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Original Article

Utilization of parathyroidectomy for secondary hyperparathyroidism in end-stage renal disease

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Abstract

Background. The utilization of parathyroidectomy (PTX) to manage secondary hyperparathyroidism (SHPT) refractory to medical management (MTX) in end-stage renal disease (ESRD) in the era of calcimimetics is not well known.

Methods. Adult ESRD patients receiving dialysis between August 2007 and December 2011 at our institution with an intact parathyroid hormone (iPTH) level ≥ 88 pmol/L for 6 months associated with hypercalcemia and/or hyperphosphatemia for at least 50% of that period were included. Baseline characteristics and iPTH, calcium, phosphorus, calcium–phosphorus product and alkaline phosphatase (ALP) at baseline, 6 and 12 months were compared between the two groups (PTX versus MTX) using the χ^2 and paired t-tests.

Results. Of the total population of 687 patients, 80 (11.6%) satisfied KDOQI criteria for PTX, most of whom did not receive PTX (81.2%). At baseline, PTX patients had been on dialysis longer ($P = 0.001$), with higher iPTH ($P < 0.001$), calcium ($P = 0.008$) and ALP ($P = 0.001$) and were less likely to be African-American ($P = 0.007$). Complete follow-up data at 6 months were available on 75 patients (PTX = 15; MTX = 60). PTX had significantly greater reduction in iPTH (93 versus 23%) and ALP (68 versus 0%) compared with MTX. Changes from baseline in calcium, phosphate or calcium–phosphorus product levels and proportion of patients achieving KDOQI target values were not significant for either intervention. Findings were consistent at 12 months.

Conclusions. A significant proportion of ESRD patients who met indications for PTX did not receive it. Additional studies are needed to understand the barriers that prevent patients from receiving PTX, thereby resulting in underutilization.

Keywords: cinacalcet; ESRD; parathyroidectomy; secondary hyperparathyroidism

Introduction

Secondary hyperparathyroidism (SHPT) is a frequent complication of end-stage renal disease (ESRD) [1]. Numerous studies have demonstrated that high serum calcium, phosphorus, calcium–phosphorus product and intact parathyroid hormone (iPTH) levels in ESRD patients on dialysis are associated with an elevated incidence of bone disease and vascular calcification resulting in an increased all-cause and cardiovascular morbidity and mortality [1–4]. Surgical parathyroidectomy (PTX) is the definitive therapy to manage uncontrolled SHPT and is generally considered only when medical management (MTX) has failed. The indications for PTX, however, are not well defined. KDOQI recommends surgery in patients with severe hyperparathyroidism (persistent serum levels of iPTH >88 pmol/L) associated with hypercalcemia and/or hyperphosphatemia refractory to medical therapy. Pathologic bone fractures, bone pain, pruritus and vascular calcification in the setting of elevated iPTH levels are also considered strong indicators for surgery [5, 6]. With

the introduction of the oral calcimimetic cinacalcet in 2004, the role of PTX has become less clear. Many ESRD patients who would have undergone PTX are likely to continue on medical therapy with cinacalcet. Also, patients with uncontrolled SPHT who would have initially been referred for surgery are now first being given a trial with cinacalcet. We hypothesized that PTX was underutilized even though it may have better outcomes than MTX, in terms of controlling biochemical abnormalities as well as symptoms and possibly have a mortality benefit. In this study, we present the utilization rate of PTX at our institution and the comparative outcomes of patients treated with PTX and those patients who received only medical treatment despite being indicated for PTX.

Materials and methods

Participants

After obtaining approval from the institutional review board, we retrospectively reviewed the medical records of

all adult patients receiving chronic renal replacement therapy at our institution from 1 August 2007 through 31 December 2011. We initially identified all patients that received peritoneal dialysis or hemodialysis. Of these patients, those found to have persistently elevated levels of iPTH (>88 pmol/L for 6 months) associated with hyper-calcemia (>2.63 mmol/L) and/or hyperphosphatemia (>1.77 mmol/L) for at least 50% of that time period were considered eligible for PTX. Patients with complete follow-up data at 6 and 12 months were included for analysis. Note: In 2009, Kidney Disease: Improving Global Out-comes (KDIGO) proposed wider range for serum iPTH (two to nine times the upper reference limit for the assay) and calcium (2.12–2.75 mmol/L), while reducing phosphorus levels toward the reference range (0.77–1.52 mmol/L) [7]. However, since most of our patients received care before these guidelines were widely accepted, we chose to use the KDOQI criteria for the purposes of this study.

