Parathyroidectomy Improves Blood Pressure Control: A Longitudinal Study of Patients on Maintenance Hemodialysis with Secondary Hyperparathyroidism

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Abstract

BACKGROUND. Secondary hyperparathyroidism (SHPT) and its associated complications, such as hypertension, are common sequelae of end stage kidney disease (ESKD). We aimed to evaluate the post-parathyroidectomy (PTX) effects on blood pressure (BP) (including predialysis and intradialytic BP), as well as determine the predictive factors involved in BP reduction post PTX.

METHODS. Between 2002 and 2007, 17 hemodialysis patients who underwent PTX for SHPT were evaluated. Laboratory values, dry body weight (DBW) and predialysis and intradialytic BP at 6 months and 1 month prior to surgery as well as 1, 6 and 12 months postoperatively were evaluated. Factors affecting the decline in BP were also studied.

RESULTS. The serum levels of calcium, serum phosphorus and intact parathyroid hormone significantly decreased following PTX and remained decreased up until 12 months postoperatively. There was no significant difference in predialysis and intradialytic BP in the 6 months prior to surgery. Compared to both systolic BP (SBP) and diastolic BP (DBP) (151.8 ± 22.7 mmHg and 80.7 ± 9.0 mmHg) at 1 month prior to PTX, predialysis BP decreased significantly at 6 months postoperatively (125.8 ± 19.0 mmHg; P < 0.001 and 73.3 ± 8.0 mmHg; P = 0.004), and remained decreased up until 12 months postoperatively (125.2 ± 19.0 mmHg; P < 0.001 and 73.3 ± 6.8 mmHg; P = 0.006). Similar results were found for intradialytic BP. DBW (55.9 ± 8.9 kg) decreased significantly (P = 0.011) following PTX but increased over time and showed a significant difference at 12 months postoperatively (57.3 ± 8.5 kg; P = 0.007). In addition, predialysis diastolic BP was the only predictor of the hypotensive effect of PTX.

CONCLUSION. A decline in BP, including predialysis and intradialytic BP, was noted in hemodialysis patients with SHPT after PTX. Therefore, intensified BP control could be achieved by PTX to prevent complicating hypertension. (Acta Nephrologica 2011; 25: 5-11)

KEY WORDS: secondary hyperparathyroidism, parathyroidectomy, blood pressure

Introduction

The pathogenesis of hypertension in hemodialysis patients is multifactorial. It includes the following: sodium and water retention as a result of the impaired excretory capacity of the kidneys, excessively increased activity of the renin-aldosterone system and sympathetic nervous system, increased level of the vasoconstrictor endothelin-1 and accumulation of endogenous inhibitors of nitrite oxide (NO) synthesis (1, 2). Another important factor in the development of hypertension might relate to secondary hyperparathyroidism (SHPT). Parathyroid hormone (PTH) can cause hypertension by stimulating activity of the renin-aldosterone system, increased sympathetic activity or increased artery wall stiffness (1, 3). It has been theorized the vascular stiffness in...
these hemodialysis patients was caused by vascular calcification, which can reduce vascular compliance, and, as a result, systolic blood pressure (BP) rises, pulse pressure widens, and pulse wave velocity increases (4-7). The use of calcimimetic agents has been proven to attenuate progression of vascular calcification, as does parathyroidectomy (PTX) (8). These effects improve hypertension, although the effect on high blood pressure has not been proven in large clinical trials (9, 10). The prevalence of SHPT and hypertension are high and these two factors play an important role in increasing cardiovascular mortality in hemodialysis patients, thus warranting suitable measures to vigorously control hyperparathyroidism (11).

Some studies report BP reduction is observed after PTX, especially in the middle term (about 6 to 9 months postoperatively) but other research fails to corroborate this finding. In addition, most research to date has studied the alteration of predialysis BP after PTX but not the changes in intradialytic BP (12-14).

We aimed to study patients who underwent PTX, and analyze both their predialysis BP as well as their intradialytic BP before and after PTX. Factors predictive of a decline in BP are also evaluated to study the hemodynamic changes following PTX, since identification of such factors may improve the clinical outcome in patients with SHPT comitant with severe hypertension.

