Parathyroidectomy reduces cardiovascular events and mortality in renal hyperparathyroidism

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Background. *Secondary hyperparathyroidism (SHPT) and its associated abnormalities in mineral metabolism increase the risk of cardiovascular morbidity and death in chronic renal failure (CRF). The effect of parathyroidectomy (PTX) on the incidence of major cardiovascular events in CRF patients with SHPT is unknown. We tested the hypothesis that PTX reduces the incidence of cardiovascular complications and death in CRF patients with severe SHPT scheduled for PTX, comparing the outcome of patients treated or not treated by PTX.*

Methods. *The study comprised 118 CRF patients with SHPT on maintenance hemodialysis, unresponsive to medical treatment and scheduled for PTX. Patients underwent comprehensive cardiovascular evaluations at baseline. They were followed up until death, occurrence of major cardiovascular events, or kidney transplantation.*

Results. *No deaths related to PTX occurred. After a median follow-up of 30 months, 50 patients (42%) had undergone PTX whereas 68 (58%) had not. The groups were comparable in terms of age, sex, race, serum parathyroid hormone, calcium or phosphate, calcium x phosphate product, and all major cardiovascular variables, except diastolic blood pressure. PTX was associated with a reduced incidence of major cardiovascular events (*$P = .02$*) and overall mortality (*$P \leq .001$*). Cox proportional multivariate analysis showed that variables associated independently with events were No-PTX (RR = 2.36, CI 1.11-6.32,* $P = .02$*) and age (RR = 1.07, IC 1.02-1.14,* $P = .009$*). All-cause mortality was related to No-PTX (RR = 2.34, CI 1.25-5.14,* $P = .007$*) and hematocrit (RR = 1.15, CI 1.03-1.29,* $P = .01$*).*

Conclusion. *PTX confers protection against future major cardiovascular events and death in select CRF patients with severe refractory SHPT. (Surgery 2007;142:699-703.)*

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Secondary hyperparathyroidism (SHPT) is a common complication of chronic renal failure (CRF). Both primary HPT[1-3] and SHPT[4] are associated with increased mortality, mainly due to an overrepresentation of cardiovascular death. Data from patients with primary HPT suggest that parathyroidectomy (PTX) may reduce the overall death rate, although its impact on cardiovascular mortality and morbidity are controversial.[5,6] The role of PTX in the incidence of cardiovascular events and death of CRF patients with SHPT is unclear. In the present work, we tested the hypothesis that PTX reduces cardiovascular events and mortality in patients on chronic hemodialysis with severe SHPT in comparison with medical treatment alone.

SUBJECTS AND METHODS

The Institutional Ethics Committee approved the protocol, and all patients provided written informed consent. We performed a prospective analytical cohort study in a group of 118 hemodialysis patients with severe SHPT unresponsive to medical treatment selected for a PTX and sent to our service for preoperative cardiovascular assessment by the Renal Osteodystrophy Clinic of our institution. The Renal Osteodystrophy Clinic is a reference

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facility that receives patients from different dialysis services with resistant SHPT for further evaluation and treatment. Patients were selected for PTX based on resistance to medical treatment that was defined as serum levels of parathyroid hormone (PTH) and phosphate greater than 800 pg/mL and 6.5 mg/100 mL, respectively, after a minimum of 6 months of treatment. Patients who had the diagnosis of medically resistant SHPT confirmed after this period were selected for PTX and were entered in a waiting list for PTX. Patients were followed from the time of initial decision to undergo PTX, not from the time of PTX. During the follow-up, 50 subjects were submitted to PTX, whereas 68 did not undergo PTX. The PTX was performed according to the chronological order of entering in the waiting list and consisted of total PTX with autotransplantation in the forearm. Follow-up varied from 4 to 78 months (median 30 months). The primary end-points were major cardiovascular events (myocardial infarction, sudden death, unstable angina, heart failure, and stroke) and the secondary end-point was death by any cause. Smokers, individuals using lipid-lowering drugs, patients with diabetes, and those with a history of heart failure, stroke, unstable angina, or myocardial infarction within 12 months preceding the initiation of the study were excluded. We also excluded patients who had received previously a renal transplant and those with previous myocardial revascularization. Patients underwent a comprehensive cardiovascular evaluation at study inception that included chest X-ray, 12-lead ECG, and bi-dimensional echocardiograms. PTH (intact hormone molecule) was determined by radioimmunoassay at inception in all participants. Hemodialysis was performed 3 times/week for 4 hours. The adequacy of hemodialysis was determined by the fractional clearance of urea, normally referred as KT/V. A KT/V of at least 1.2 is considered an index of adequate dialysis treatment, and the dialysis treatment of our patients was modeled in such a way as to achieve at least this level. Medical treatment was based on reduction of phosphate intake and calcitriol. Sevelander, a blocker of intestinal phosphate absorption, was also prescribed to all patients to achieve and maintain an adequate serum phosphate concentration. Antihypertensive medications consisted of renin-angiotensin system inhibitors, beta-blockers, and calcium channel blockers, alone or in combination, in 35%, 28% and 30% of the patients, respectively. Erythropoetin was used to maintain hematocrit levels at 33-35% whenever possible.