Data collection

Data such as demographics, medical comorbidities, medications and biochemistry [iPTH, calcium, phos-phorus, calcium–phosphorus product, albumin and alka-line phosphatase (ALP)] were collected at the time of inclusion. Accurate medication information was not avail-able for six MTX patients. Biochemistry, medications and date of last follow-up or death were recorded at 6 and 12 months thereafter. In addition for patients who un-derwent PTX, preoperative details such as symptoms of bone pain or pruritus, and post-operative resolution of symptoms were collected.

Outcome measures

The clinical effectiveness of PTX compared with contin-ued medical treatment was evaluated based on the control of iPTH (reference range = 1.2–10.8 pmol/L), total corrected calcium (reference range = 2.1–2.62 mmol/L), phosphorus (reference range = 0.80–1.62 mmol/L), calcium–phosphorus product (reference range = 1.1–3.6 $mmol^2/L^2$), albumin (reference range = 35–55 g/L) and ALP (reference range = 0.76–2.84 µkat/L) from the time of inclusion to follow-up at both 6 and 12 months. In addition, we com-pared the proportion of patients in each cohort attain-ing KDOQI targets for serum iPTH (16.5–33 pmol/L), phosphorus (1.13–1.77 mmol/L), total corrected calcium (2.1–2.37 mg/dL) and calcium–phosphorus product (Ca × P; <4.4 $mmol^2/L^2$) at 6 and 12 months.

Statistical analysis

Categorical variables were presented as counts and per-centages, and continuous variables as mean with stan-dard deviations. Categorical variables were compared using the χ^2 test and continuous variables were com-pared with the Student *t*-test for paired and unpaired samples within and between cohorts. Values of P < 0.05 were considered statistically significant for all tests. All analyses were performed with SPSS for Windows (version 19.0; SPSS, Chicago, IL).

Results

Of the initial population of 687 adult patients receiv-ing dialysis, 231 patients (33.6%) had elevated iPTH

(>88 pmol/L) at least once during their care, 117 (17%) of which had persistently elevated levels for at least 6 months. A total of 80 patients (11.6%) either met indi-cations for PTX or had undergone PTX. Seventy-five patients (MTX—60, PTX—15) and 61 patients (MTX—51, PTX—10) had adequate follow-up data available at 6 and 12 months, respectively. All patients were receiving medical therapy in the form of dietary phosphate restric-tion, calcium supplementation, phosphate binders and vitamin D sterols, and/or cinacalcet. The demographic characteristics of 75 patients who had follow-up available for at least 6 months are shown in Table 1. Patients who underwent PTX had been on dialysis significantly longer (mean 12 years) than those treated with MTX (mean 5.2 years) (P < 0.001). In addition, 47% of patients under-going PTX were African-American when compared with 72% of MTX patients (P = 0.05). PTX patients were also more likely to have received a kidney transplant in the past (53 versus 25%), although this difference did not reach statistical significance (P = 0.06). Moreover, PTX patients were also more likely to have a history of cancer (33%) compared with MTX patients (8%) (P = 0.023).

