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Original Article

Management of Persistent Hyperparathyroidism after Renal Transplantation

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ABSTRACT

Objective: Even after successful kidney transplantation, persistent hyperparathyroidism (HPT) with hypercalcemia is common, which is considered to be a risk factor for progressive bone loss, fractures, tubulointerstitial calcifications, vascular calcification, and development of graft dysfunction. The subtotal parathyroidectomy (PTX) is the standard treatment, but currently, it has been replaced by the calcimimetic cinacalcet. The aim of this single-center, retrospective study was to compare the long-term effects of PTX and cinacalcet on calcium, phosphorus, and parathyroid hormone (PTH) levels, as well as graft function in renal transplantation patients.

Methods: The study population consisted of 24 patients followed between January 2004 and December 2020, 13 of whom underwent PTX and 12 of whom take cinacalcet therapy. The surgical group and the medical treatment group were compared. A control group with similar characteristics in terms of age, gender, transplant time, and kidney donor was formed, and the results were also compared with this group. The median PTH, calcium, phosphorus, creatinine levels, and eGFR values were recorded before/after PTX and cinacalcet therapy.

Results: There was nonnegative effect of both PTX and cinacalcet groups on long-term and short-term allograft functions compared with control groups. Allograft functions were similar in comparison between PTX and cinacalcet groups.

Conclusion: In conclusion, both cinacalcet treatment and PTX were found to be similarly effective and safe in reducing intact PTH and normalizing serum calcium in renal allograft recipients with hypercalcemia due to persistent HPT.

INTRODUCTION

While metabolic and endocrine imbalances are expected to improve after a successful kidney transplant, parathyroid hormone (PTH) secretion can still be found to be high in 25%–50% of patients at the end of the first year.[1,2] Although improvement in parathyroid function is reported due to a decrease in parathyroid functional mass 3–6 months after transplantation,[3] there are also opinions that posttransplant involution of the gland may last up to several years due to the longevity of parathyroid cells.[4,5]

Tertiary hyperparathyroidism (HPT) is an important risk factor for bone fractures during the first 5 years after transplantation. One study found that a PTH level of >130 pg/mL at 3 months after transplantation was associated with a 7.5-fold increased risk of fracture at 5 years.[6] In one study, the prevalence of hypercalcemia due to any cause (serum calcium >10.5 mg/dL) was found to be 31% in the first year after transplantation.[7] With hypercalcemia, there is vasoconstriction of the graft and volume reduction due to natriuresis. In addition, vascular calcifications, nephrolithiasis, and tubular microcalcifications have also been associated with impaired kidney transplant function and reduced graft survival.[8] HPT potentially leads to increased cardiovascular risk due to increased vascular calcification.[9] In a multivariate analysis of transplant recipients in the Assessment of Lescol in Renal Transplantation study, PTH values >65 pg/mL were found to be associated with an increase in all-cause mortality.[10]

Parathyroidectomy (PTX) is the treatment of choice in patients with persistent HPT and serum calcium values >12 mg/dL or symptomatic hypercalcemia. In a study with serum calcium concentrations >10.5 mg/dL, subtotal PTX was found to be more likely to result in normocalcemia after 12 months compared with treatment with cinacalcet.[11] Cinacalcet is a calcimimetic agent that activates calcium-sensing receptors in the parathyroid glands and lowers

plasma PTH levels in primary and secondary HTTP and is an alternative treatment option in milder forms of HPT. Some studies have reported that it has been used successfully to control moderate HPT and hypercalcemia.[12–14] However, because discontinuation of cinacalcet treatment leads to a rapid increase in PTH level, the result is not permanent and long-term cinacalcet treatment may be required in these patients after transplantation, which increases the cost. In some studies, it has been suggested that PTX be performed before transplantation despite the possibility of causing sudden deterioration in graft function.[15] However, some data have shown that glomerular filtration rate (GFR) improves in the long term in patients who underwent PTX after transplantation, and allograft survival is not low.[16] PTX is the best treatment option if hypercalcemia is resistant to medical therapy for more than 1 year after transplantation.[17] However, it should be kept in mind that PTX is an invasive treatment with complications such as acute and chronic hypocalcemia and permanent hypoparathyroidism that will develop if the amount of parathyroid gland tissue to be excised cannot be adjusted correctly. In addition, both of these treatments lead to decreased bone turnover, paving the way for the development of a dynamic bone disease.[15,18] The data from two small, randomized studies have shown that cinacalcet reduces PTH levels and serum calcium levels without short-term adverse effects on allograft function.[19,20] Another study found that PTX was associated with a lower rate of allograft failure compared with cinacalcet in patients with posttransplant HPT.[21]

The aim of this single-center, retrospective study was to compare the long-term effects of PTX and cinacalcet on calcium, phosphorus, and PTH levels, as well as eGFR in renal transplantation patients.

