33)	*P*
Age, y	57 ± 9	65 ± 9	64 ± 10	< .05
Male, %	10 (45.5%)	5 (35.7%)	19 (57.6%)	> .05
Vintage, y	11.3 ± 4.5	14.2 ± 5.4	10.8 ± 6.2	> .05
Primary Disease, n (%)				
Glomerulonephritis	15 (68.2%)	7 (50.0%)	14 (42.4%)	> .05
Diabetes	2 (9.1%)	1 (7.1%)	6 (18.2%)	
Hypertension	3 (13.6%)	2 (14.3%)	10 (30.3%)	
Others	2 (9.1%)	4 (28.6%)	3 (9.1%)	
Dry Weight, kg	58.9 ± 9.5	53.4 ± 8.1	62.2 ± 10.2	< .05
Filtration, mL/treatment	3099.2 ± 944.8	2684.7 ± 663.3	3050.2 ± 732.6	> .05
Systolic Blood Pressure, mmHg	133.2 ± 14.1	120.1 ± 17.5	131.9 ± 20.6	> .05
Diastolic blood Pressure, mmHg	78.1 ± 11.2	65.4 ± 11.9	75.2 ± 11.6	< .05
Single-pool Kt/V	1.37 ± 0.32	1.51 ± 0.28	1.34 ± 0.27	> .05
nPCR, g/kg/d	1.18 ± 0.26	1.14 ± 0.21	1.11 ± 0.28	> .05
Laboratory Variables				
Prealbumin, mg/dL	29.7 ± 6.5	33.0 ± 8.6	33.6 ± 6.6	> .05
Hemoglobin, g/dL	10.6 ± 1.2	11.0 ± 1.5	11.1 ± 1.6	> .05
Calcium, mg/dL	10.5 ± 0.9	10.1 ± 0.8	10.0 ± 1.2	> .05
Phosphorus, mg/dL	7.6 ± 1.4	6.7 ± 1.2	6.1 ± 1.7	< .05
Intact PTH, pg/mL	1285 (966, 1578)	886.5 (650, 1235)	375 (322, 576)	< .001
Alkaline Phosphatase, U/L	189.9 ± 104.2	95.9 ± 37.0	81.3 ± 22.8	< .001
Iron saturation, %	31.2 ± 12.5	27.5 ± 5.2	33.7 ± 13.7	> .05
CRP, mg/L				
< 10	18 (81.8%)	14 (100%)	30 (90.9%)	> .05
≥ 10	4 (18.2%)	0%	3 (9.1%)	
Ferritin, ug/L				
< 200	10 (45.5%)	6 (42.9%)	12 (36.4%)	> .05
200 to 500	4 (18.2%)	5 (35.7%)	7 (21.2%)	
≥ 500	8 (36.4%)	3 (21.4%)	14 (42.4%)	

Note: Values are appropriately expressed as mean ± SD, median (IQR), or percentage.
Abbreviations: PTH, parathyroid hormone; nPCR, normalized protein catabolic rate.
Conversion factors for units: prealbumin in mg/dL to mg/L, 10; hemoglobin in g/dL to g/L, 10; calcium in mg/dL to mmol/L, 0.2495; phosphorus in mg/dL to mmol/L, 0.3229.
No conversion is necessary for ferritin in ng/mL and ug/L.

group underwent carpal tunnel decompression operation. We did not take the hospitalization into account in the following analysis, since they were hospitalized only for one day and this had no effects on the long-term blood pressure.