Table 1. Patient demographics and medication usage at inclusion[a]

	MTX cohort (n = 60)	PTX cohort (n = 15)	P-value
Male, n (%)	32 (53)	6 (40)	0.40
Ethnicity, n (%)			
Caucasian	1 (2)	2 (3)	
African American	43 (72)	7 (47)	**0.05**
Hispanic	7 (12)	5 (33)	
Other	9 (15)	1 (7)	
Age in years, mean (SD)	46.0 (15.8)	44.6 (11.9)	0.75
Comorbidities, n (%)			
Hypertension	54 (90)	13 (87)	0.66
Diabetes mellitus	14 (23)	4 (27)	0.75
Coronary artery disease	17 (28)	3 (20)	0.75
Myocardial infarction	3 (5)	2 (13)	0.26
Chronic heart failure	13 (22)	3 (20)	1.00
Cerebrovascular disease	6 (10)	3 (20)	0.37
Peripheral vascular disease	6 (10)	0 (0)	0.34
Dyslipidemia	7 (12)	2 (13)	1.00
Anemia	30 (50)	5 (33)	0.39
Cancer	5 (8)	5 (33)	**0.023**
History of fractures	2 (3)	1 (7)	0.49
Current smoker, n (%)	18 (30)	4 (27)	1.00
Time on dialysis in years, mean (SD)	5.2 (5.6)	12.0 (7.7)	**<0.001**
History of kidney transplant, n (%)[b]	15 (25)	8 (53)	0.06
Medications at inclusion, n (%)[b]			
Vitamin D sterols	39 (74)	4 (27)	**0.002**
Phosphate binders	29 (55)	11 (73)	0.24
Calcium acetate	5 (9)	1 (7)	1.0
Sevelamer	27 (51)	10 (67)	0.38
Lanthanum carbonate	2 (4)	0 (0)	1.0
Cinacalcet	15 (28)	11 (73)	**0.002**
Unknown	7 (13)	0 (0)	
Length of follow-up in years, mean (SD)	2.2 (1.0)	1.6 (1.0)	0.07
Current status, n (%)			
HD	27 (45)	8 (53)	
PD	6 (10)	2 (13)	
Functioning transplant	3 (5)	1 (7)	
Deceased	15 (25)	2 (13)	0.50
Not known	9 (15)	2 (13)	

[a]Bold values represent statistically significant results.
[b]Accurate medication information was not available for six patients in the MTX cohort, and these were excluded from the analysis regarding medication usage at inclusion.

Seventy-three percent ($n = 11$) of surgical patients were receiving cinacalcet at the time of inclusion compared with 28% ($n = 15$) of patients in the MTX cohort (P = 0.002). In contrast, 74% ($n = 39$) of MTX patients and 27% ($n = 4$) of PTX patients were using vitamin D sterols (P = 0.002). The two cohorts were otherwise similar in demographic composition, medical comorbidities and medication usage at inclusion. Follow-up averaged 2.2 (1.0) years for MTX patients and 1.6 (1.0) years for PTX patients. Twenty-five percent ($n = 15$) of MTX patients and 13% ($n = 2$) of PTX patients died during the study period for reasons unrelated to management for SHPT. There was no significant difference in mortality between the two cohorts (P = 0.5). These findings were consistent for patients with 12 months of follow-up.

Changes in iPTH

At inclusion, PTX patients had iPTH levels of 293.6 (±113.2) pmol/L compared with MTX patients, which had iPTH levels of 155.5 (±81.5) pmol/L. The surgical cohort of patients had significantly higher baseline iPTH levels than the MTX cohort (P < 0.001). Six months after intervention, PTX patients had significantly reduced iPTH levels of 21.5 (±37.1) pmol/L (P < 0.001). This decrease persisted for 12 months after intervention with PTX patients having significantly reduced iPTH levels of 11.8 (±24.2) pmol/L (P < 0.001). The mean percentage reduction was 93% at 6 months and >96% at 12 months. In comparison, MTX patients had decreased iPTH levels of 119 (±93.6) pmol/L at 6 months and 121.8 (±82.4) pmol/L at 12 months with a mean reduction from baseline of 30% at 6 months (P = 0.001) and 23% at 12 months (P = 0.006). Thus, patients in the PTX cohort had a more significant reduction from baseline compared with those in the MTX cohort (P < 0.001) (Table 2). Seventy-three percent ($n = 11$) of PTX patients attained KDOQI target values for iPTH (<33 pmol/L) compared with only 22% ($n = 13$) in the MTX cohort (P < 0.001) (Table 3). This difference was similar both at 6 and 12 months. Two surgical patients developed hypoparathyroidism 12 months following intervention. No MTX patients experienced hypoparathyroidism.

