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Improved Long-Term Survival of Dialysis Patients after Near-Total Parathyroidectomy

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Abstract

Background—Severe secondary hyperparathyroidism, which is associated with life-threatening complications, can develop in dialysis-dependent end-stage renal disease patients. The aim of this study was to compare short- and long-term mortality in dialysis patients who underwent near-total parathyroidectomy (NTPTX) and matched nonoperated controls.

Study Design—We identified 150 dialysis patients who underwent NTPTX (1993–2009) at our institution and compared them with 1,044 nonoperated control patients identified in the US Renal Data System registry, matched for age, sex, race, diabetes as cause of kidney failure, years on dialysis, and dialysis modality. Survival outcomes were estimated using multivariable Cox proportional hazards models with stratification on the matching sets, adjusted for cardiovascular comorbidities, smoking, inability to ambulate/transfer, and payor status.

Results—During a follow-up of a mean of 3.6 years (range 0.1 month to 16.4 years), NTPTX patients had a significant reduction in the long-term risk of all-cause death (hazard ratio = 0.68; 95% CI, 0.52–0.89; $p = 0.006$) compared with controls. Thirty-day mortality rates for NTPTX patients and controls were 246 vs 105 per 1,000 person-years ($p = 0.21$). In adjusted analyses, NTPTX patients had a 37% reduced risk of all-cause death and a 33% reduced risk of cardiovascular death compared with controls. A durable reduction in mean parathyroid hormone was observed after NTPTX; from $1,776 \pm 1,416.6$ pg/mL to 301 ± 285.7 pg/mL ($p < 0.0001$).

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Conclusions—In our center, NTPTX in dialysis patients was associated with a significant reduction in long-term risk of death compared with matched control patients, without a significantly increased short-term risk.

Secondary hyperparathyroidism (sHPT) is a known complication of advanced chronic kidney disease (CKD) and has been linked to increased mortality in dialysis populations.¹ In its extreme forms, this disease can cause severe bone fragility and uremic arteriopathy (previously known as calciphylaxis).^{2,3} The traditional approach to treatment of sHPT has included the use of binders to reduce serum phosphate concentration, vitamin D, and its analogs, and, more recently, calcimimetics. Despite the use of the best available medical therapies, sHPT can require surgical intervention to reduce serum parathyroid hormone (PTH) concentrations and limit end-organ damage to the bone and vasculature. The rate of parathyroidectomy (PTX) declined in the United States in the 10 years between 1988 and 1998, but increased after 1998, despite the availability of expanded medical therapies.⁴ Earlier survival analyses indicated an initial increase in mortality in dialysis patients (CKD stage 5D) after PTX, followed by a later recovery and improved survival compared with matched medically treated patients.⁴⁻⁶

At our institution, we have performed near-total parathyroidectomy (NTPTX), a variant of subtotal PTX, in the surgical treatment of dialysis patients for nearly 2 decades; accordingly we investigated the short-term and long-term survival of our patients after NTPTX. We identified comparable patients from the US Renal Data System (USRDS) database matched for age, sex, race, diabetes as the primary cause of end-stage renal disease diagnosis, dialysis vintage, starting date of dialysis, and dialysis treatment modality (hemodialysis and peritoneal dialysis) at the time of NTPTX. Our goal was to compare all-cause and cardiovascular mortality in patients who underwent NTPTX in a single referral center with that of CKD-stage 5D patients with similar characteristics who were receiving dialysis at multiple centers around the country and had no record of PTX.

Methods

Patient selection

This study was approved by the Institutional Review Board of Emory University. Emory University is a tertiary referral center and patients are referred from multiple outlying hospitals and clinics. The database of secondary hyperparathyroidism patients operated at Emory University between 1993 and 2009 includes 218 patients whose records were found in the USRDS. Of these, 50 were excluded because they had undergone renal transplantation, 2 had no record of modality of dialysis, and 16 patients were excluded because of a history of PTX. Patients submitted to NTPTX at our institution were included in this study if no record of PTX before NTPTX was found for the patient from the USRDS Hospitalization Standard Analysis Files (SAFs) since the start of dialysis and patients were undergoing either hemodialysis or peritoneal dialysis at the time of their NTPTX. The USRDS Hospitalization SAF includes PTX procedures covered by Medicare.