Changes in Blood Pressure During the Study Period

With focusing on the original data for delta SBP and delta DBP, we found that SBP and DBP decreased significantly over time in the surgery group ($P_{\text{for change in SBP}} < .05$, $P_{\text{for change in DBP}} < .001$), DBP increased significantly over time in the cinacalcet group ($P_{\text{for change in DBP}} < .05$), and no significant changes of SBP and DBP were observed in the calcitriol group ($P_{\text{for change in SBP}} > .05$, $P_{\text{for change in DBP}} > .05$) (Figure 1). Also, no significant changes in ultrafiltration have been found in three groups over time ($P_{\text{for change in ultrafiltration}} > .05$ all for surgery, cinacalcet, calcitriol group) (Figure 2). The complete magnitude of changes in SBP and DBP in each group during the study estimated from the MMRM with multiple variable adjustment, is shown in Table 3. After adjusting for multiple variables, the least squares mean changes in SBP (95% CI) from baseline for patients in the surgery group were -5.18 (-12.79 to 2.43) mmHg, -10.88 (-18.57 to -3.19) mmHg, -12.50 (-19.95 to -5.05) mmHg, and -12.16 (-19.70 to -4.62) mmHg at the 1st,3rd, 6th, and 12th month; respectively. Using similar analyses, the mean changes in DBP from baseline were -4.18 (-7.98 to -0.39) mmHg, -6.39 (-10.22 to -2.56) mmHg, -7.30 (-11.01 to -3.59) mmHg, and -6.82 (-10.58 to -3.06) mmHg at the 1st, 3rd, 6th, and 12th month;

Table 2. Characteristics of 69 Hemodialysis Patients at 1 Year After Treatment Stratified by Therapies for Secondary Hyperparathyroidism

Characteristics	Surgery (n = 22)	Cinacalcet (n = 14)	Calcitriol (n = 33)	*P*
Ultrafiltration, mL/treatment	3278.7 ± 1019.2	2507.9 ± 609.8	3031.9 ± 800.3	< .05
Systolic Blood Pressure, mmHg	123.6 ± 22.8*	128.4 ± 20.4*	135.1 ± 22.6	> .05
Diastolic blood Pressure, mmHg	73.7 ± 15.6	70.7 ± 12.6*	74.6 ± 11.5	> .05
Single-pool Kt/V	1.46 ± 0.28	1.43 ± 0.18	1.25 ± 0.25*	< .05
nPCR, g/kg/d	1.28 ± 0.22	1.01 ± 0.17	1.13 ± 0.21	< .05
Laboratory Variables				
Prealbumin, mg/dL	32.9 ± 6.8*	30.5 ± 9.0	33.7 ± 6.8	> .05
Hemoglobin, g/dL	11.3 ± 1.2	10.8 ± 1.8	10.9 ± 1.0	> .05
Calcium, mg/dL	9.1 ± 1.2**	9.9 ± 0.7	9.8 ± 1.1	< .05
Phosphorus, mg/dL	4.5 ± 2.0**	5.8 ± 1.3	5.6 ± 1.4	> .05
Intact PTH, pg/mL	34.2 (5.0, 96.8)**	305 (216, 529)*	445 (345, 664)	< .001
Alkaline phosphatase, U/L	77.9 ± 25.2**	72.6 ± 33.4*	85.0 ± 26.8	> .05
Iron saturation, %	36.5 ± 14.3	26.2 ± 9.8	34.4 ± 13.9	> .05
CRP, mg/L				
< 10	19 (86.4%)	12 (85.7%)	27 (81.8%)	> .05
≥ 10	3 (13.6%)	2 (14.3%)	6 (18.2%)	
Ferritin, ug/L				
< 200	11 (50.0%)	9 (64.3%)	12 (36.4%)	
200 to 500	3 (13.6%)	2 (14.3%)	11 (33.3%)	> .05
≥ 500	8 (36.3%)	3 (21.4%)	10 (30.3%)	
Medication				
Hemopoietin, u/week	10000 (6000, 15000)	10000 (9000, 14000)	10000 (6000, 14000)	> .05

Note: Values are appropriately expressed as mean ± SD, median (IQR), or percentage.
Abbreviations: PTH, parathyroid hormone; nPCR, normalized protein catabolic rate.
Conversion factors for units: prealbumin in mg/dL to mg/L, 10; hemoglobin in g/dL to g/L, 10; calcium in mg/dL to mmol/L, 0.2495; phosphorus in mg/dL to mmol/L, 0.3229.
No conversion is necessary for ferritin in ng/mL and ug/L.
*P < .05 intra-group difference between baseline and the 12th month after treatment, **P < .001 intra-group difference between baseline and the 12th month after treatment.

respectively. Thus, surgery resulted in significant decreases in SBP and DBP over the 1-year follow up (P < .001 and P < .001, respectively). In the cinacalcet group, SBP tended to increase by 7.76 (-0.19 to 15.71) mmHg at the 12th month, but the change was not statistically significant in of all the visits (P > .05). However, there was a significant increase of DBP in the cinacalcet group (P < .05), and the mean change in DBP from baseline were -1.43 (-5.34 to 2.49) mmHg, 2.14 (-1.73 to 6.02)