Table I. Characteristics of the patients (N = 118)

Variable	*PTX (N = 50)*	*No PTX (N = 68)*	*P value*
Age (years)	43 ± 10	45 ± 12	0.84
Males N(%)	26 (52)	40 (59)	0.58
Females N(%)	24 (48)	28 (41)	
Caucasians N(%)	34 (68)	43 (63)	0.88
African-Brazilians (N/%)	15 (30)	24 (35)	
Orientals (N/%)	1 (2.0)	1 (1.5)	
Duration of dialysis treatment (months)	89 ± 44	78 ± 44	0.08
Systolic blood pressure (mm Hg)	139 ± 24	145 ± 27	0.91
Diastolic blood pressure (mm Hg)	85 ± 13	92 ± 17	0.01
Body mass index (kg/m^2)	24 ± 4	25 ± 5	0.83
PTH (pg/mL)	1278 ± 699	1243 ± 753	0.40
Calcium (mg/100 mL)	10.2 ± 0.8	10.0 ± 1.0	0.20
Phosphate (mg/100 mL)	6.8 ± 1.5	6.7 ± 1.6	0.90
Ca X P product	70 ± 17	68 ± 19	0.59
Hematocrit (%)	36 ± 7	36 ± 6	0.89
Renal transplantation (N/%)	6 (12)	7 (10)	0.29

Note: Continuous variables are presented as means ± standard deviation.

The data were analyzed with the JMP statistical program (JMP for Windows – version 6.0.0, SAS Institute Inc., Cary, NC). Unless otherwise stated, figures are expressed as means ± standard deviation of the mean. Differences between groups were assessed with Fisher's exact test or the 2-tailed Student *t* test, as appropriate. Univariate and multivariate Cox regression models were used to investigate the association between modality of treatment and events or death. Survival curves were constructed by using the Kaplan-Meier method and compared by log-rank test. Patients were censored at the time of the last contact, at the time of an event (lethal or not lethal), or at the date of transplantation. A *P* value less than .05 was considered significant.

RESULTS

PTX was performed in 50 patients (42%), while the other 68 subjects (58%) were kept on clinical treatment alone. Serum PTH decreased in all patients after PTX. Mean serum PTH decreased from 1260 ± 151 to 104 ± 142 (pg/mL) after PTX ($P < .01$).

Table I shows the main characteristics of patients who did or did not undergo PTX. PTX patients had lower diastolic blood pressures. Age, sex, race, duration of dialysis, systolic blood pressure, hematocrit, serum PTH, calcium or phosphate, and calcium x phosphate product did not

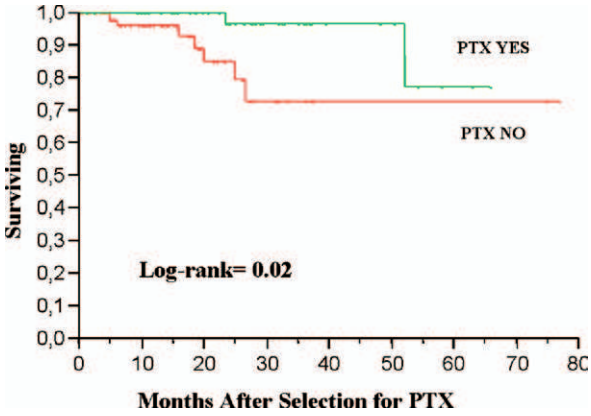

Fig 1. Effect of parathyroidectomy on event-free survival of CRF patients with SHPT.

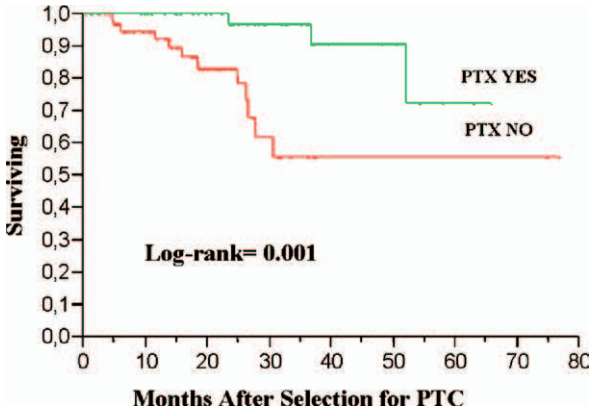

Fig 2. Effect of parathyroidectomy on overall survival of CRF patients with SHPT.

differ among groups. No deaths were associated with PTX.

