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Cinacalcet *versus* Parathyroidectomy in the Treatment of Secondary Hyperparathyroidism Post Renal Transplantation

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Background. Persistent hyperparathyroidism (HPT) with hypercalcemia is prevalent after transplant and is considered a risk factor for progressive bone loss and fractures and vascular calcification, as well as the development of tubulointerstitial calcifications of renal allografts and graft dysfunction. The subtotal parathyroidectomy is the standard treatment, although currently it has been replaced by the calcimimetic cinacalcet.

Aim. The hypothesis of this study is that subtotal parathyroidectomy is superior to cinacalcet for treatment of persistent secondary parathyroidectomy post renal transplant, with minimal morbidity and significantly it reduces the cost of treatment after transplantation.

Methods. We report our long-term clinical experience with either cinacalcet or parathyroidectomy in 59 kidney transplant recipients with hyperparathyroidism. Group one included medical treatment with cinacalcet and had 45 patients while parathyroidectomy patients (group 2) were 16 patients with two of them excluded because of surgical failure.

Results. No difference was found between groups for any parameter. A greater short-term change of calcium and phosphorus homeostasis obtained by surgery than by cinacalcet, and in long term change, no significant difference between the two groups.

Conclusions: The main findings of this study are that correction of severe hyperparathyroidism was similar in both surgical and cinacalcet groups with the absence of a difference of long-term serum iPTH 1-84 levels between the two groups.

Key words: Hyperparathyroidism, Cinacalcet hydrochloride, Parathyroidectomy, Kidney transplantation.

INTRODUCTION

Persistent hyperparathyroidism (HPT) with hypercalcemia is prevalent after transplant and is considered a risk factor for progressive bone loss and fractures and vascular calcification, as well as the development of tubulointerstitial calcifications of renal allografts and graft dysfunction [1-3], therefore it negatively affects graft and patient outcome.

The subtotal parathyroidectomy is the standard treatment, although currently it has been replaced by the calcimimetic cinacalcet. Therapeutic options are limited for patients with milder forms of hypercalcemic hyperparathyroidism and those not eligible for parathyroid surgery [4, 5].

The calcimimetic cinacalcet offers a new treatment strategy for these patients. Cinacalcet has been successfully used to control secondary hyperparathyroidism in chronic hemodialysis patients and was shown to reduce the risk of parathyroidectomy in those patients [6, 7]. Several studies guarantee that cinacalcet is effective in controlling hypercalcemia derived of persistent hyperparathyroidism after renal transplantation. However, maintenance treatment has a main drawback that hypercalcemia increases quickly after the treatment is stopped. This fact makes increase a lot of the cost of transplantation in those patients. Due to the slow regression of hyperparathyroidism after transplantation, the treatment with cinacalcet may be required for a prolonged period in these patients. So far, only few data on the long-term use of cinacalcet in kidney transplant recipients are available [8, 9].

The hypothesis of this study is that subtotal parathyroidectomy is superior to cinacalcet for treatment of persistent secondary HPT post renal transplant, with minimal morbidity and it significantly reduces the cost of treatment after transplantation. Here, we report our long-term clinical experience with either cinacalcet or parathyroidectomy in 59 kidney transplant recipients with hyperparathyroidism.

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MATERIAL AND METHODS

STUDY DESIGN AND SETTING

It is an interventional prospective open label efficacy controlled study with parallel assignment. It was approved by the local ethics committee of our hospital. Between January 2005 and December 2013, 59 stable kidney transplant recipients with hyperparathyroidism were included in the study. Patients were recruited from our nephrology outpatient clinics. Group one included medical treatment with cinacalcet and had 45 patients while parathyroidectomy patients (group 2) were 16 patients with two of them excluded because of surgical failure.

Inclusion criteria were age between 18 and 80 years with functioning renal transplant, GFR ≥ 30 mL/min, time post-transplant > 6 months, iPTH > 100 pg/mL, serum ionised calcium ≥ 5.4 mg/dL, serum phosphorus ≤ 3 mg/dL.

Exclusion criteria were any contraindication to surgery and patients with a history of parathyroidectomy. Primary outcome measures are changes in blood calcium and parathyroid hormone levels with a time frame of 12 months. Starting from the date of inclusion, we prospectively analyzed the course of biochemical parameters of interest over time until one year follow-up.