For each NTPTX patient, controls were individually matched for age (± 2 years), sex, race, diabetes as cause of end-stage renal disease, dialysis duration (vintage), year they started

dialysis (± 1 year), and dialysis modality (hemo- vs peritoneal dialysis). On the potential NTPTX date, matched controls were required to be alive, have no record of PTX from the USRDS Hospitalization SAFs since dialysis start, and receive the same dialysis modality (hemodialysis or peritoneal dialysis) as the NTPTX patient. The potential NTPTX date for a control was defined as the patient's dialysis start date plus the same time interval that lapsed between dialysis start date and surgery date for the patient in question. For example, for a patient who started dialysis on January 1, 2006 and underwent NTPTX on February 1, 2006, an acceptable control could have started dialysis on July 1, 2006 and his potential NTPTX date was then assumed to be August 1, 2006. Review of the USRDS registry for patients with these preselected matching characteristics yielded a maximum number of 7 nonoperated controls per each operated patient. The target number of 7 matched controls for each NTPTX patient was obtained for 148 patients. For 1 patient the match was 1:5 controls and for 1 patient the match was 1:3 controls. The total number of controls was therefore 1,044. One NTPTX patient and its multiple controls constituted a matching set.

For dialysis patients who underwent NTPTX, the USRDS Coordinating Center deidentified the data by assigning unique USRDS patient identifiers. Data for individual NTPTX patients were then linked at the USRDS Special Studies Center at Emory with information available in the USRDS SAFs 2010.

Patient demographic characteristics (ie, age, sex, and race), clinical characteristics, and dialysis start date were obtained from the 2010 USRDS SAFs. Intravenous vitamin D use was determined in 1998–2008 Medicare Part A outpatient claims files, using Healthcare Common Procedure Coding System codes J0635 and J0636 for calcitriol, J2500 and J2501 for paricalcitol, and J1270 for doxercalciferol. PTX procedure dates were identified by ICD-9-CM surgical procedure code 06.81 (total PTX) or 06.89 (other PTX). Mortality data were available through September 30, 2009. Cardiovascular causes of death were acute myocardial infarction, pericarditis, atherosclerotic heart disease, cardiomyopathy, cardiac arrhythmia, cardiac arrest, valvular heart disease, pulmonary edema, congestive heart failure, pulmonary embolus, cerebrovascular accident, ischemic brain damage/anoxic encephalopathy, non-gastrointestinal hemorrhage, and mesenteric infarction/ischemic bowel, determined by Centers for Medicare and Medicaid Services form CMS-2746 cause of death codes 23, 25–32, and 35–44.

NTPTX technique

The procedure of choice at our institution, NTPTX, is a variant of a subtotal PTX; during NTPTX a vascularized remnant of 1 parathyroid gland, which approximates the size of 2 normal parathyroid glands, is left in situ.⁷ All patients undergo bilateral neck exploration and all parathyroid glands are identified before resection. The viability of the remnant is ensured before resection of the other enlarged parathyroid glands, and the remnant is functional immediately after surgery. Size determination of the parathyroid gland remnant is done intra-operatively to confirm that the parathyroid remnant is no larger than 2 normal parathyroid glands (80 to 100 mg).⁸ Intraoperative PTH levels are obtained before and after resection of each enlarged parathyroid gland with the goal to attain a final intraoperative PTH ≈ 100 pg/mL.⁸ (Fig. 1).