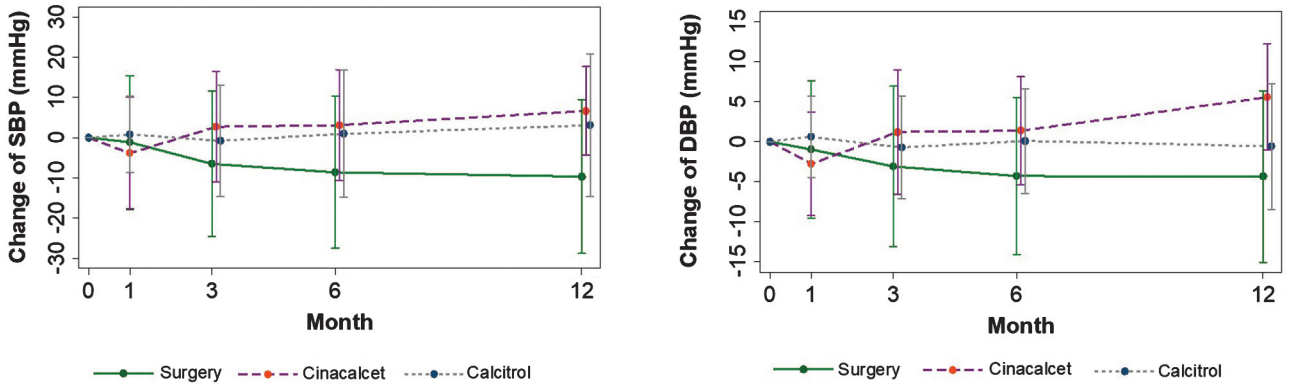

Figure 1. Changes in systolic blood pressure and diastolic blood pressure over one-year follow-up of three therapy groups for secondary hyperparathyroidism. Changes in systolic blood pressure and diastolic blood pressure at baseline, the 1st month, the 3rd month, the 6th month, and the 12th month in three therapy groups for secondary hyperparathyroidism. Circles and bars represent mean ± SD of delta SBP/DBP (change of SBP/DBP). Month 0 represents baseline.

