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ORIGINAL ARTICLE

Hypoparathyroidism after total parathyroidectomy with immediate autotransplantation or subtotal parathyroidectomy for hyperparathyroidism after renal transplantation

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Abstract

Introduction: Hypoparathyroidism is a nocuous complication. Parathyroidectomy (PTx) is the treatment of choice for persistent hyperparathyroidism after renal transplantation (HPT-RT). **Objective:** Analyze the postoperative hypoparathyroidism rate after total parathyroidectomy with immediate autotransplantation (PTxT+AT) and subtotal parathyroidectomy (PTxST), due to HPT-RT. **Materials and Methods**: Retrospective, cohort study of patients who underwent PTx due to HPT-RT between 2013 and 2018. The following serum parameters were analyzed before surgery, in the immediate postoperative period, and one and two years after surgery: total calcium (CaT), ionic calcium (Cai), phosphorus (P), parathormone (PTH), and creatinine; in addition, a search was conducted in the patients' medical records to verify whether they received calcium and/or calcitriol oral supplementation at the same time intervals. **Results:** Thirty-eight patients underwent PTx (57.5% PTxT+AT; 42.5% PTxST). Mean CaT, Cai and P values and median PTH and creatinine values were similar. Significant difference was observed before and immediately after surgery for CaT, Cai, P, and PTH ($p< 0.0001$). There was also difference pre- and post-surgery for creatinine ($p=0.0004$ PTxT+AT; $p=0.028$ PTxST). The PTxST group needed less calcium supplementation ($p=0.0003$; $p=0.01$). One year after surgery, PTxT+AT and PTxST hypoparathyroidism rates were 61.9 and 11.8%, respectively ($p=0.0025$). **Conclusion:** There was similarity between the groups. Biochemical improvement was observed from the preoperative to the immediate postoperative periods in each group separately. One year after surgery, there was stability in calcium levels in both groups. Serum PTH and calcium levels tended to be higher in the PTxST group after two years. Both groups presented transient deterioration of renal function. The PTxST group needed less $CaCO_3$ supplementation. Both techniques had satisfactory outcomes. More patients required calcium and calcitriol supplementation after PTxT+AT. The PTxST group presented a lower hypoparathyroidism rate.

Keywords: hyperparathyroidism; parathyroidectomy; hypoparathyroidism; renal transplantation.

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Introduction

Chronic kidney disease (CKD) causes disorders in bone and mineral metabolism, stimulating increased function of the parathyroid glands. This hyperfunction, in search of metabolic adaptation, is called secondary hyperparathyroidism (HPT)[1]. Secondary HPT can manifest itself clinically in different ways, predominantly through musculoskeletal signs and symptoms, increasing morbidity and even mortality[1].

When renal transplantation is successful, there is restitution, even if partial, of several functions. With the improvement of mineral metabolism, it is assumed that the stimulus to high PTH secretion is interrupted. In fact, many patients present improved metabolic conditions after renal transplantation[2,3]. However, in some of them, HPT persists or develops later[4]. It is believed that this occurs because the previously stimulated parathyroid tissue is autonomously functioning. This tissue no longer responds to the stimulation of circulating calcium, phosphorus, and vitamin D[5]. This condition is sometimes called tertiary HPT. HPT-RT is a serious complication, as it has the potential to worsen the patient's clinical condition and even result in loss of the transplanted kidney[6].

Despite the small frequency compared with other problems faced by patients that have undergone renal transplantation, the progressive increase and the absolute number of kidney transplant recipients justify the attention to HPT complications in this population[7]. In 2011, renal transplantation accounted for approximately 21% of all transplants in Brazil. In that year, 4,939 kidney transplants were performed, almost double the number recorded in 2001[8].

There has been progress in the non-surgical treatment (invasive or not) of HPT-RT[9-12]. Some authors suggest the use of calcimimetics, for example. However, surgical treatment is still the standard therapy for this condition, and the use of these substances (employed in 0.6 to 5.6% of transplanted individuals[5]) can sometimes delay the operation and, during this delay, lead to complications attributable to the underlying disease[5,13].