Methods

Patients

Between 2002 and 2007, an estimated 210 patients received regular hemodialysis at the hemodialysis center of Changhua Christian Medical Center. A total of 75 patients had severe SHPT with elevated parathyroid hormone (PTH) > 800 pg/mL. Among them, 24 underwent PTX and 17 of those patients (with complete medical records) were enrolled as study subjects. The subjects included 6 men and 11 women with a mean age of 56.9 ± 9.4 years. Their mean hemodialysis duration was 102.6 ± 73.9 months before PTX. The etiology of their renal failure included chronic glomerulonephritis in 7 patients, hypertensive nephrosclerosis in 3, hereditary nephritis in 1, and unknown in 6. They underwent regular hemodialysis for about 4 to 5 hours, 3 times a week using dialysis membranes that were not reused.

Preoperatively, all patients were clinically symptomatic with joint pain, skin itchiness, muscle weakness, irritability, or persistent hypercalcemia, preoperatively. Thirteen of the 17 patients had hypertension before PTX (mean predialysis systolic BP above 140 mmHg). Among the 17 patients, 15 patients underwent total parathyroidectomy and autotransplantation (PTX+AT) of the parathyroid tissue into the forearm muscle, 1 patient underwent a repeat operation for recurrence of parathyroid hyperplasia in the neck, and in 1 patient the type of surgical procedure remained unknown. Postoperatively, the patients were supplemented with calcium carbonate, and a high dialysate calcium (Ca) concentration (3.5 meq/L) was used during hemodialysis.

Laboratory Investigation and BP Measurements

The dialysis records of all study subjects were reviewed. Data were obtained for each patient six months prior to PTX (pre-M6), the month prior to PTX (pre-M1), the month after PTX (post-M1), 6 months after PTX (post-M6) and 12 months after PTX (post-M12). This data included serum albumin (Alb) (bromocresol green), total serum calcium, serum phosphorus (P), Ca × P product, alkaline phosphatase (ALP), intact PTH, KT/V, predialysis BP, intradialytic BP, and dry body weight (DBW); the latter was obtained using standard automatic BP machines (Welch Allyn, 52000, Armstrong Medical, Lincolnshire, IL, USA) for BP measurement for each patient while sitting down. For predialysis BP and DBW, we calculated the mean of the values from the twelve dialysis sessions (1 month) at each time course of the study. For intradialytic BP, we calculated the mean values of the lowest systolic and diastolic BP in the hemodialysis course from the twelve dialysis sessions. Measurement of the lowest BP aimed to examine the maximum hypotensive effect of PTX during the hemodialysis sessions. Each BP measurement included the mean systolic BP and mean diastolic BP. Besides, the dialysate Ca concentration values, mean dialysate sodium (Na) and numbers of anti-hypertensive agents at each time course were also recorded. All patients were also educated to withhold anti-hypertensive agents the day before the dialysis session.

In addition, the nurses would reset the DBW according to the duty nephrologists’ recommendations. The patient’s nephrologist estimated the dry weight based on the finding of the physical examination, plain chest x-ray and blood pressure status.

To identify factors that might predict the BP lowering effect of PTX, the patients were divided into two groups according to a change in predialysis BP of more than 10% between pre-M1 and post-M6. There was a clear distinction between these two groups that was responsible for BP reduction. Group A consisted of 10 patients defined by a change in BP of greater than 10% (range from 18.77 to 41.23%), while group B consisted of 7 patients defined by a change in BP of less than 10% (range from -5.96 to 9.43%). The factors studied included dialysis age, pre-PTX predialysis systolic and diastolic BP, pre-PTX serum calcium, pre-PTX
Table 1. Serial changes in the laboratory values, KT/V value, dialysate calcium concentration value and dialysate sodium concentration value in the preoperative and postoperative observation periods (mean ±SD)