TREATMENT WITH CINACALCET

Cinacalcet (Mimpara) was initiated at 30 mg once daily with dinner. The dose of cinacalcet was titrated to achieve total serum calcium levels within the normal range. The maximum daily dose was 180 mg, administered as 90 mg twice daily. In case of side effects, cinacalcet at any dose was given twice daily. If intact PTH levels were not controlled with cinacalcet alone, the participants additionally received active vitamin D analogues. The participants did not receive any phosphate supplements or bisphosphonates during treatment with cinacalcet.

SURGICAL PARATHYROIDECTOMY

The indication of Parathyroidectomy was made because of medically uncontrollable, long-standing, and marked osteitis fibrosa. Surgical procedures were subtotal parathyroidectomy, a fraction of one gland (one third to one half) being left in place. The surgeon always attempted to identify four or more parathyroid glands in the neck and the superior retrosternal area accessible to exploration without sternotomy. Tissue cryopreservation was done in all cases.

Postoperative Calcium and Vitamin D Therapy: All patients had been without calcium or vitamin D supplementation several weeks before surgery. Postoperative calcium, phosphorus and vitamin D supplementation were prescribed by the attending nephrologist on a daily basis. A record was made of the cumulative doses of minerals and vitamins administered during the 8 weeks after surgery, and these data were used as an indicator of the individual's response to surgery.

STATISTICAL ANALYSES

All values have been expressed as means ± SD. Group means were compared by t test. Distribution data were analyzed by $\chi 2$ test. Comparison between groups was done by one-way analysis of variance or unpaired t test as appropriate. Simple linear regression was used to evaluate the relationship between biochemical data and other quantitative parameters. Multiple regression (SAS Software version 603; SAS Institute Inc., Cary. NC) was used to identify predictive factors of long-term outcome after Parathyroidectomy.

RESULTS

BASELINE AND DEMOGRAPHIC DATA

Group one included medical treatment with cinacalcet and was 45 patients while parathyroidectomy patients (group 2) were 16 patients with two of them excluded because of surgical failure. No difference was found between groups for any parameter. Baseline serum APT was also well correlated with lowest postoperative serum calcium levels ($r = 0.485$; $P < 0.001$). Preoperative APT values were 295 ± 49 IU/L for surgical group and 318 ± 62 IU/L for the cinacalcet group (P = not significant). Baseline plasma PTH levels were not statistically different between the two groups.

IMMEDIATE POSTOPERATIVE TIME PERIOD

At least two of the following three criteria were required to ascertain short-term success of surgery, namely decrease of serum calcium, phosphorus and PTH. By these criteria, only two patients had to be considered surgical failures. Fourteen patients had a significant decrease of

serum calcium, phosphorus, and iPTH levels after parathyroidectomy. Table 2 shows the post-operative short-term data. When we consider overall PTH results, both groups had comparable results. Although the change of these indices was similar in both groups, patients in surgical group required higher total doses of calcium and vitamin D supplementation in the first 8 week period (calcium carbonate, 1275 ± 123 g in surgical patients compared with 709 ± 181 g in cinacalcet patients; $P < 0.001$; 1-alpha-vitamin D3, 146 ± 19 μg compared to 157 ± 17 μg in Cinacalcet patients; $P < 0.02$). This observation was suggestive of a greater short-term change of calcium and phosphorus homeostasis obtained by surgery than by cinacalcet.

Table 1
Baseline data of renal transplant patients presented as data ± SD

Secondary hyperparathyroidism		Medical group	Surgical group	P value
Patients	unit			
Number		45	14	
Age	year	41.1 ± 2.5	44.5 ± 2.2	NS
Age range	Year	18-61	19-58	NS
Gender (male/female)		24/21	10/4	
Years on dialysis	years	7.5 ± 0.8	8.1 ± 0.9	NS
Dialysis range	years	3-14	2-12	
Laboratory data	Normal range			
Total calcium mg/dL	8.5-10.2	10.68 ± 0.20	10.64 ± 0.25	NS
Ionized calcium mg/dL	4.4-5.4	5.62 ± 0.11	5.60 ± 0.12	
Phosphorus mg/dL	3.5-4.5	3.12 ± 0.30	2.81 ± 0.30	NS
Alkaline phosphatase (IU/L)	25-200	318 ± 62	295 ± 49	NS
Aluminum μmol/L		2.7 ± 0.3	2.2 ± 0.4	NS
PTH (1-84) pg/mL	15-65	695 ± 52	721 ± 58	NS
Serum creatinine (mg/dL)	0.8-1.4	1.4 ± 0.4	1.5 ± 0.3	NS