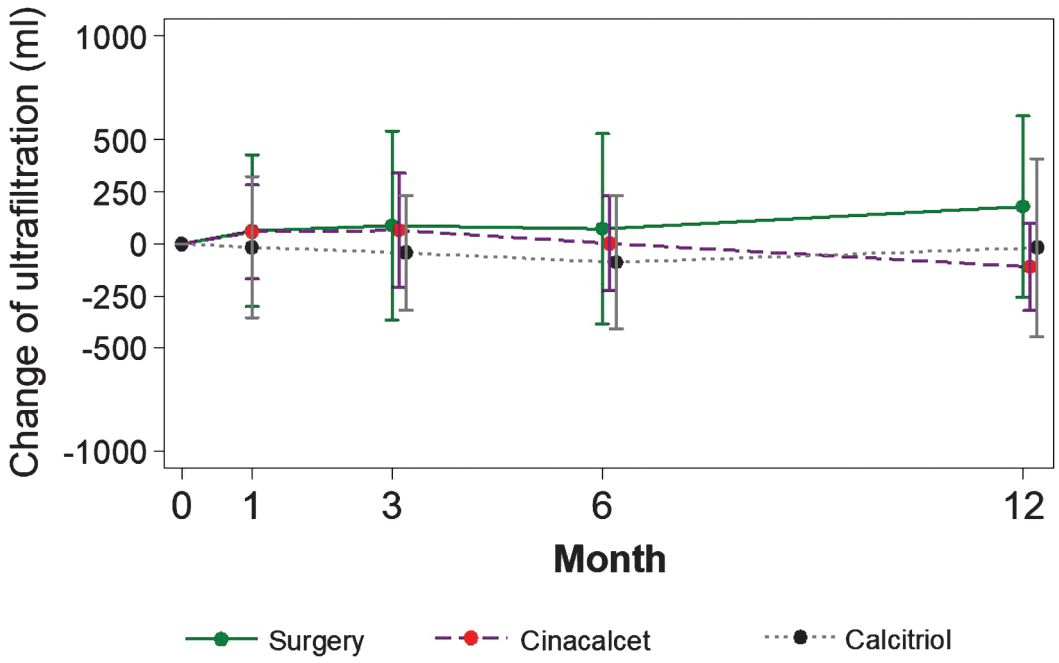

Figure 2. Changes in ultrafiltration over one-year follow-up in three therapy groups for secondary hyperparathyroidism. Changes in ultrafiltration at baseline, 1st, 3rd month, 6th, and 12th months in three therapy groups for secondary hyperparathyroidism. Circles and bars represent mean ± SD of delta ultrafiltration (change of ultrafiltration). Month 0 represents baseline.

mmHg, 2.38 (-1.48 to 6.23) mmHg and, 6.03 (2.08 to 9.98) mmHg at the 1st, 3rd, 6th, and 12th month; respectively. No significant changes of SBP and DBP were found in the calcitriol group. Test of significance of group and group× month interaction for the overall effect from the mixed effect models further support different trends in SBP and DBP among three groups (SBP: $P_{\text{for group}} < .05$, $P < 0.05$ $_{\text{for group} \times \text{month}}$ interaction, DBP: $P_{\text{for group}} < .05$, $P < .001$ $_{\text{for group} \times \text{month}}$ interaction) (Table 3).

Inter-Group Comparisons in Change of Blood Pressure Over 1-year Follow-up

The model-based estimates of mean differences of SBP and DBP between cinacalcet group versus surgery group and cinacalcet group versus calcitriol group, are shown in Figure 3. Treatment using cinacalcet was associated with a significant increase in SBP and DBP compared with surgery at the 3rd ($P_{SBP} < .05$, $P_{DBP} < .05$), 6th ($P_{SBP} < .05$, $P_{DBP} < .05$), and 12th ($P_{SBP} < .05$, $P_{DBP} < .001$) month, and a significant increase in DBP compared with calcitriol at the 12th month ($P < .05$). However, no difference was observed in SBP between cinacalcet and calcitriol groups over the one-year follow up (Figure 3).

Inter-Group and Intra-Group Comparisons of Serum Renin, Angiotensin 1 and 2, Aldosterone, Endothelin and Ultrasonography

Serum levels of renin, angiotensin 1 and 2, aldosterone, and endothelin were measured in available serum samples of a number of patients both at baseline and the 12th month after treatment (Tables 4 and 5). Based on the available measurements, serum levels of angiotensin I and II were higher in surgery group after 1 year follow up, which may be associated with the reduced blood pressure. There were no differences in the serum levels of aldosterone, renin and endothelin among the three groups at baseline and at 12th month after the treatment (Table 4). Intra-group comparison showed that serum levels of renin and angiotensin I decreased significantly in the calcitriol group and serum angiotensin I increased significantly at 12th month in surgery group (Table 5). The result of the cardiac ultrasonography showed that there was no significant change of LVIDd, IVSd, LVPWd, LVEF in the three groups over time, except that LVPWd was lower in cinacalcet group at baseline (Table 4).

DISCUSSION

Secondary hyperparathyroidism is commonly

Table 3. Repeated Measures Analysis of Changes in Systolic Blood Pressure and Diastolic Blood Pressure from Baseline to the 1st, the 3rd, the 6th, and the 12th Month After Treatment