<table>
<thead>
<tr>
<th></th>
<th>Normal Range</th>
<th>Pre-PTX</th>
<th>Post-PTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-PTH, pg/mL (n = 14)</td>
<td>16-87</td>
<td>1249.0 ± 368.2*</td>
<td>47.1 ±62.1*</td>
</tr>
<tr>
<td>Total Ca, mg/dL (n = 17)</td>
<td>8.7-10</td>
<td>10.1 ±0.8</td>
<td>10.1 ±1.0</td>
</tr>
<tr>
<td>P, mg/dL (n = 17)</td>
<td>2.5-4.5</td>
<td>6.2 ±0.8</td>
<td>6.4 ±1.3</td>
</tr>
<tr>
<td>Ca × P, mg²/dL² (n = 17)</td>
<td>62.3 ±10.9</td>
<td>64.0 ±12.3</td>
<td>19.9 ±5.8*</td>
</tr>
<tr>
<td>Albumin, g/dL (n = 17)</td>
<td>3.5-5.5</td>
<td>4.0 ±0.4</td>
<td>4.0 ±0.3</td>
</tr>
<tr>
<td>Dialysate Na, meq/L (n = 17)</td>
<td>36-108</td>
<td>48.4 ±47.7*</td>
<td>196.7 ±76.4</td>
</tr>
<tr>
<td>KT/V (n = 13)</td>
<td>1.56 ±0.20</td>
<td>1.58 ±0.20</td>
<td>1.53 ±0.20</td>
</tr>
<tr>
<td>Dialysate Ca, meq/L (n = 17)</td>
<td>2.65 ±0.23*</td>
<td>2.52 ±0.12</td>
<td>3.44 ±0.24*</td>
</tr>
<tr>
<td>Dialysate Na, meq/L (n = 17)</td>
<td>139.56 ±1.86</td>
<td>139.89 ±1.60</td>
<td>139.96 ±1.62</td>
</tr>
<tr>
<td>Numbers of AHA</td>
<td>0.91 ±1.29</td>
<td>1.05 ±1.46</td>
<td>0.95 ±1.48</td>
</tr>
</tbody>
</table>

*P < 0.001, †P < 0.05 compared with the pre-PTX month 1 value, based on paired t-tests.

I-PTH: intact parathyroid hormone; Ca: calcium; P: phosphorus; Ca × P: calcium × phosphorus product; ALP: alkaline phosphatase; PTX: parathyroidectomy; Dialysate Ca: dialysate calcium concentration; Dialysate Na: dialysate sodium concentration; AHA: anti-hypertensive agents.

Statistics

The results were expressed as the mean ± standard deviation (SD) or standard error (SE). The laboratory values, KT/V value, dialysate Ca concentration value, dialysate Na concentration and numbers of anti-hypertensive agents post-PTX at each time course and pre-PTX (pre-M1) were compared with the paired t-tests. A statistical analysis comparing the predialysis BP, intradialytic BP and DBW at each time course was performed with the repeat measures one way ANOVA. The mean values of the subgroup analysis were compared with the independent sample t-tests. A P value of < 0.05 was considered to be significant. All calculations were performed using SPSS version 15.

Results

Effects of a Parathyroidectomy on Laboratory Values, KT/V, Dialysate Calcium Concentration and Dialysate Sodium Concentration

The intact PTH level showed a rapid decrease following PTX with a percentage fall of 97% compared to the starting value (1557.9 ± 333.7 to 47.1 ± 62.1 pg/mL). Similarly, the serum total calcium level rapidly decreased after PTX (10.1 ± 1.0 to 7.2 ± 1.1 mg/dL; P < 0.001), but substantially increased at post-M6 (7.9 ± 1.1 mg/dL) and post-M12 (8.0 ± 0.7 mg/dL) under vitamin D and calcium supplementation. Compared to serum total calcium, the trends in both serum phosphorus and Ca × P product were also the same. However, there was no significant change in the albumin levels and KT/V values throughout the study period. There was a significant change in the dialysate Ca and dialysate Na concentration at post-M12. Besides, there was a declining trend in the numbers of anti-hypertensive agents throughout the study period. (Table 1)

Effect of a Parathyroidectomy on Predialysis BP, Intradialytic BP and DBW

As shown in Table 2 and Fig. 1, there was no significant difference in predialysis BP and intradialytic BP between pre-M6 and pre-M1 (P = NS). However, there were significant decreases in predialysis BP and intradialytic BP at post-M12 for all patients (all P < 0.05).