MATERIALS AND METHODS

The study population consisted of 24 kidney transplant recipients followed between January 2004 and December 2020, 13 of whom underwent PTX and 12 of whom take cinacalcet therapy. The cinacalcet treatment group and PTX group were compared. A control group with similar characteristics in terms of age, gender, transplant time, and kidney donor was formed and the results were also compared with these groups. The median PTH, calcium, phosphorus, creatinine levels, and eGFR values were recorded before/after PTX and cinacalcet therapy. Measurements were made at the clinical laboratory of our institution. Demographic data, such as age, gender, time on dialysis, time to start medical cinacalcet treatment, time of PTX after transplantation, immunosuppressive treatment applied, and usage of vitamin D were obtained from medical records. We checked the blood concentrations of PTH, calcium, phosphorus, creatinine, and eGFR before PTX and cinacalcet treatment at postoperative first month, first year, and the last record of follow-up. The Chronic Kidney Disease Epidemiology Collaboration formula is used to determine eGFR. Intact PTH levels were determined using double-antibody chemiluminescent assay (Diagnostics Products Corp., Los Angeles, CA, USA) with normal range being 12–72 pg/mL and were measured on morning fasting samples approximately 24 h after the last cinacalcet dose.

Cinacalcet was started at 30 mg once daily. The dose of cinacalcet was adjusted so that serum calcium levels were within normal limits. The indication for PTX was medically uncontrollable, long-standing, osteitis fibrosa, and surgery was performed subtotal.

The study was approved by the local ethics committee (13.01.2021-514/193/4). The clinical and research activities reported are consistent with the "Principles of the Declaration of Helsinki."[22]

Statistical analysis

Descriptive data were presented as median and range for the continuous variables and frequency and percentage (%) for the categorical variables. The Mann–Whitney U test was used for comparing the groups. Categorical variables were compared using the Chi-squared test or Fisher's exact test for proportion. All significance tests were two-tailed, and values of $p<0.05$ were considered statistically significant. All statistical analyses were performed by SPSS software version 21 (Chicago, IL).

RESULTS

Of the patients included in the study, 54.2% were male (n=13), 45.8% were female (n=11). Of the patients, 66.67% (n=16) were using immunosuppressives containing tacrolimus, 12.5% (n=3) containing cyclosporine, and 20.83% (n=5) containing certican. Pretreatment vitamin D use was 15.4% in patients who underwent PTX, while it was 36.4% in those using cinacalcet. When cinacalcet and PTX groups were compared, the duration of dialysis was found to be longer in the PTX group than in the cinacalcet group ($p<0.05$). In the posttransplant and pre-PTX/cinacalcet period, calcium levels were higher, although not significantly, in the PTX group. Also, phosphorus values were significantly lower in this group ($p<0.001$). The mean PTH value before treatment was significantly higher in the medical group than in the surgical group ($p<0.001$). After treatment, there was no significant difference between the two groups in terms of creatinine, calcium, phosphorus, and GFR at 1st, 3rd, 12th months and final values (Table 1).

When the PTX and control groups were compared, dialysis time was higher in the PTX group ($p<0.05$). While calcium value before PTX was significantly higher in the PTX group, phosphorus values were also found to be significantly lower ($p<0.001$). Creatinine 1st month values were higher and eGFR values were lower in the control group ($p<0.05$). However, no difference was found between the two groups in the comparison of all values in the follow-ups (Table 2).