	Surgery					**$P^{§}$ Value for Effects in MIXED**
	1mo	**3mo**	**6mo**	**12mo**	**$P^{‡}$**	**< .05 FOR group × month interaction**
	-5.18 (-12.79 to 2.43)	-10.88 (-18.57 to -3.19)	-12.50 (-19.95 to -5.05)	-12.16 (-19.70 to -4.62)	< .05	
	Cinacalcet					
Change of SBP†	**1mo**	**3mo**	**6mo**	**12mo**	**$P^{‡}$**	
	-1.51 (-9.40 to 6.38)	4.50 (-3.31 to 12.31)	4.98 (-2.80 to 12.76)	7.76 (-0.19 to 15.71)	> .05	
	Calcitriol					
	1mo	**3mo**	**6mo**	**12mo**	**$P^{‡}$**	
	1.88 (-3.30 to 7.07)	-0.05 (-5.16 to 5.06)	1.90 (-3.24 to 7.03)	4.00 (-1.20 to 9.15)	> .05	
	Surgery					**$P^{§}$ Value for Effects in MIXED**
	1mo	**3mo**	**6mo**	**12mo**	**$P^{‡}$**	**<0.001 FOR group× month interaction**
	-4.18 (-7.98 to- 0.39)	-6.39 (-10.22 to -2.56)	-7.30 (-11.01 to -3.59)	-6.82 (-10.58 to -3.06)	< .001	
	Cinacalcet					
Change of DBP†	**1mo**	**3mo**	**6mo**	**12mo**	**$P^{‡}$**	
	-1.43 (-5.34 to 2.49)	2.14 (-1.73 to 6.02)	2.38 (-1.48 to 6.23)	6.03 (2.08 to 9.98)	< .05	
	Calcitriol					
	1mo	**3mo**	**6mo**	**12mo**	**$P^{‡}$**	
	1.40 (-1.18 to 3.98)	-0.18 (-2.71 to 2.36)	0.70 (-1.85 to 3.25)	0.08 (-2.49 to 2.65)	> .05	

†Values are adjusted least-squares means and 95% CI is estimated from the mixed effect models. Models include group (treatment), month (visit), group × month interaction, age, gender, weight, vintage, delta averaged ultrafiltration at the visit month, spKt/V at the visit month, medication usage for antihypertension, and log transformed PTH at the visit month.
‡Test of significance of month (visit) differences by group (treatment) from the mixed effect models.
§Test of significance of group × month interaction for the overall effect from the mixed effect models.

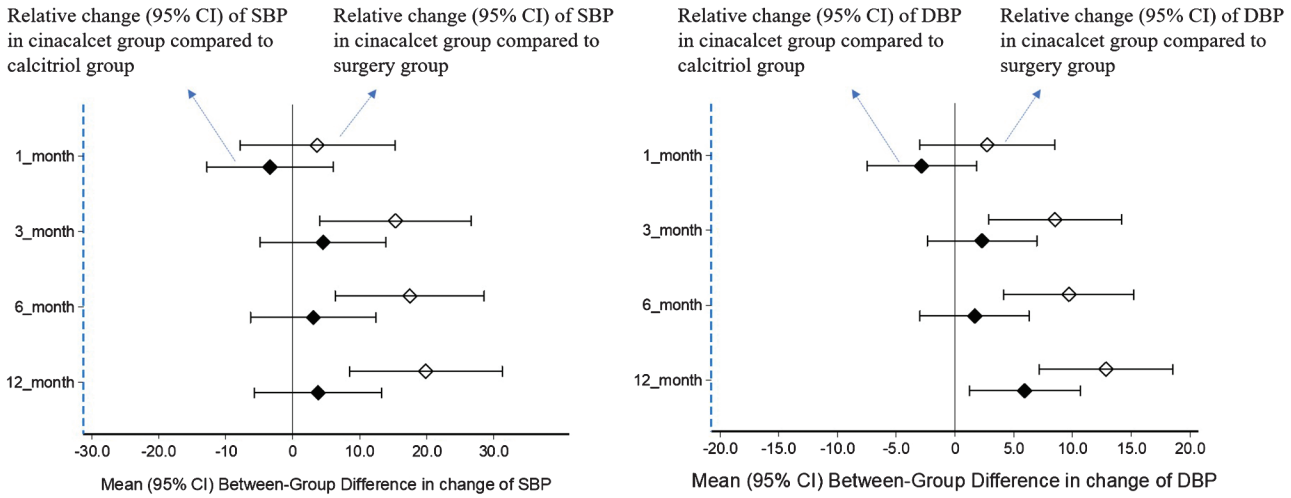

Figure 3. Differences in changes of blood pressure in cinacalcet group vs. surgery group, and in cinacalcet group vs calcitriol group over one-year follow-up. Points and bars represent mean estimates and 95% CIs of differences in changes of blood pressure (delta SBP/DBP) in cinacalcet group vs surgery group (open rhombus), and in cinacalcet group vs calcitriol group (closed rhombus) over 1-year follow-up from the mixed effect models. To be specific, the differences in change of SBP between cinacalcet group vs surgery group = delta SBP in cinacalcet group - delta SBP in surgery group. (Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure).