Outcome measures

Outcome measures included mortality rates and all-cause and cardiovascular mortality estimated by Cox proportional hazards models. Study start date was the NTPTX date for a patient or the potential NTPTX date for a control. Survival time was censored by a renal transplantation or the study end date of September 30, 2009, whichever occurred earlier. In the case of cardiovascular mortality, death from other causes was treated as additional censoring.

Clinical assessment

Preoperative and postoperative clinical assessments were performed in our surgery clinic on all patients undergoing NTPTX. Demographics, intraoperative findings, complications, and follow-up laboratory parameters were maintained in an IRB-approved prospective database. For long-term follow-up of serum PTH, serum calcium, phosphorus, albumin, and vitamin D levels, the electronic medical record was queried. For each patient, postoperative PTH values were available from 6 months up to 13 years of follow-up. Hematocrit values were obtained from USRDS claims files.

Data analysis

Demographic and baseline clinical characteristics were summarized using means for continuous variables and percentages for categorical variables. Crude mortality rates were determined to provide a descriptive overview of postoperative all-cause mortality and cardiovascular mortality.

Laboratory values obtained before and after NTPTX for PTH, calcium, phosphorus, serum albumin, hematocrit, and vitamin D levels were compared using paired *t*-tests.

Kaplan-Meier estimators were used to describe the survival rates of the NTPTX patients and control patients, for both all-cause mortality and cardiovascular mortality. To compare these 2 groups of patients, the stratified log-rank test was used with stratification on the matching sets to control for the matching variables. The 2 groups also were compared with additional adjustment for other clinical covariates, as well as insurance status in a Cox proportional hazards model with stratification on the matching sets.

Results

Baseline characteristics

In the 2 patient cohorts, the following were the baseline characteristics used for matching patients and controls: mean age 42 years; approximately 47% men; 82% African American, 17% white, and 0.7% Asian; 22% had diabetes as the primary cause of renal failure, and 93% were receiving hemodialysis (7% peritoneal dialysis). Similar proportions of patients and controls used intravenous vitamin D in the preceding year (72.4% of patients, 75.5% of controls; $p = 0.45$). In addition, there was no statistically significant difference between patients and controls in history of hypertension, congestive heart failure, coronary artery disease, myocardial infarction, or atherosclerotic heart disease; history of peripheral vascular

disease, cardiac arrest, cardiac arrhythmias or other cardiac conditions; smoking status, or inability to ambulate/transfer (Table 1).

The average dialysis vintage was 7.2 ± 4.7 years. A diagnosis of uremic arteriopathy was present in 11 patients and none of the controls. Patients were more likely than controls to have ever had private insurance as a payor (13.3% vs 7.8%; $p = 0.02$) (Table 1), although these proportions were small in both groups.

Immediate biochemical effects of NTPTX

After NTPTX, there was a dramatic and durable reduction in PTH from a mean preoperative PTH of $1,770 \pm 1,416$ pg/mL to a mean postoperative PTH of 301 ± 285 pg/mL ($p < 0.0001$) during a mean follow-up of 2.8 years (range 0.3 to 13.8 years) (Table 2 and Fig. 1).

Significant decreases in serum calcium and serum phosphorus and increases in hematocrit and albumin were also observed in patients after NTPTX.

Main outcomes measures

Mean duration of follow-up was 4.1 ± 2.9 years (range 0.2 months to 13.8 years) for patients and 3.5 ± 2.8 years (range 0.1 months to 16.4 years) for controls. Overall mortality rates per 1,000 person-years were 107 (66/224,610) for patients vs 150 (556/1,353,428) for controls; cardiovascular mortality rates per 1,000 person-years were 47 (29/224,610) for patients and 78 (290/1,353,428) for controls. Three patients who underwent NTPTX died during the first 30 days postoperatively. The 30-day mortality from the day of surgery (patients) or equivalent (controls) per 1,000 person years was 246 (3/4,458) and 105 (9/31,152), respectively, which represented a nonsignificant increased risk of death (matching set-stratified log-rank test, $p = 0.21$). NTPTX patients showed better overall survival than controls (matching set-stratified log-rank test; $p = 0.006$, Fig. 2). Median survival times were 6.5 and 4.6 years for the patients and controls, respectively. The difference in cardiovascular mortality between the 2 groups was statistically significant also (matching set-stratified log-rank test; $p = 0.01$, Fig. 2).