Figure 1 depicts the survival curves for cardiovascular events in patients treated by PTX. Cardiovascular events were decreased in PTX patients (log-rank = 0.02). Seven major cardiovascular events (6 lethal) occurred among patients kept on medical treatment alone (3 strokes, 2 myocardial infarctions, 1 sudden death, and 1 heart failure), but 2 sudden deaths occurred in patients who underwent PTX. After adjusting for confounding factors, the only variables that influenced independently the incidence of major cardiovascular events were No-PTX (RR = 2.36, CI 1.11-6.32, $P = .02$,) and age (RR = 1.07, CI 1.02-1,14, $P = .009$). The relative risk to developing major cardiovascular events was more than two times greater in subjects who did not undergo PTX compared with patients who did. Age (mean ± SD) was 55 ± 13 years for patients who developed events and 44 ± 11 for those who did not ($P = .02$).

Overall mortality was also decreased in PTX patients (Fig 2; log-rank = 0.001). Multivariate analysis showed that the factors associated independently with overall mortality were No-PTX (RR = 2.34, CI 1.25-5.14, $P = .007$) and hematocrit (RR = 1.15, CI 1.03-1.29, $P = .01$). Hematocrit was 41 ± 5 for patients who died and 36 ± 6 among survivals ($P = .002$). Nine of 30 patients belonging to the higher quartile, corresponding to a hematocrit of 40% or greater, died, but only 5 of 80 with lesser hematocrits had the same destiny ($P = .002$). Body mass index, sex, race, duration of dialysis treatment, systolic and diastolic blood pressure, and serum levels of creatinine, lipids, PTH, calcium, phosphate, calcium x phosphate product, and glucose did not independently influence either cardiovascular events or death.

DISCUSSION

PTX was associated with a decreased incidence of serious cardiovascular events and overall mortality in CRF individuals with severe, medically resistant hyperparathyroidism compared with clinical treatment alone. The 2 groups (PTX/No PTX) were well-balanced regarding the main factors affecting the cardiovascular system, and our patients also did not have diabetes or current cardiovascular disease. The risk of events and deaths was less in patients treated by PTX even after adjustment for several important confounding factors. Therefore, in spite of the small number of subjects, the observed association between treatment and prognosis appears to be genuine.

Other factors affecting the outcome were age (for cardiovascular events) and hematocrit (for all-cause mortality). The importance of age on prognosis is a well-known phenomenon. The negative impact of normal or near-normal hematocrit on survival of CRF patients has also been reported and is related to the overuse of erythropoietin.[7] In support of this interpretation, we found a significant association between mortality and greater hematocrit quartile in our patients.

The negative impact of primary HPT on survival has been documented in many studies. The risk of death associated with single[3,8,9] or multiple[6] parathyroid adenomas is attributed to premature cardiovascular and urogenital diseases, diabetes, and malignancy that occur more frequently in these patients. Accordingly, individuals with primary HPT have an increased incidence of cardiovascular disorders, such as myocardial infarction, stroke, and heart failure, that may persist even after PTX.[10,11]

Cardiovascular morbidity and mortality are also increased in SHPT and appear to be mainly related

to alterations in mineral metabolism, particularly phosphate, rather than to serum PTH levels.[4,12-14] CRF patients with SHPT show an increased prevalence of cardiovascular calcification, including in the coronary arteries, left ventricular hypertrophy, hypertension, left ventricular interstitial fibrosis, dyslipidemia, and insulin resistance[15] that may explain its unfavorable impact on prognosis.

PTX decreases the overall mortality of patients with primary HPT, and in this group of individuals, PTX is considered the treatment of choice. For renal patients with SHPT, the situation is more complex, because medication may afford at least partial control of the syndrome. Moreover, involution of parathyroid glands may occur after successful renal transplantation, making PTX unnecessary. PTX is an invasive procedure not without risks, especially in patients with a high prevalence of cardiac and coronary diseases. Also, persistent SHPT as well as hypoparathyroidism may occur, sometimes associated with hypothyroidism.[16] In spite of these considerations, for symptomatic patients with medically resistant SHPT, PTX is the standard procedure. But, even under these circumstances, it is important to know what the other advantages of PTX might be, beyond the control of symptoms. Except for the rare, life-threatening condition of calciphylaxis, which usually regresses after PTX,[17] there is scant information on the subject in the literature. In particular, the consequences of PTX on cardiovascular prognosis of these patients have not been evaluated. There is only one study on long-term survival of CRF patients after PTX.[18] In a large group of patients in the United States treated by dialysis, the authors observed that PTX was associated with a greater short-term (90 days) but lesser long-term overall mortality compared with patients who did not undergone PTX.[18] This study, however, was a retrospective investigation, and the impact of PTX on cardiovascular events was not reported. Moreover, no information exists regarding the levels of serum PTH, calcium, and phosphate in their patients. Therefore, ours is the first known study reporting a positive effect of PTX on the cardiovascular outcome of CRF patients with SHPT in agreement with findings about primary HPT. In conclusion, we found that PTX confers protection against future major cardiovascular events and death in selected CRF patients with severe refractory SHPT. The results suggest that PTX may improve prognosis of CRF patients with SHPT.