diagnosed in ESKD patients owing to their dysregulated bone and mineral metabolism. Population-based observational studies have shown a close association between severely elevated PTH levels and poor patient outcomes in ESKD patients.[1,2] Currently, conventional therapy for SHPT involves treatment with agonists of Vitamin D receptors, which in turn has been found to be associated with adverse events such as hypercalcemia and hyperphosphatemia, in ESKD patients.[23,24] Cinacalcet is a calcimimetic agent that inhibits PTH secretion from parathyroid cells

Table 4. Baseline and One-year Characteristics of 69 Hemodialysis Patients Stratified by Therapies for Secondary Hyperparathyroidism

Visit Time	Characteristics	Surgery (n = 22)	Cinacalcet (n = 14)	Calcitriol (n = 33)	*P*†
Baseline	Angiotensin I, μg/L	1.60 ± 1.30 (18‡)	1.20 ± 0.86 (8‡)	1.58 ± 1.14 (27‡)	> .05
1-year	Angiotensin I, μg/L	2.27 ± 1.88 (21)	1.48 ± 1.26 (11)	1.32 ± 1.08 (30)	< .05
Baseline	Angiotensin II	94.1 ± 59.0 (18)	96.0 ± 82.8 (8)	75.7 ± 28.1 (27)	> .05
1-year	Angiotensin II	99.0 ± 56.2 (21)	81.0 ± 24.2 (11)	72.4 ± 20.0 (30)	< .05
Baseline	Aldosterone, ng/L	564.7 ± 652.3 (17)	193.2 ± 71.3 (7)	290.1 ± 398.9 (21)	> .05
1-year	Aldosterone, ng/L	669.0 ± 599.9 (19)	297.5 ± 243.3 (11)	351.2 ± 427.8 (28)	> .05
Baseline	Renin, μg/L/h	2.19 ± 0.91 (18)	1.32 ± 0.80 (8)	2.17 ± 1.05 (27)	> .05
1-year	Renin, μg/L/h	2.18 ± 1.25 (21)	1.78 ± 1.02 (11)	1.62 ± 0.85 (30)	> .05
Baseline	Endothelin, pg/mL	128.4 ± 29.2 (18)	109.2 ± 28.6 (8)	134.1 ± 26.0 (27)	> .05
1-year	Endothelin, pg/mL	113.0 ± 34.3 (21)	108.2 ± 30.4 (11)	118.1 ± 30.1 (30)	> .05
Baseline	LVIDd, cm	48.0 ± 5.0 (20)	44.8 ± 3.7 (4)	50.6 ± 5.9 (14)	> .05
1-year	LVIDd, cm	47.6 ± 3.0 (11)	48.8 ± 9.1 (6)	49.0 ± 4.2(20)	> .05
Baseline	IVSd, cm	11.5 ± 3.1 (20)	9.5 ± 0.6 (4)	12.2 ± 2.9 (14)	> .05
1-year	IVSd, cm	11.1 ± 2.2 (11)	11.5 ± 3.0 (6)	11.7 ± 3.2 (20)	> .05
Baseline	LVPWd, cm	10.5 ± 1.7 (20)	8.3 ± 0.5 (4)	10.8 ± 1.8 (14)	< .05
1-year	LVPWd, cm	10.3 ± 1.8 (11)	10.3 ± 2.2 (6)	10.3 ± 2.1 (20)	> .05
Baseline	LVEF, %	67.0 ± 5.1 (20)	62.5 ± 1.3 (4)	64.9 ± 10.8 (14)	> .05
1-year	LVEF, %	69.4 ± 4.4 (11)	61.7 ± 14.1 (6)	64.8 ± 5.3 (20)	> .05

Note: Values are expressed as mean ± SD.
Abbreviations: LVIDd, left ventricular internal diameter at the end-diastole; IVSd, intraventricular septal thickness at the end diastole; LVPWd, left ventricular posterior wall thickness at end-diastole, LVEF, Left Ventricular Ejection Fractions.
†*P* values for comparisons among three groups.
‡Numbers in the parentheses are available patients' number with the data for each characteristic.