Table 1. Comparison of parathyroidectomy and cinacalcet groups

	Parathyroidectomy group (n=13)	Cinacalcet group (n=11)	p
Male, n (%)	7 (53.8)	6.0 (54.5)	0.683
Age	53.0 (35.0–64.0)	46.0 (35.0–66.0)	0.601
Dialysis year	10.0 (0–13.0)	7.0 (2.0–12.0)	0.002
Treatment time (month)	9.0 (1.0–64.0)	24.0 (14.0–72.0)	0.228
PTH before surgery/medical treatment	287.0 (102.8–1129.0)	700.0 (421.0–1620.0)	<0.001
Ca before surgery/medical treatment	11.0 (9.0–12.6)	9.8 (7.8–11.5)	0.072
P before surgery/medical treatment	2.5 (1.7–3.0)	4.6 (3.0–6.0)	<0.001
PTH 1st month	114.4 (13.2–571.6)	127.2 (52.9–271.8)	0.459
Ca 1st month	10.3 (5.6–11.8)	10.2 (8.4–11.3)	0.392
P 1st month	3.3 (1.9–5.8)	2.9 (2.2–3.6)	0.252
Creatinine 1st month	1.04 (0.6–1.6)	0.98 (0.59–1.75)	0.910
eGFR 1st month	80.0 (34.7–120.2)	81.3 (45.0–117.8)	0.569
PTH 12th month	84.4 (571.6–563.1)	116.0 (35.4–285.0)	0.494
Ca 12th month	9.8 (7.1–11.2)	10.0 (8.9–11.3)	0.691
P 12th month	3.2 (2.2–4.2)	2.9 (1.8–3.4)	0.093
Creatinine 12th month	0.89 (0.58–2.02)	0.91 (0.73–1.82)	0.531
eGFR 12th month	79.0 (26.4–114.8)	79.0 (42.7–106.0)	0.608
PTH final value	67.5 (8.0–185.0)	133.9 (25.2–185.0)	0.147
Ca final value	9.2 (6.9–10.4)	9.4 (8.3–10.4)	0.434
P final value	3.0 (2.0–4.7)	3.0 (2.3–3.9)	0.450
Creatinine final value	1.1 (0.7–1.8)	1.1 (0.7–2.0)	0.524
eGFR final value	64.2 (31.2–114.0)	74.7 (39.9–109.8)	0.901

PTH: Parathyroid hormone; GFR: Glomerular filtration rate; Ca: Calcium; P: Phosphorus.

Table 2. Comparison of parathyroidectomy and control groups

	Parathyroidectomy group (n=13)	Cinacalcet group (n=13)	p
Male, n (%)	7.0 (53.8)	7.0 (53.8)	0.652
Age	53.0 (35.0–64.0)	56.0 (39.0–65.0)	0.487
Dialysis year	10.0 (0.0–13.0)	6.0 (3.0–15.0)	0.058
PTH before surgery	287.0 (102.8–1129.0)	193.0 (84.5–771.9)	0.293
Ca before surgery	11.0 (9.0–12.6)	8.7 (7.9–10.5)	0.001
P before surgery	2.5 (1.7–3.0)	5.2 (2.4–6.8)	0.001
PTH 1st month	114.4 (13.2–571.6)	145.9 (43.7–546.3)	0.555
Ca 1st month	10.3 (5.6–11.8)	8.7 (7.9–10.2)	0.228
P 1st month	3.3 (1.9–5.8)	2.6 (1.9–5.5)	0.277
Creatinine 1st month	1.0 (0.6–1.6)	1.6 (0.8–6.2)	0.040
eGFR 1st month	80.0 (34.7–120.1)	49.0 (6.9–87.2)	0.045
PTH 12th month	84.4 (8.5–571.6)	94.9 (44.4–208.1)	0.939
Ca 12th month	9.8 (7.1–11.2)	9.9 (9.0–10.8)	0.939
P 12th month	3.2 (2.2–4.2)	3.0 (2.2–4.9)	0.625
Creatinine 12th month	0.9 (0.6–2.0)	1.1 (0.6–1.8)	0.112
eGFR 12th month	79.0 (26.4–114.8)	60.0 (29.1–116.5)	0.317
PTH final value	67.5 (8.0–185.0)	77.1 (43.4–318.7)	0.397
Ca final value	9.2 (6.9–10.4)	9.6 (9.0–10.5)	0.270
P final value	3.0 (2.0–4.7)	3.3 (2.7–3.7)	0.471
Creatinine final value	1.1 (0.7–1.8)	1.4 (0.6–8.9)	0.151
eGFR final value	64.2 (31.2–114.0)	62.4 (12.0–113.9)	0.521

PTH: Parathyroid hormone; GFR: Glomerular filtration rate; Ca: Calcium; P: Phosphorus.