Table 2
Eight weeks short term data (eight weeks after the intervention)

Parameters	Medical group n = 45	Surgical group n = 14	P value
PTH (parathormone level)			
Plasma i PTH (1-84)(pg/mL)	120 ± 2	108 ± 11	NS
Δ PTH (preoperative PTH or premedical - post PTH)	562 ± 39	617 ± 43	NS
Biochemical data			
Serum creatinine (mg/dL)	1.47 ± 0.4	1.60 ± 0.3	NS
Serum total calcium (mg/dL)	6.88 ±1.1	6.84 ± 1.2	NS
Serum ionized calcium (mg/dL)	3.78 ± 0.8	3.61 ± 0.12	NS
Δ ionized calcium (pre - lowest post)	1.84 ± 0.07	2.01 ± 0.08	NS
Phosphorus (mg/dL)	3.11 ± 0.20	2.91 ± 0.16	NS
Δ phosphorus (pre - post)	4.01 ± 0.08	3.90 ± 0.09	NS
Alkaline phosphatase (IU/L)	276 ± 56	251 ± 42	NS
Δ Alkaline phosphatase	42 ± 32	44 ± 39	NS
Δ Ca × Δ p	7.37 ± 0.55	7.83 ± 0.72	NS
Calcium and vitamin D treatment			
Calcium total dose during first 8 weeks (gm)	709 ± 181	1275 ± 123	< 0.001
1-alpha-OH vitamin D3 in μg during first 8 weeks (μg)	157 ± 17	146 ± 19	< 0.02

LONG-TERM PARATHYROID STATUS

Long term one year parameters of calcium and phosphorus metabolism including iPTH 1-84 levels observed in both surgical and medical groups have been summarized in Table 3. A wide variation of iPTH levels existed within both groups. Mean values were not significantly different between groups: 205 ± 91 pg/mL in surgical group compared with 372 ± 99 pg/mL in cinacalcet patients. We further analyzed in more detail the distribution of iPTH 1-84 levels in both groups by allocating the patients to subgroups according to the following criteria: PTH < 15 pg/mL; hypoparathyroidism; PTH between 15 and 150 pg/mL; euparathyroid state; and PTH > 150 pg/mL; hyperparathyroidism. When such a subclassification was used, there was also no significant difference between the two groups (Table 3).

Table 3
Long term evaluation (one year)

Parameters	Medical group n = 45	Surgical group n = 14	P value
Biochemical data			
i PTH (1-84) pg/mL	372 ± 99	205 ± 91	NS
Serum ionized calcium	3.52 ± 0.1	3.71 ± 0.07	< 0.05
Serum phosphorus (mg/dL)	4.1 ± 0.4	3.85 ± 0.3	NS
Serum creatinine (mg/dL)	1.6 ± 0.3	1.5 ± 0.3	NS
Serum albumin (g/dL)	3.7 ± 0.3	3.8 ± 0.3	NS
Follow-up months	15 ± 5	12 ± 4	NS
Parathyroid status			
Hyperparathyroidism (n)	17	6	NS
PTH > 150 pg/ml (%)	378	42.8	
Euparathyroidism	15	4	NS
15 < PTH < 150 pg/mL (%)	33.3	28.6	
Hypoparathyroidism	13	4	NS
PTH < 15 pg/ml (%)	28.9	28.6	

Results are expressed as mean ± SD
n = number of patients

DISCUSSION

The main findings of this study are that correction of severe hyperparathyroidism was similar in both surgical and cinacalcet groups with the absence of a difference of long-term serum iPTH 1-84 levels between the two groups. The lack of differences might be due to the low statistical power (the difference concerning iPTH seems clinically important, but it did not reach statistical significance), because the sample size was small (especially the surgery group). Moreover, achievement of euparathyroid state was seen in only about one third of the patients in the long run. The short-term efficacy of parathyroidectomy and calcimimetic therapy in the treatment of secondary hyperparathyroidism after kidney transplantation has been well demonstrated in this study. Hypercalcemia associated with hyperparathyroidism is a common complication after kidney transplantation [10]. Typically, serum calcium levels decrease in the immediate posttransplant period and then progressively increase and stabilize at approximately six months after transplantation with only minor variations thereafter. In 5% to 25% of cases, serum calcium levels remain elevated even in long-term kidney transplant recipients [11]