Serial changes in predialysis BP are shown in Fig. 1A. The trends in both systolic BP and diastolic BP were similar. There was no difference among pre-M6 (149.8 ± 20.0/81.6 ± 8.2 mmHg), pre-M1 (151.8 ± 22.7/80.7 ± 9.0 mmHg) and post-M1 BP (147.8 ± 16.4/80.1 ± 6.1 mmHg). Compared to pre-M1, BP at post-M6 (125.8 ± 19.0/73.3 ± 8.0 mmHg; P < 0.001/P = 0.004) and post-M12 (125.2 ± 19.0/73.3 ± 6.8 mmHg; P < 0.001/P = 0.006) were significantly lower. However, there was no significant decrease between post-M6 and M12.

As shown in Fig. 1B, the trends in intradialytic systolic BP and diastolic BP were also the same. Co-
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pared to pre-M1 (125.9 ± 19.5/72.2 ± 10.0 mmHg), the post-M1 BP (137.4 ± 16.8/75.2 ± 7.2 mmHg) increased significantly (P < 0.001). At Post-M6, the systolic BP was significantly lower than the pre-M1 (P = 0.004) but not the diastolic BP. Post-M12 BP (104.0 ± 19.5/65.8 ± 9.9 mmHg) was lower, but insignificantly than post-M6. However, it was significantly lower than pre-M1 BP (P = 0.002/P = 0.033).

As shown in Fig. 2, there was no difference in DBW between pre-M6 and pre-M1. DBW had a contrary trend compared with predialysis and intradialytic BP. Compared to pre-M1 (55.9 ± 8.9 kg), the post-M1 DBW (55.6 ± 8.8 kg) decreased significantly (P = 0.011). However, DBW at post-M12 (57.3 ± 8.5 kg) was markedly higher than post-M6 (P < 0.001) and it was also significantly higher than pre-M1 DBW (P = 0.007).

Predictors of the BP Lowering Effect of Parathyroidectomy

Mean values of change in predialysis BP (systolic/diastolic) in group A and group B were 24.57/16.36%
PTX Lowers BP in HD Patients with SHPT

and 4.43/-2.87%, respectively. The diastolic BP in patients of group B even increased. As shown in Table 3, group A had significantly higher pre-PTX predialysis diastolic BP ($P = 0.005$), and slightly higher change in Intact PTH ($P = 0.072$) compared to group B.

**Discussion**

SHPT is an important complication of ESKD, which usually begins during the early stages of chronic kidney disease (CKD). Later, hyperphosphatemia becomes the predominant factor with worsening SHPT (15, 16). SHPT has been proven to be a contributing factor in extraskeletal calcification including vascular calcification, calciphylaxis, hypertension, erythropoietin resistance and cardiomyopathy and all of these events directly contribute to morbidity and mortality (15, 17)

In our study, we found predialysis and intradialytic BP improvement was observed after PTX was performed in hemodialysis patients with SHPT and hyperphosphatemia. To our knowledge, our findings are the first to report the effects of PTX on intradialytic BP. To show the BP lowering effect was related to PTX, we determined DBW, predialysis and intradialytic BP in the 6 months prior to PTX as the control data in this study. There was no significant difference in predialysis and intradialytic BP in the 6 month interval prior to surgery ($i.e.$, pre-M1 and pre-M6). This suggests BP did not fall during the pre-PTX study period and PTX had a profound hypotensive effect on these patients.

Ifudu et al. studied 19 hemodialysis patients and
compared predialysis BP, predialysis weight and the dose of antihypertensive medications before and after total PTX (12). Their results showed PTX failed to correct hypertension in patients on maintenance hemodialysis. The data supporting our findings have also been confirmed by other authors. Coen et al. reported 45 patients with SHPT on dialysis (13). A fall in blood pressure in the middle to long term (1-2 years) was statistically significant and an improvement in anemia was confirmed. Goldsmith et al. observed a fall in BP after 6-9 months following PTX in 21 patients on maintenance hemodialysis (18). Pizzarelli et al. also documented a fall in BP in 7 of 11 uremic patients from the 3rd quarter onwards (6-9 months) after PTX (14). In renal transplant patients presenting with persistent hypercalcemic hyperparathyroidism, subtotal PTX was also associated with a significant but transient decrease in systolic BP, diastolic BP and mean BP (19).