Changes in ALP

PTX patients had significantly higher ALP levels at inclusion compared with MTX patients, 6.16 (±3.64) µkat/L and 2.7 (±2.07) µkat/L, respectively (P < 0.001). ALP among PTX patients had decreased to 1.97 (±0.8) µkat/L at 6 and 1.6 (±0.92) µkat/L at 12 months, representing a reduction of 68% (P = 0.001) and 74%, respectively (P = 0.003). In contrast, MTX patients experienced a decrease in ALP to 2.43 (±1.9) µkat/L at 6 and 2.49 (±1.68) µkat/L at 12 months that was not statistically significant (P = 0.19 and 0.199, respectively). Overall, surgical patients had a more significant decline from baseline compared with MTX patients (P < 0.001) (Table 2).

Changes in calcium, phosphorus and calcium–phosphorus product

The two cohorts had similar calcium, phosphorus and calcium–phosphorus product values at inclusion. Among surgical patients, 40% ($n = 6$), 53% ($n = 8$) and 60% ($n = 9$) attained KDOQI target values for phosphorus, calcium and calcium–phosphorus product, respectively. In the MTX cohort, 23% ($n = 14$), 50% ($n = 30$) and 48% ($n = 29$) attained KDOQI target values for phosphorus, calcium and calcium–phosphorus product, respectively (Table 3). This proportion was maintained at 12 months. Changes from baseline in the calcium, phosphate or calcium–phosphorus product levels and proportions of patients achieving KDOQI target values were not statistically significant for either intervention at 6 or 12 months.

Changes in medications

Total daily and weekly doses at baseline, 6 and 12 months of calcium acetate, sevelamer, paracalcitol and cinacalcet are presented in Table 4. All patients who underwent PTX were off cinacalcet at 6 and 12 months. The total daily dose of cinacalcet for the MTX group increased from 69.2 mg/day at baseline to 79.3 mg/day at 12 months, but this change was not statistically significant (P = 0.17).

Table 2. Comparison of changes in bone profile at 6 months[a]

	MTX cohort ($n = 60$)	MTX cohort: significance of change, P-value	PTX cohort ($n = 15$)	PTX cohort: significance of change, P-value	PTX versus MTX: significance at baseline, P-value	PTX versus MTX: significance of change, P-value
Baseline serum iPTH (pmol/L)	155.5 (±81.5)	**0.001**	293.6 (±113.2)	**<0.001**	**<0.001**	**<0.001**
6-month serum iPTH (pmol/L)	119 (±93.6)		21.5 (±37.1)			
Baseline serum calcium (mmol/L)	2.17 (±0.19)	0.10	2.34 (±0.33)	0.12	**0.008**	0.33
6-month serum calcium (mmol/L)	2.22 (±0.24)		2.15 (±0.28)			
Baseline serum phosphorus (mmol/L)	2.23 (±0.42)	**0.032**	2.32 (±0.59)	0.12	0.48	0.73
6-month serum phosphorus (mmol/L)	2.09 (±0.51)		2.03 (±0.67)			
Baseline serum albumin (g/L)	37.1 (±4.7)	0.98	37.2 (±3.4)	0.95	0.96	0.95
6-month serum albumin (g/L)	37.2 (±5.2)		37.3 (±6.0)			
Baseline serum alkaline phosphatase (µkat/L)	2.7 (±2.07)	0.19	6.16 (±3.64)	**0.001**	**<0.001**	0.42
6-month serum alkaline phosphatase (µkat/L)	2.43 (±1.9)		1.97 (±0.8)			
Baseline Ca×P (mmol^2/L^2)	4.82 (±0.93)	0.18	5.45 (±1.5)	**0.043**	**0.043**	0.61
6-month Ca ×P (mmol^2/L^2)	4.6 (±1.07)		4.42 (±1.7)			

[a]Bold values represent statistically significant results.