Depending on the institution, some experts prefer early surgical intervention, while others recommend waiting for approximately one year for spontaneous resolution of mild to moderate hyperparathyroidism before therapeutic intervention [12]. One concern about parathyroidectomy in kidney transplant recipients is related to the fact that PTH levels remain below the target range as recommended for chronic kidney disease patients in more than half of the cases [13]. It is expected that persistent hypoparathyroidism after parathyroidectomy might exacerbate low turnover bone disease, which was commonly observed after kidney transplantation. Especially in kidney transplant recipients treated with steroids, PTH is considered to play an important role in maintaining bone metabolism. Consequences of persistent and irreversible hypoparathyroidism after parathyroidectomy could be particularly detrimental in case of graft loss and return to dialysis. Hyperparathyroidism is regarded an important adaptive response to decreased renal function in order to maintain mineral and bone metabolism, a regulatory mechanism that is lost after parathyroidectomy [14].

A more flexible and reversible control of hyperparathyroidism can be achieved by medical treatment with calcimimetics. Calcimimetics increase the sensitivity of the calcium sensing receptor towards calcium, thereby exerting PTH-suppressive and calcium lowering effects [15]. Since cinacalcet has become available for treatment of secondary hyperparathyroidism in chronic dialysis patients, there has also been increasing interest in the use of this drug after transplantation [16].

Regarding calcium homeostasis, we achieved a reduction in total serum calcium levels which is in accordance with previous short-term studies. Kruse and colleagues described beneficial effects of cinacalcet on serum calcium levels even after drug withdrawal after twelve months of treatment, with hypercalcemia being persistently controlled in half of the patients at nine months after cessation. In general, data on the effect of cinacalcet on graft

function are contradictory. Some studies reported a stable graft function following treatment with cinacalcet after short-term use while others showed deterioration [17]. In this study, no significant difference was seen in serum creatinine from baseline data with stable graft function in both groups. We believe that in future, the performance of long-term studies will be challenging. We are convinced that, despite its limitations, the present study provides valuable experience on the comparable long-term experience of use of cinacalcet after transplantation compared to surgical parathyroidectomy.

Declaration of interest: All authors declare that they have no conflict of interest.

Introducere. *Hiperparatiroidismul persistent cu hipercalcemia apare frecvent post transplant renal şi este considerat factor de risc pentru osteodistrofie, fracturi şi calcificări vasculare precum şi calcificări tubulointerstiţiale. Paratiroidectomia subtotală este tratamentul de elecţie deşi acum este înlocuită din ce în ce mai mult de terapia cu cinacalcet, un medicament calcimimetic. Studiul pleacă de la premiza faptului că paratiroidectomia subtotală este superioară tratamentului cu cinacalcet pentru tratamentul hiperparatiroidismului persistent post transplant renal, cu o morbiditate minimă şi care reduce semnificativ costurile tratamentului post transplant renal.*

Materiale şi metode. *Prezentăm experienţa noastră clinică cu tratament fie cu cinalacet fie cu tratament chirurgical (paratiroidectomie subtotală) la 59 de transplantaţi renali. Primul grup a avut 45 de pacienţi trataţi cu cinalacet şi grupul al doilea a avut 16 pacienţi trataţi cu paratiroidectomie subtotală, doi pacienţi fiind excluşi din acest grup deoarece nu au avut tratament chirurgical corespunzător.*

Rezultate. *Nu a fost găsită nicio diferenţă semnificativă statistic între cele două grupuri. A fost observată o îmbunătăţire pe termen scurt a homeostaziei calciului şi fosforului obţinută prin tratament chirurgical mai degrabă decât cu cinacalcet însă pe termen lung nu a fost observată nicio diferenţă între cele două grupuri.*

Concluzii. *Corecţia hiperparatiroidismului sever a fost similară atât la pacienţii trataţi chirurgical, cât şi la pacienţii trataţi cu cinacalcet cu absenţa unei diferenţe semnificative statistic a nivelurilor serice ale iPTH 1-84 între cele două grupuri.*

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