This work has several limitations. The main limitations are that it is not a randomized study and that the number of patients is relatively small. The study also was not conceived to compare the efficacy of 2 different modalities of treatment (PTX versus medical intervention), because all subjects had already been treated and were resistant to medical intervention alone. We also do not have means to verify the changes in different cardiovascular variables associated with PTX. Notwithstanding, we believe that the data are relevant, because they suggest the possibility that PTX, in selected patients with SHPT, may offer not only relief from the classic clinical manifestations of SHPT but also may improve prognosis. If this proves to be true, PTX should be performed as soon as resistance to medical treatment is detected. Randomized prospective studies would be necessary to clarify this important issue.

REFERENCES

1. Raue F. Increased incidence of cardiovascular diseases in primary hyperparathyroidism—a cause for more aggressive treatment? Eur J Clin Invest 1998;28:277-8.
2. Hedback G, Odén A. Increased risk of death from primary hyperparathyroidism—an update. Eur J Clin Invest 1998; 28:271-6.
3. Lundgren E, Lind L, Palmer M, Jakobsson S, Ljunghall S, Rastad J. Increased cardiovascular mortality and normalized serum calcium in patients with mild hypercalcemia followed up for 25 years. Surgery 2001;130:978-85.
4. Ganesh SK, Stack AG, Levin NW, Hulbert-Shearon T, Port FK. Association of elevated serum PO(4), Ca x PO(4) product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. J Am Soc Nephrol 2001; 12:2131-38.
5. Vestergaard P, Mosekilde L. Cohort study on effects of parathyroid surgery on multiple outcomes in primary hyperparathyroidism. BMJ 2003;327:530-34.
6. Nilsson IL, Wadsten C, Brandt L, Rastad J, Ekbom A. Mortality in sporadic primary hyperparathyroidism: nationwide cohort study of multiple parathyroid gland disease. Surgery 2004;136:981-7.
7. Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, et al. CHOIR Investigators. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med 2006; 355:2085-98.
8. Andersson P, Rydberg E, Willenheimer R. Primary hyperparathyroidism and heart disease—a review. Eur Heart J 2004;25:1776-87.
9. Walgenbach S, Hommel G, Junginger T. Outcome after surgery for primary hyperparathyroidism: ten-year prospective follow-up study. World J Surg 2000;24:564-9.
10. Palmer M, Adami HO, Bergstrom R, Akerstrom G, Ljunghall S. Mortality after surgery for primary hyperparathyroidism: a follow-up of 441 patients operated on from 1956 to 1979. Surgery 1987;102:1-7.
11. Wermers RA, Khosla S, Atkinson EJ, et al. Survival after the diagnosis of hyperparathyroidism: a population-based study. Am J Med 1998;104:115-22.
12. Block GA, Hulbert-Shearon TE, Levin NW, Port FK. Association of serum phosphorus and calcium x phosphate prod-

uct with mortality risk in chronic hemodialysis patients: a national study. Am J Kidney Dis 1998;31:607-17.
13. Marco MP, Craver L, Betriu A, Belart M, Fibla J, Fernandez E. Higher impact of mineral metabolism on cardiovascular mortality in a European hemodialysis population. Kidney Int Suppl 2003;(suppl 85):S111-S4.
14. Young EW, Albert JM, Satayathum S, Goodkin DA, Pisoni RL, et al. Predictors and consequences of altered mineral metabolism: the Dialysis Outcomes and Practice Patterns Study. Kidney Int 2005;67:1179-87.
15. Horl WH. The clinical consequences of secondary hyperparathyroidism: focus on clinical outcomes. Nephrol Dial Transplant 2004;19:(Suppl 5):v2-v8.
16. Stracke S, Jehle PM, Sturm D, Schoenberg MH, Widmaier U, Beger HG, et al. Clinical course after total parathyroidectomy without autotransplantation in patients with end-stage renal failure. Am J Kidney Dis 1999;33:304-11.
17. Girotto JA, Harmon JW, Ratner LE, Nicol TL, Wong L, Chen H. Parathyroidectomy promotes wound healing and prolongs survival in patients with calciphylaxis from secondary hyperparathyroidism. Surgery 2001;130:645-50.
18. Kestenbaum B, Andress DL, Schwartz SM, Gillen DL, Seliger SL, Jadav PR, et al. Survival following parathyroidectomy among United States dialysis patients. Kidney Int 2004;66:2010-16.