Table 3. Comparison of cinacalcet and control groups

	Cinacalcet group (n=11)	Control group (n=11)	p
Male, n (%)	6.0 (54.5)	6.0 (54.5)	0.665
Age	46.0 (35.0–66.0)	48.0 (35.0–65.0)	0.974
Dialysis year	7.0 (2.0–12.0)	6.0 (0.0–15.0)	0.887
PTH before medical treatment	700.0 (421.0–1620.0)	193.0 (83.4–771.9)	0.002
Ca before medical treatment	9.8 (7.8–11.5)	8.4 (7.9–9.5)	0.011
P before medical treatment	4.6 (3.0–6.0)	4.6 (2.4–6.0)	0.530
PTH 1st month	127.2 (52.9–271.8)	166.1 (43.7–314.5)	0.694
Ca 1st month	10.2 (8.4–11.3)	9.2 (7.9–10.2)	0.008
P 1st month	2.9 (2.2–3.6)	2.8 (2.1–5.5)	0.576
Creatinine 1st month	0.9 (0.6–1.8)	1.5 (0.8–6.6)	0.071
eGFR 1st month	81.3 (45.0–117.8)	47.0 (10.0–106.0)	0.033
PTH 12th month	116.0 (35.4–285.0)	115.3 (64.9–252.4)	0.818
Ca 12th month	10.0 (8.9–11.3)	9.5 (1.3–10.2)	0.157
P 12th month	2.9 (1.8–3.4)	2.8 (2.2–4.4)	0.292
Creatinine 12th month	0.9 (0.7–1.8)	1.1 (0.6–1.7)	0.533
eGFR 12th month	79.0 (42.7–106.0)	64.0 (49.0–116.5)	0.922
PTH final value	133.0 (25.2–185.0)	91.7 (45.3–318.7)	0.818
Ca final value	9.4 (8.3–10.4)	9.4 (8.8–10.1)	0.818
P final value	3.0 (2.3–3.9)	2.8 (2.2–3.8)	0.576
Creatinine final value	1.1 (0.7–2.0)	1.1 (0.6–4.4)	0.998
eGFR final value	74.7 (39.9–109.8)	66.2 (12.0–113.9)	0.944

PTH: Parathyroid hormone; GFR: Glomerular filtration rate; Ca: Calcium; P: Phosphorus.

In cinacalcet and control groups comparison, there was a significant difference between the medical group and the control group in terms of PTH values and calcium values before cinacalcet treatment ($p<0.05$). It was found to be statistically significantly higher in the 1st month calcium cinacalcet group ($p<0.05$). eGFR values were statistically significantly lower in the control group at 1st month ($p<0.05$). No difference was found between the two groups in the comparison of all values in the follow-ups (Table 3).

There was no negative effect of both PTX and cinacalcet on long-term and short-term allograft functions compared with control groups. The decrease in PTH was more pronounced in the PTX group, which may also be due to the higher pretreatment median PTH in the cinacalcet group. The decrease in calcium was more striking in the PTX group. Although the last mean phosphorus values were the same, phosphorus recovered in a shorter time in the PTX group. Also, allograft functions were similar in comparison between PTX and cinacalcet groups. Prolonged cinacalcet therapy and PTX were also well tolerated, did not lose efficacy, and at these doses did not cause hypocalcemia and recurrent hypercalcemia. However, in spite of all of these beneficial metabolic and endocrine changes, the normalization of parathyroid function is not complete 12 months after transplantation. According to the last follow-up values, while PTH was within normal limits in the PTX group, PTH was slightly elevated in the cinacalcet group, and all other follow-up values were within the normal limits.

DISCUSSION

Bone disease is a challenging problem associated with immunosuppressive therapy, phosphate losses, and persistent HPT after kidney transplantation.[23,24] PTH concentrations above 230 pg/mL at transplantation have been shown to correlate with long-term persistent HPT.[25]

PTX accounts for 31% of all operative diseases of kidney transplant patients[26] and is the most appropriate approach in patients with severe or symptomatic hypercalcemia although temporary deterioration in graft function may be detected. However, in two studies supporting the long-term positive effects of PTX, graft survival rates of 3–10 years were found to be similar to those of patients who underwent kidney transplantation without PTX.[27] Cinacalcet is a safe alternative for patients with posttransplant HPT and mild hypercalcemia. Cinacalcet increases the avidity of the parathyroid calcium sensor and decreases serum calcium levels by directly reducing PTH secretion. The beneficial effects of cinacalcet therapy after transplantation have been demonstrated.[12–14]

Although cinacalcet is considered an alternative or option to delay PTX, it remains unclear whether delaying or avoiding surgical treatment provides clinical benefit to the patient. Cruzado et al.[11] showed that PTX was superior to the use of cinacalcet in the treatment of hypercalcemia in kidney transplant recipients. However, since it has been observed that HPT can resolve spontaneously in a certain number of renal graft recipients, it is stated that up to 12

months after transplantation can be waited for PTX and medical treatment may be sufficient in this period.