A previous study showed that 3.1% of kidney transplant recipients needed to undergo parathyroidectomy (PTx) at the Hospital das Clínicas of the University of Sao Paulo Medical School (HC-FMUSP)[14]. However, this figure is expected to grow, both because of the increase in the number of renal transplantations and the proportion of pre-transplant HPT[7]. There is evidence that referral to surgery is also smaller than the necessary in some institutions, which suggests that these figures are underestimated[13]. Prevalence of severe secondary HPT was estimated at 10.7% of dialysis patients in Brazil[15]. Thus, this theme is of great relevance in the Brazilian context.

The extent of PTx varies according to personal preferences and experiences, and is associated with pathophysiological knowledge[7]. In cases of renal transplantation, bilateral cervical exploration and more extensive resections are recommended. The most commonly accepted techniques are subtotal parathyroidectomy (PTxST) or total parathyroidectomy with immediate autotransplantation (PTxT+AT)[1].

Overall, PTx is a safe operation with low complication rates. Transient hypocalcemia is the most common complication, affecting nearly 100% of patients undergoing PTxT+AT. In these individuals, the grafted tissue usually regains its function within a few months after surgery[5,16]. However, interpretation in the acute phase is hindered by the possibility of intense remineralization, called hungry bone syndrome[17]. Thus, not all surgeons accept that transient hypocalcemia be, in fact, mentioned as a complication. In contrast, permanent hypocalcemia is a complication reported in up to 10% of patients, and is more present in PTxT+AT[5]. In addition, in PTxST, the concern with the possibility of recurrence and new cervical intervention is also present[1].

Therefore, the concern with relapse or post-surgical permanent hypoparathyroidism in renal transplanted HPT patients is the center of attention for surgeons regarding the choice of technique to be performed, with the midpoint as the desired goal[5].

Considering that post-PTx hypoparathyroidism, in addition to occasional symptoms of hypocalcemia or more severe hypocalcemia crises, can affect bone metabolism with deleterious effects on health, it is important to identify which characteristics of patients and aspects of the surgical technique can contribute to parathyroid autograft hypofunction. The possible knowledge of these factors may allow the surgeon to modify their technique and postoperative care, as well as enable greater attention in the follow-up and establishment of earlier therapeutic measures[16].

In the Brazilian context, the outcomes of surgical treatment of HPT-RT have been little commented, which would already justify its study and report. The HC-FMUSP has accumulated significant experience in the treatment of HPT-RT through both PTxT+AT and PTxST.

This study aims to analyze and compare 1) the rate of patients who developed parathyroid hypofunction and presumed hypoparathyroidism after undergoing PTxT+AT or PTxST due to persistent HPT-RT, 2) the curves of total calcium (CaT), ionic calcium (Cai), phosphorus (P), parathormone (PTH) and creatinine, and 3) oral supplementation with calcium and/or calcitriol regarding the outcomes of the two surgical techniques.

Materials and methods

This is a retrospective study conducted with a cohort of patients undergoing PTxT+AT or PTxST to treat HPT-RT at HC-FMUSP between January 2013 and December 2018 with a post-surgical 2-year follow-up. This study is part of a line of research and a project that were submitted to and approved by the HC-FMUSP Research Ethics Committee, with Certificate of Presentation and Ethical Appraisal (CAAE) no. 0949.0.015.000.08. The study was approved on 04 Feb 2009 and its electronic registration was obtained on 17 Feb 2009, through extension also approved under protocol no. 1072/08 on 16 Dec 2015.

At the HC-FMUSP, HPT in patients undergoing successful renal transplantation is defined as PTH-dependent hypercalcemia.

Data regarding age at surgery and sex were investigated. The following serum parameters were analyzed before surgery, in the immediate postoperative period, and one and two years after surgery: total calcium (CaT), ionic calcium (Cai), phosphorus (P), systemic parathormone (PTH) (collected in the limb not grafted with the parathyroid in the case of PTxT+AT), and creatinine. In addition, a search was conducted in the patients' medical records to verify whether they received calcium and/or calcitriol oral supplementation at the same time intervals.