Overall survival of NTPTX patients and controls was compared after adjustment for cardiovascular comorbidities, ambulatory status, smoking, and payor status, in addition to the matching variables, in a proportional hazards model. Although the sample was reduced for these analyses because covariate information is not available in the USRDS database for patients who started treatment before 1995, the difference in all-cause mortality remained statistically significant (hazard ratio = 0.63; 95% CI, 0.41–0.97; $p = 0.03$). The reduction in risk of cardiovascular mortality with NTPTX approached but did not reach significance compared with controls (hazard ratio = 0.67; 95% CI, 0.38–1.19; $p = 0.07$) (Table 3).

Discussion

In this retrospective and matched-cohort study, we observed reduced all-cause and cardiovascular mortality rates in dialysis patients who were treated with NTPTX. Our patients' enhanced survival was sustained for a decade when compared with medically managed dialysis patients, making this the longest follow-up of dialysis patients treated with NTPTX in the literature (Fig. 3). The mechanisms responsible for these remarkable

beneficial effects of NTPTX are not certain; however, the dramatic reductions in PTH, calcium, and phosphorus, and the significant increases in serum albumin and hematocrit after NTPTX are notable. A salient finding in our study is the durability of NTPTX. The majority of our patients (87.5%) maintained a postoperative serum PTH <600 pg/mL for up to 10 years (Fig. 1). We believe that the biochemical outcomes are related to operative technique, specifically the selection of a very small vascularized remnant to be left in situ and use of intraoperative PTH monitoring to guide the extent of resection, with the goal of attaining a PTH level of approximately 100 pg/mL at the completion of the procedure.

Although cardiovascular management variables are not available for the patients included in this study, we observed an overall improvement in mortality from cardiovascular diseases in our patients undergoing NTPTX. Abnormalities in glucose and lipid metabolism and elevation in blood pressure levels are known to occur in CKD and have been reported in patients affected by primary hyperparathyroidism as well.⁹ Improvement in these variables has also been reported after PTX.¹⁰⁻¹² In our study, NTPTX was associated with improved hematocrit and serum albumin levels and reduced phosphorus, calcium, and PTH levels. Elevated serum phosphorus, calcium, and PTH have been associated with increased mortality in dialysis patients.¹³⁻¹⁵ Our institution has recently reported a negative impact of elevated PTH levels >200 pg/mL on survival in CKD-stage 5D patients undergoing cardiac valve surgery.¹⁵ The exact mechanisms by which altered mineral metabolism increases mortality and morbidity remain unclear, but vascular calcification has been proposed as a possible link.¹⁶⁻¹⁹ Previous studies have documented the association between disturbed mineral metabolism and calcification of the coronary arteries and cardiac valves.^{15,17} It has been proposed that serum phosphorus stimulates the transformation of vascular smooth muscle cells into osteoblast-like cells, creating a promineralization environment.²⁰ Of interest, a laboratory experiment showed calcification inception and progression when administering PTH to parathyroidectomized animals²¹ and a small human study showed slowing of calcification progression after PTX.²² PTH's negative impact on survival has been reported previously in the general dialysis population, and there have been a few reports of improved survival post-PTX.^{7,8,23,24} Multiple favorable and potentially unfavorable effects of PTH and PTH-related protein on cardiovascular cell physiology have been described in experimental models. PTH stimulates the release of several cytokines from monocyte-macrophages, and parathyroid adenomas produce high levels of the proinflammatory cytokine interleukin-6.²⁵ Whether all or some of these factors contributed to the observed improvement in cardiovascular outcomes in our patients undergoing NTPTX remains unknown.