Table 3. Attainment of KDOQI targets at baseline and 6 months[a]

	MTX cohort (*n* = 60)	PTX cohort (*n* = 15)	P-value
Serum iPTH: <33 pmol/L			
Baseline	0 (0%)	0 (0%)	1.00
At 6 months	13 (22%)	11 (73%)	**<0.001**
Serum phosphorus: 1.1–1.8 mmol/L			
Baseline	8 (13%)	3 (20%)	0.68
At 6 months	14 (23%)	6 (40%)	0.21
Serum calcium: 2.1–2.4 mmol/L			
Baseline	36 (60%)	5 (33%)	0.08
At 6 months	30 (50%)	8 (53%)	1.00
Calcium–phosphorus product: <4.4 mmol^2/L^2			
Baseline	23 (38%)	4 (27%)	0.55
At 6 months	29 (48%)	9 (60%)	0.57

[a]Bold values represent statistically significant results.

Recurrence following PTX

One patient underwent a repeat PTX 1 year later as iPTH, although substantially lower (>60%) continued to be high. None of the other patients experienced recurrence at 1 year. Longer-term recurrence could not be evaluated due to lack of adequate follow-up data in 8 of the remaining 14 patients.

Discussion

To improve the care of dialysis patients, the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) has recommended targets for serum iPTH (16.5–33 pmol/L), phosphorus (1.13–1.77 mmol/L), total corrected calcium (2.10–2.37 mmol/L) and calcium–phosphorus product (Ca × P; <4.4 mmol^2/L^2) [6]. Consistent control of biochemical markers within KDOQI recommended values strongly predicts survival [8, 9]; however, traditional treatment of SHPT with dietary phosphate restriction, phosphate binders, calcium supplementation and vitamin D sterols has been insufficient for achieving KDOQI targets [10, 11]. An increasing number of therapies are available that assist in achieving these targets, including calcium salts, calcitriol, alfacalcidol and more recently, active vitamin D analogs, cinacalcet hydrochloride and non-calcium/aluminum-based phosphate binders. However, the use of calcium salts and vitamin D sterols to achieve consistent control of biochemical markers within published targets may cause hypercalcemia and/or hyperphosphatemia, which are associated with cardiovascular and soft tissue calcification. This generally necessitates treatment interruption, potentially contributing to inadequate iPTH control and disease progression [12–14]. Calcium-free phosphate binders, such as sevelamer and lanthanum carbonate, decrease serum phosphate levels, but do not significantly control iPTH levels [15]. Calcimimetics have improved the medical treatment options for SHPT. These agents increase the sensitivity of the calcium-sensing receptor on parathyroid cells to extracellular calcium, thereby suppressing serum iPTH, calcium, phosphorus and calcium–phosphorus product levels [16, 17]. Cinacalcet is the only currently available calcimimetic. Therapy with cinacalcet has many physiologic and clinical advantages and multiple randomized, controlled trials and observational studies have shown that cinacalcet improves the likelihood of achieving KDOQI targets for dialysis patients and decreases fracture risk, cardiovascular hospitalization and the number of patients undergoing PTX [18–20].

Table 4. Comparison of changes in medication dosages at baseline, 6 and 12 months[a]

	MTX cohort (*n* = 60 and 51)	PTX cohort (*n* = 15 and 10)	P-value
Cinacalcet (mg/day)			
Baseline	69.2 (37.5)	67.5 (26.6)	0.87
At 6 months	67.5 (31.9)		
At 12 months	79.3 (41.8)		
Paracalcitol (mg/week)			
Baseline	18.6 (12.8)	25.1 (18.3)	0.20
At 6 months	24.6 (17.8)	22.6 (11.7)	0.60
At 12 months	21 (20.8)	19.9 (12.1)	0.79
Calcium acetate (mg/day)			
Baseline	4562.5 (1399.9)	3000.0 (1414.2)	**<0.001**
At 6 months	4450.0 (1571.45)	7000.0 (1414.2)	**<0.001**
At 12 months	4277.8 (1563.5)	5333.3 (3055.1)	0.06
Sevelamer (mg/day)			
Baseline	5515.4 (2928.6)	5640.0 (2266.3)	0.88
At 6 months	5322.6 (2738.7)	5000.0 (2674.3)	0.68
At 12 months	5577.8 (2889.9)	5800.0 (2449.5)	0.79

[a]Bold values represent statistically significant results.