Table 5. Paired Baseline and One-year Characteristics of 69 Hemodialysis Patients Stratified by Therapies for Secondary Hyperparathyroidism

Visit Time	Characteristics	Surgery (n = 22)	Cinacalcet (n = 14)	Calcitriol (n = 33)
Baseline	Angiotensin I, μg/L	1.61 ± 1.30 (18‡)	1.23 ± 0.92 (7‡)	1.58 ± 1.14 (27‡)
1-year	Angiotensin I, μg/L	2.42 ± 1.99 (18)	1.09 ± 0.60 (7)	1.36 ± 1.12 (27)
	P†	< .05	> .05	< .05
Baseline	Angiotensin II	94.1 ± 59.0 (18)	100.4 ± 88.4 (7)	75.7 ± 28.1 (27)
1-year	Angiotensin II	102.4 ± 60.2 (18)	82.0 ± 23.1 (7)	73.4 ± 20.9 (27)
	P†	> .05	> .05	> .05
Baseline	Aldosterone, ng/L	564.8 ± 652.3 (17)	198.6 ± 76.5 (6)	287.7 ± 409.2(20)
1-year	Aldosterone, ng/L	730.4 ± 605.6 (17)	247.4 ± 108.7 (6)	295.5 ± 360.3(20)
	P†	> .05	> .05	> .05
Baseline	Renin, μg/L/h	2.19 ± 0.91 (18)	1.36 ± 0.85 (7)	2.17 ± 1.05 (27)
1-year	Renin, μg/L/h	2.23 ± 1.31 (18)	1.58 ± 0.72 (7)	1.66 ± 0.88 (27)
	P†	> .05	> .05	< .05
Baseline	Endothelin, pg/mL	128.4 ± 29.2 (18)	108.5 ± 30.8 (7)	134.1 ± 26.0 (27)
1-year	Endothelin, pg/mL	118.1 ± 33.7 (18)	113.8 ± 27.9 (7)	119.5 ± 31.3 (27)
	P†	> .05	> .05	> .05

Note: Values are expressed as mean ± SD. Abbreviations: LVIDd, left ventricular internal diameter of end-diastole; IVSd, intraventricular septal thickness at end-diastole; LVPWd, left ventricular posterior wall thickness at end-diastole, LVEF, Left Ventricular Ejection Fractions.
†*P* values for comparisons within each group at two different visits.
‡Numbers in the parentheses are available patients' number with the data for each characteristic at both baseline and one-year later.

by modulating the activity of the calcium-sensing receptors. Cinacalcet therapy has been associated with significantly decreased serum levels of PTH, calcium, and inorganic phosphorus, thereby reducing the risks of vascular calcification and its associated mortality.[25,26] Currently, cinacalcet is routinely used to treat SHPT in uremic patients undergoing hemodialysis. However, KDIGO guidelines recommended parathyroidectomy for patients with severe SHPT who have failed to respond to any of the recommended treatments. Notably, parathyroidectomy has reportedly been shown to improve long-term survival outcomes in SHPT patients.[27-29] Given that severe increase in serum PTH can induce arterial calcification and associated changes in blood pressure and cardiac complications significantly predispose the patients with SHPT to death, we investigated the effects of various treatments of SHPT in restoring systemic arterial blood pressure and subsequently explored the underlying mechanisms of changes in blood pressure. We found variable degrees of changes in SBP and DBP levels between different treatment modalities of SHPT. Interestingly, SBP and DBP were drastically decreased following parathyroidectomy, while DBP was significantly increased in those receiving cinacalcet. However, no significant changes in blood pressure were found by administration of calcitriol. Thus, our findings provided promising clues in choosing appropriate therapy in SHPT patients considering the blood pressurestatus. This needs further studies specially to clarify the cinacalcet-mediated blood pressure regulation.

The levels of serum PTH and alkaline phosphatase in the were higher parathyroidectomy and cinacalcet- treated groups than the levels in calcitriol- treated group at baseline, most probably because of the therapeutic decision choice was based upon severity of the disease. At the one-year follow-up, the parathyroidectomy group exhibited significantly decreased serum PTH, ALP, calcium, and phosphorus levels, while cinacalcet treatment only could reduce serum PTH and ALP levels without any significant changes in other etiological factors, but calcitriol treated patients failed to show improvement in any of these outcome parameters, and these findings were consistent with previously reported findings.[30, 31]

Moreover, we found that both SBP and DBP were significantly reduced in the parathyroidectomy group over the 1 year follow up. Notably, this blood pressure-lowering effect of parathyroidectomy has also been demonstrated in patients with primary HPT, SHPT in patients under hemodialysis, and also in the renal transplant recipients.[10,32-,34] Furthermore, it has also been shown that parathyroidectomy can reduce intradialytic hypotension in SHPT patients under MHD.[35] Vascular calcification and arterial stiffness may be considered as major contributors

to hypertension in these subset of SHPT patients.[36] Importantly, how the elevated levels of serum PTH directly modulate the RAAS and/or related contributing factors, has not been explored in details to date.