Although Kestenbaum and colleagues⁵ reported an increased short-term mortality risk in dialysis patients undergoing PTH, they noted an improved survival up to 5 years after PTX. The follow-up period was considerably longer in our study and 30-day postoperative mortality did not differ significantly between NTPTX patients and controls. However, our numbers were small and we cannot exclude the possibility that a larger sample would have demonstrated a mortality difference in the first 30 days after surgery.

The proportion of African American patients in our study reflects the demographics of dialysis patients in the Atlanta metropolitan area and is markedly higher than other studies

that investigated outcomes in dialysis patients after PTX. Using USRDS data for the decade from 1992 to 2002, Foley and colleagues⁴ showed that white patients were considerably more likely than non-white patients to receive PTX. PTH levels are generally higher and cardiovascular complications are prominent among African Americans, and we believe that our study contributes important information relevant to the care of African-American patients who require maintenance dialysis.

Patient selection could be an important bias and might account for the survival benefit shown in our study. In our practice, dialysis patients are referred for surgery only after they are deemed refractory to medical therapy. Typically, they have very high phosphorus and PTH levels and multiple co-morbidities. Patient matching took into account potential confounding variables and adjusted for patient insurance status, an indicator of overall socioeconomic status. We acknowledge that a lack of PTH, serum albumin, calcium, and phosphorus information in controls represents a limitation of this study and a source of potential selection bias. However, the use of intravenous vitamin D during the year before the assigned surgery date was very similar between controls and patients. Controls from the USRDS database might not have had as bad a disease state as the patients referred to surgery in our institution, because the former did not undergo surgery and, in our experience, patients referred for surgery are doing poorly and not responding to medical therapy. Alternatively, one could posit that the lack of referral to surgery might have been due to a state of extreme debilitation and high risk of complications. We believe that this is less likely to have been a factor given the large number of controls we used. A randomized trial of medical vs surgical therapy for dialysis-dependent patients with sHPT would be the most appropriate way to obtain definitive evidence of enhanced survival of CKD-stage 5D patients after NTPTX. There is currently no medical therapy that can reduce PTH levels as effectively and for as long a period of time as PTX.

Conclusions

We have documented an improved long-term all-cause and cardiovascular survival during an extended follow-up period in dialysis patients submitted to NTPTX vis-à-vis medically treated patients with comparable clinical characteristics. Mechanisms leading to improved survival in patients undergoing PTX to control sHPT will require continued investigation in future studies. (Fig. 3).

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Abbreviations and Acronyms

CKD	chronic kidney disease
NTPTX	near-total parathyroidectomy
PTH	parathyroid hormone
PTX	parathyroidectomy
SAF	Standard Analysis File
sHPT	secondary hyperparathyroidism
USRDS	US Renal Data System

Figure 1.

Parathyroid hormone (PTH) levels after near-total parathyroidectomy. PTH levels stay <600 pg/mL in 87.5% of the patients during a follow-up ranging from 6 months to >10 years. IOPTH, intraoperative parathyroid hormone.

Figure 2. Kaplan-Meier estimates of cumulative (A) and cardiovascular (B) survival among patients undergoing near-total parathyroidectomy (NTPTX) (black dotted line) and matched controls (red solid line); $p = 0.006$ and $p = 0.01$, respectively. PTX, parathyroidectomy.

Figure 3.

Schematic of a near-total parathyroidectomy (NTPTX) in a 52-year-old female patient with secondary hyperparathyroidism on hemodialysis for 7.2 years. Sequential intraoperative parathyroid hormone (IOPTH) measurements predict an adequate parathyroid mass reduction. *All parathyroid hormone (PTH) values are in pg/mL. LL, left lower; LU, left upper; RL, right lower; RU, right upper; Rx, resected.