However, the utility of PTX versus medical therapy remains debatable [21]. A retrospective analysis of United States Renal Database System (USRDS) data showed higher short-term but lower long-term mortality rates among dialysis patients undergoing PTX [22]. A recent observational study showed that PTX was superior to cinacalcet in controlling iPTH and ALP at 18 months from baseline [23]. Additionally, the data on long-term utility and outcomes of cinacalcet remain inconclusive [24, 25]. A recent analysis showed that cinacalcet therapy was only cost-effective if the anticipated stay on dialysis was <16 months. This would only include those with a high risk of mortality or those who could expect to receive a transplant quickly. PTX was found to be significantly more cost-effective for all other subgroups [26]. Finally, given its significant gastrointestinal adverse effects, its tolerability as well as patient compliance is questionable. In the recently published EVOLVE study [25], almost two-thirds of patients in the cinacalcet group discontinued active therapy, many of these due to adverse events or patients requests.

In this study, we found that one out of every six dialysis patients had persistently elevated levels of iPTH and a majority (68.3%) of these patients satisfied KDOQI criteria for PTX. Only a minority (12.8%) underwent surgery, while the others were continued on MTX despite being indicated for PTX. Of the patients on MTX who were eligible for cinacalcet therapy, only a few (28%) were prescribed the medication, highlighting the complexity of real-world practice implementations of published recommendations. Patients in the PTX group in general had relatively more severe disease (as suggested by the differences in serum calcium, ALP and iPTH levels). However, both groups met KDOQI criteria for consideration of PTX. In addition, nearly all patients in the MTX group continued to satisfy criteria for PTX at the end of 1 year of follow-up, a result of either inadequacy or failure of MTX. It is unclear why a significant proportion of patients did not receive PTX despite satisfying criteria. Patients who received PTX were on dialysis for a significantly longer period of time compared with those who received MTX. So the duration of SHPT could have been a deciding factor for referral. The racial distribution of the two groups was significantly different with the MTX group having a higher proportion of African-American patients

compared with the PTX group, suggesting the possibility of racial disparity. PTX patients were also more likely to have received a kidney transplant in the past, potentially implicating the ability to access resources and navigate the system. There were no significant differences in the comorbidities between the two groups. In our study, patients in both the PTX and MTX groups were on dialysis for significantly longer than 16 months. Therefore, PTX would have been more cost-effective for this patient cohort. It is possible that with the availability of cinacalcet patients who otherwise meet the criteria for PTX were not referred for surgery. Since the treating nephrologist is the primary source of referral, personal clinical bias may be one of the factors contributing to this underutilization. Data in the literature indicate that PTX can be associated with a high prevalence of low PTH values [27], which could be regarded as undesirable for hard clinical outcomes. Adynamic bone disease is a clear long-term risk, as PTX is irreversible and the PTH suppression resulting from the procedure non-dosable. Finally, a significant proportion of patients who might have been referred for PTX may have refused the intervention due to the potential risks associated with this surgery. Studies on the attitudes of ESRD patients toward PTX are lacking, therefore data on this disparity are limited.

The limitations of the study largely pertain to the small sample size and single-center experience. The small sample size precluded effective matching of the two groups, thereby resulting in significant and important differences in the baseline characteristics and potentially impacting results. Due to its retrospective design, measures of causation cannot be assessed.

In conclusion, our study shows that a significant proportion of ESRD patients who met the indications of PTX did not receive it. For reasons still unclear, there continues to be reluctance or lack of enthusiasm for the PTX procedure in actual practice. At our center, PTX was successful at achieving the intended biochemical goals as well as resolution of symptoms (bone pain) in the small number of patients who underwent the procedure. This study, though limited in nature, lays the groundwork for further large-scale, prospective studies to assess the utility of early PTX and better understand the barriers that prevent patients from receiving it in a timely fashion.

Conflict of interest statement. None declared.

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