Based on the findings of Ifudu et al., PTX did not correct hypertension but was followed by increased mean predialysis weight (dry weight) over time after PTX (12). The authors did not have an explanation for the trend. It is unclear whether it resulted from the duty nephrologist resetting dry weight because of low predialysis BP. This might have obscured the hypotensive effect of PTX.

In contrast with other studies, our patients presented with a higher predialysis BP and this probably caused a wider range of BP reduction. In this study, there was a discordant trend between BP and DBW. This occurred because the nurses increased DBW in patients with lower predialysis BP and hypertensive episodes when hemodialysis was administered at a later period of the study. In some patients, the antihypertensive agents were even stopped. In addition, we also found intradialytic BP declined after PTX.

The role of SHPT in the development of early hypertension has been attributed to vascular calcification, which involves a complex process of increased osteogenic changes in vascular smooth muscle cells in the presence of elevated calcium and phosphate and loss of calcification inhibitors (4, 5). The subsequent vascular calcification has several adverse hemodynamic consequences that can result in cardiovascular events including LVH and altered coronary perfusion, particularly in ESKD patients (20, 21). Some authors have even demonstrated vascular calcification in ESKD patients is correlated with increased stiffness of large, elastic-type arteries like the aorta and common carotid artery, thereby inducing hypertension (22, 23).

Vascular calcification may play a role in pre-PTX hypertension, but its role post-PTX is unclear. In our study, a decline in BP did not immediately follow PTX but developed over a few months. Intradialysis diastolic BP took a longer time to decline, which was not observed until the 12th postoperative month. Besides, intradialytic BP even increased in the first postoperative month, most likely due to the effect of high dialysate Ca concentration (3.5 meq/L). It is unclear how to explain the decline in BP except as a consequence of PTX. Similar findings were also published by Pizzarelli and Goldsmith et al. (14, 18). The changes in serum calcium and intact PTH were immediate following PTX but the change in BP occurred later. These discordant changes are complex, perhaps involving a slower process of calcium efflux from the wall of the blood vessels, thereby increasing vascular compliance (particularly in larger arteries) (18). This hypothesis is supported by a relatively large reduction in systolic BP over diastolic BP post-PTX because systolic BP is significantly determined by conduit arterial wall stiffness (24). Thus, a possible regression of vascular calcification (a major cause contributing to vascular stiffness) may have occurred post-PTX.

In human clinical studies, Bleyer et al. reported subtotal PTX in suitable patients may prevent or reverse progression of vascular calcification (25). In theory, this may improve BP (20, 22). Improvement in blood pressure may cause a regression in left ventricular hypertrophy (LVH) and decreased mortality in patients with ESKD (10). However, it is unknown whether improved intradialytic BP is correlated with any beneficial or adverse outcomes. Recently published studies demonstrate the setting of more rigorous BP reduction led to increased intradialytic hypotension (26). As we know, intradialytic hypotension is the condition of an imbalance between the decrease in plasma volume during dialysis and the counter-regulatory cardiovascular hemodynamic and neuro-hormonal mechanism, and it has been shown mortality is increased in those hemodialysis patients prone to intradialytic hypotension (27). Further studies are required to determine the hypotensive effects of PTX on cardiovascular mortality in these hemodialysis patients.

In conclusion, in this analysis, a decline in BP...
including predialysis and intradialytic BP was observed in hemodialysis patients with SHPT after PTX. Therefore, intensified BP control could be achieved by PTX to prevent the development of complicating hypertension. However, these findings suggest further investigations be performed to clarify the long-term effects of PTX on cardiovascular morbidity and mortality among hemodialysis patients with SHPT.

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References