The following reference values were adopted: CaT: 8.6-10.2 mg/dL, Cai: 4.4-5.2 mg/dL, P: 2.7-4.5 mg/dL, PTH: 15-65 pg/mL, and creatinine: 0.5-1.1 mg/dL (for women) and 0.6-1.2 mg/dL (for men). Based on personal experience and judgments, these authors considered severe hypocalcemia when patients presented CaT values <8 mg/dL. Although there is, in fact, no consensus on this matter in kidney transplant recipients, this value is used to diagnose hypoparathyroidism postoperatively[18].

Autografts (in PTxT+AT) or parathyroid remnants (in PTxST) were considered as hypofunctioning when patients, at least after one year of follow-up, presented PTH levels persistently below the lower limit of normality for the procedure used and/or when they needed oral supplementation to maintain adequate serum calcium levels, regardless of the PTH value.

The Kolmogorov-Smirnov test was used to verify whether data distribution was parametric among continuous quantitative variables. Parametric data were presented as arithmetic mean and standard deviation, whereas nonparametric data were described as median and interquartile range. Considering that the mean and median values are very close in normal distributions, a choice of made to show the median values even in data with parametric distribution to facilitate their combined presentation in a single table. Qualitative (or categorical) variables were presented as number and frequency.

A significance level of 5% ($p<0.05$) was adopted for all statistical analyses. The unpaired *t*-test was used to analyze the continuous quantitative variables, analysis of variance (ANOVA) with the Bonferroni multiple comparison test was applied to the variables with normal distribution, and the Kruskal-Wallis test and Dunn's post hoc test were used to assess the continuous quantitative variables with non-parametric distribution in the multiple comparisons. In addition, the Wilcoxon test was applied to multiple paired comparisons of variables with nonparametric distribution. The categorical variables were compared using the Fisher's exact test.

The data were analyzed and synthetically plotted on graphs generated using the PRISMA® software.

Results

The study sample consisted of 40 patients undergoing surgery due to HPT-RT. The participants were divided into two groups: PTxT+AT and PTxST. Two patients were excluded from the study due to loss of follow-up and lack of late data, both belonging to the PTxT+AT group. Mean age was 49.8 ±2.6 years in the PTxT+AT group and 51.0 ±2.9 years in the PTxST group (p=0.752, unpaired *t*-test). The PTxT+AT group was composed of 12 (57.1%) women and 9 (42.9%) men, whereas the PTxST group included 10 (58.8%) women and 7 (41.01%) men. PTxT+AT and PTxST were performed in 23 (57.5%) and 17 (42.5%) patients, respectively.

Table 1 shows the descriptive statistics of data regarding CaT, Cai, P, PTH, and creatinine. No statistically significant difference was observed for the values of these parameters between groups.

Table 1. Pre- and post-operative values of total calcium (CaT), ionic calcium (Cai), phosphorus (P), parathormone (PTH), and creatinine.

Surgical period	Pre		Post		After 1 year		After 2 years	
	PTxT+AT	PTxST	PTxT+AT	PTxST	PTxT+AT	PTxST	PTxT+AT	PTxST
CaT (mg/dL)*	11.0 (±1.0)	11.0 (±1.1)	9.83 (±1.0)	9.9 (±1.3)	9.1 (±1.0)	9.2 (±0.6)	9.0 (±0.8)	9.4 (0.6)
Cai (mg/dL)*	6.1 (±0.6)	6.0 (±0.6)	5.4 (±0.5)	5.4 (±0.7)	4.8 (±0.5)	4.9 (±0.3)	4.8 (±0.4)	5.0 (±0.4)
P (mg/dL)*	2.4 (±0.7)	2.2 (±0.6)	3.4 (±0.9)	3.2 (±0.8)	3.7 (±1.2)	3.0 (±0.8)	3.5 (±0.9)	3.2 (±1.0)
PTH (pg/mL)#	284 (171-646)	460 (230-786)	6.5 (0-10)	12 (7-31)	43 (27-77)	80 (54-131)	49 (28-75)	71 (54-118)
Creatinine (mg/dL)#	1.1 (0.9-1.9)	1.3 (1.0-2.2)	1.7 (1.0-3.1)	1.9 (1.4-2.6)	1.2 (1.0-2.0)	1.4 (0.9-2.2)	1.2 (0.8-1.7)	1.6 (1.1-2.4)

*Mean ±SD; #Median (Q1-Q3).
Caption: PTxT+AT = total parathyroidectomy with immediate autotransplantation; PTxST = subtotal parathyroidectomy.