In this study, comparative analysis of various treatment outcomes for SHPT at one-year follow-up revealed that cinacalcet had the most significant impact on DBP increased in comparison with both parathyroidectomy and calcitriol therapies. Recent studies have shown that successful surgical subtotal parathyroidectomy in combination with cinacalcet therapy, significantly decreases the high blood pressure.[8,9,11,37] However, our findings supported the results of the previous animal studies, in which MAP increased following the CaR activation.[13,14] This might be attributed to the differences in the baseline blood pressure among the three groups in our study. Cinacalcet group exhibited lower baseline SBP and DBP compared to other two treatment groups and especially the level of DBP was significantly lower than that of surgery group and the calcitriol group. We thus concluded that in contrast to patients with normal or high blood pressure, cinacalcet treatment in MHD patients with low blood pressure might increase blood pressure, especially DBP.

To explore the underlying mechanism, serum levels of renin, angiotensin I and II, aldosterone, and endothelin were tested at the one-year follow-up. There were no differences in the levels of these serum parameters between the three groups before treatment. However, levels of angiotensin I and II increased at the 12th month in the surgery group, compared with that of other two groups, possibly because of the low blood pressure 12 months after surgery. In addition, the serum levels of renin and angiotensin I were significantly lower in the calcitriol group at the 12th month compared with the baseline. These results were consistent with the findings in several recent studies, suggesting that calcitriol could reduce the angiotensin level by modulating the tubular level of ACE.[38-40] Interestingly, there were no significant changes in the serum levels of angiotensin I and II, aldosterone, and endothelin following the cinacalcet treatment, indicating that the effects of cinacalcet on the blood pressure were not related to the change of RAAS regulation. Further, the cardiac ultrasonography showed that there were no significant differences in terms of LVIDd, IVSd, LVPWd, LVEF in these three groups one year after treatment, except that LVPWd was lower in the cinacalcet group at baseline, suggesting that the changes of blood pressure had no relationship with the cardiac function. Further research is required to elucidate underlying mechanisms.

There are several limitations in our study. First, we enrolled only a small number of participants in a single dialysis center. Second, this was a retrospective cohort study, in which SHPT therapy options were not assigned randomly and some of the baseline characteristics of patients differed among three groups. . However, we tried to adjust these parameters during our analysis of blood pressure modulation. Third, the effects of the SHPT treatments on serum levels of RAAS, endothelin, and cardiac ultrasonography parameters were analyzed based on available serum samples only, which might cause in selection bias. Finally, we had no information on the other prescribed medications for the enrolled SHPT patients.

CONCLUSION

This study demonstrated that parathyroidectomy and cinacalcet are more effective in reducing PTH than calcitriol in in patients with severe SHPT under MHD hemodialysis. Parathyroidectomy was followed by the decreased blood pressure, while diastolic blood pressure in cinacalcet group had an increasing trend over one year of follow-up. Subsequent mechanistic studies showed that the change of blood pressure was not associated with RAAS regulation or cardiac function.

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AUTHORS' CONTRIBUTIONS

Conceptualization: Zhang M, Wang M; Methodology: Wang M, Wen D, Zhang M, Chen J; Formal analysis and investigation: Wang M, Zhang M; Writing-original draft preparation: Wang M, Zhang M; Writing-review and editing: Wang M, Wen D, Zhang W, Chen W, Tao Y, Fan C, Huang B, Chen J, Wang H, Zhang M; Funding acquisition: Wang M, Zhang M; Resources: Wang M, Zhang M; Supervision: Zhang M, Chen J. All authors

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DECLARATION OF INTEREST STATEMENT

The authors declare that they have no relevant financial interests.

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