Table 1
Baseline Characteristics of Near-Total Parathyroidectomy Cases and Controls

Baseline characteristics used to individually match controls to NTPTX patients	NTPTX patients (n = 150)	Matched control patients (n = 1,044)	p Value
Age, y, mean (SD)	42.1 (15.1)	42.2 (15.0)	
Male, %	46.7	46.7	
Race, %			
Asian	0.7	0.7	
African American	82.7	82.6	
White	16.7	16.8	
Diabetes as cause of ESRD, %	21.2	22.1	
Hemodialysis, %	93.3	93.5	
Additional baseline characteristics			
Use of intravenous vitamin D, % [*]	72.4	75.5	0.45
Comorbid conditions			
History of hypertension, %	85.0	76.9	0.07
Congestive heart failure, %	12.0	17.9	0.14
Coronary artery disease, myocardial infarction, or atherosclerotic heart disease, %	8.0	8.3	0.93
Cerebrovascular disease, %	4.0	3.7	0.87
Peripheral vascular disease, %	3.0	6.4	0.18
Cardiac arrest, cardiac dysrhythmia or other cardiac disease (other cardiac), %	2.0	2.6	0.72
Inability to ambulate/transfer, % [†]	0.0	1.4	0.62
Smoker, %	8.0	5.4	0.29
Private insurance, %	13.3	7.8	0.02

^{*} Information was available for 127 patients and 879 controls in the 1998 to 2008 claims files.

[†] Fisher's exact test was used, due to small cell size.

NTPTX, near-total parathyroidectomy.

Table 2
Laboratory Values Pre and Post Near-Total Parathyroidectomy in 150 Patients

Laboratory values	Preoperative *	Postoperative *	p Value
PTH, pg/mL	1,770 ± 1416.6	301.2 ± 285.7 [†]	<0.0001
Serum calcium, mg/dL	9.9 ± 0.95	8.3 ± 0.94	<0.0001
Serum phosphorus, mg/dL	6.0 ± 1.7	4.3 ± 1.6	<0.0001
Serum albumin, g/dL	2.8 ± 0.6	3.1 ± 0.6 [‡]	<0.0001
Hematocrit, %	32.6 ± 5.4	35.4 ± 4.8 [‡]	0.0001
Vitamin D 25-OH, ng/mL (n = 68)	19.8 ± 5.5	21.9 ± 6.3	0.18

* Values are mean ± SD.

[†] Maximum parathyroid hormone (PTH) value observed for each patient.

[‡] Postoperative serum albumin within 1 to 2 months after surgery.

Table 3
Multivariable Cox Proportional Hazard Models Predicting All-Cause and Cardiovascular Mortality Risk

Risk factor	All-cause mortality, HR (95% CI)	Cardiovascular mortality, HR (95% CI)
NTPTX	0.63 (0.41–0.97)	0.67 (0.38–1.19)
Hypertension	1.22 (0.85– 1.74)	2.08 (1.18–3.68)
CHF	1.65 (1.16–2.34)	1.18 (0.69– 2.02)
CAD, ASHD	0.91 (0.58– 1.43)	0.95 (0.52–1.75)
CVD	1.68 (0.93–3.02)	1.67 (0.75–3.71)
PVD	1.03 (0.60– 1.75)	0.86 (0.41– 1.79)
Other cardiac disease	2.30 (1.07–4.96)	1.49 (0.38–5.77)
Smoking	1.13 (0.65– 1.97)	0.65 (0.26–1.63)
Inability to ambulate/transfer	2.06 (0.79–5.40)	2.24 (0.63–7.95)
Private insurance	0.34 (0.17–0.68)	0.45 (0.17–1.19)

ASHD, atherosclerotic heart disease; CAD, coronary artery disease; CHF, congestive heart failure; CVD, cerebrovascular accident; HR, hazard ratio; NTPTX, near-total parathyroidectomy; PVD, peripheral vascular disease.