In addition, rarely, HPT may recur from the remaining glandular tissue after total PTX, and a second intervention may be required. However, limited tolerance and uncertain safety of chronic cinacalcet therapy should also be considered.[28] Another problem with PTX is that PTH levels remain below the recommended target range in more than half of the cases.[29] Permanent hypoparathyroidism that may develop from surgery may exacerbate low-grade bone disease and may even contribute to graft loss. PTH is thought to play an important role in maintaining bone metabolism, especially in kidney transplant recipients treated with steroids.[30] A systematic review of studies reporting surgical and medical treatment concluded that surgical treatment had lower complication rates and higher recovery rates, and it was estimated that surgery would be less costly than cinacalcet when the treatment duration with cinacalcet reached 14 months.[20] During treatment with cinacalcet, 6–4% of patients discontinued treatment due to adverse effects such as gastrointestinal intolerance, and renal graft function was observed to be stable or minimally low during follow-up. It was concluded that PTX is more cost-effective due to the significant additional cost and chronic use of cinacalcet.[31]

In conclusion, in our study, both cinacalcet treatment and PTX were found to be similarly effective and safe in reducing intact PTH and normalizing serum calcium in renal allograft recipients with hypercalcemia due to persistent HPT. There was no negative effect of both treatment methods on allograft function in the long and short term when compared with the control groups. Therefore, patient-specific cinacalcet or PTX treatments may be preferred. Surgery seems to be the most appropriate treatment method in patients with severe HPT and symptomatic hypercalcemia with the traditional approach. Medical treatment may be preferred in the group with mild hypercalcemia, but the cost-effectiveness of long-term treatment with cinacalcet should also be considered.

Our study is a small-scale, single-center study, but we think it is valuable as it compares allograft function and the course of HPT in the long and short term, between both treatment groups, as well as with a control group of similar characteristics. However, there is a need for robust, well-designed randomized controlled study with long-term follow-up comparing these two treatment option trials focusing on clinical endpoints such as quality of life, cardiovascular morbidity, and renal bone disease so that the optimal treatment for an individual patient can be chosen.

Ethics Committee Approval

This study approved by the Kartal Dr. Lutfi Kirdar City Hospital Clinical Research Ethics Committee (Date: 13.01.2021, Decision No: 514/193/4).

Informed Consent

Retrospective study.

Peer-review

Internally peer-reviewed.

Authorship Contributions

Concept: M.M.; Design: M.M.; Supervision: E.P.; Materials: M.M.; Data: M.M.; Analysis: E.P.; Literature search: M.M.; Writing: M.M.; Critical revision: E.P.

Conflict of Interest

None declared.

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Böbrek Nakli Sonrası Kalıcı Hiperparatiroidizm Yönetimi

Amaç: Başarılı böbrek naklinden sonra bile, ilerleyici kemik kaybı, kırıklar, tubulointerstisyel kalsifikasyonlar, vasküler kalsifikasyon ve greft disfonksiyonu gelişimi için bir risk faktörü olarak kabul edilen hiperkalsemi ile kalıcı hiperparatiroidizm (HPT) yaygındır. Subtotal paratiroidektomi (PTX) standart tedavidir, ancak şu anda bunun yerini kalsimimetik sinakalset almıştır. Bu tek merkezli, geriye dönük çalışmanın amacı, böbrek transplantasyonu hastalarında PTX ve sinakalset'in kalsiyum, fosfor ve paratiroid hormon (PTH) düzeyleri ve greft fonksiyonu üzerindeki uzun vadeli etkilerini karşılaştırmaktır.

Gereç ve Yöntem: Çalışma popülasyonu, Ocak 2004 ile Aralık 2020 arasında takip edilen, 13'ü PTX uygulanan ve 12'si sinakalset tedavisi alan 24 hastadan oluşuyordu. Cerrahi grup ve medikal tedavi grubu karşılaştırıldı. Yaş, cinsiyet, nakil zamanı ve böbrek vericisi açısından benzer özelliklere sahip kontrol grubu oluşturulmuş ve sonuçlar yine bu grupla karşılaştırılmıştır. Ortalama PTH, kalsiyum, fosfor, kreatinin düzeyleri ve eGFR değerleri PTX ve sinakalset tedavisi öncesi/sonrası kaydedildi.

Bulgular: Hem paratiroidektomi hem de sinakalset gruplarının uzun dönem ve kısa dönem allogreft fonksiyonları üzerinde kontrol gruplarına göre negatif etkisi yoktu. Allogreft fonksiyonları paratiroidektomi ve sinakalset grupları arasında benzerdi.

Sonuç: Sonuç olarak, hiperparatiroidizm nedeniyle hiperkalsemisi olan renal allogreft alıcılarında hem sinakalset tedavisinin hem de paratiroidektominin intakt PTH'yi azaltmada ve serum kalsiyumunu normalleştirmede benzer şekilde etkili ve güvenli olduğu bulundu.

Anahtar Sözcükler: Böbrek nakli; paratiroidektomi; sinakalset.