Figure 1 shows the distribution of the CaT mean values and their respective 95% CI throughout the surgical periods in patients undergoing PTxT+AT and PTxST. ANOVA showed statistically significant difference between the CaT values in the preoperative and immediate postoperative periods ($p<0.0001$) for both groups separately. However, application of the Bonferroni multiple comparison test did not show statistically significant difference for these values before surgery, in the immediate postoperative period, and one and two years after surgery between the groups ($p>0.05$). As expected, the values of Cai were similar to those of CaT (Figure 2).

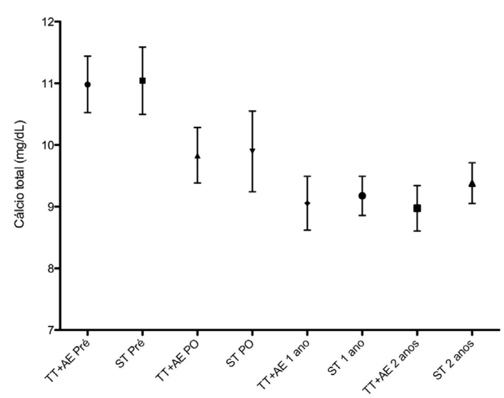

Figure 1. Distribution of the CaT mean values and their respective 95% CI throughout the surgical periods in patients undergoing PTxT+AT and PTxST.

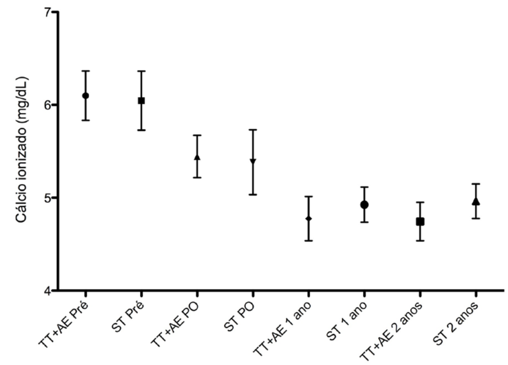

Figure 2. Distribution of the Cai mean values and their respective 95% CI throughout the surgical periods in patients undergoing PTxT+AT and PTxST.

Figure 3 shows the distribution of the P mean values and their respective 95% CI throughout the surgical periods in patients undergoing PTxT+AT and PTxST. ANOVA showed statistically significant difference between the P values in the preoperative and immediate postoperative periods (*p*<0.0001, 95% CI 1.7—0.1 in PTxT+AT and 95% CI 1.9—0.2 in PTxST) for both groups separately. However, application of the Bonferroni multiple comparison test did not show statistically significant difference for these values before surgery, in the immediate postoperative period, and one and two years after surgery between the groups (*p*>0.05).

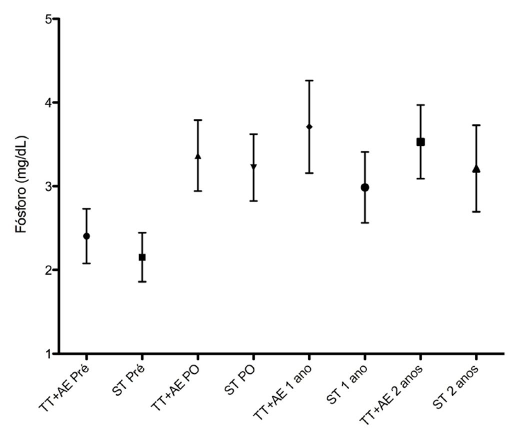

Figure 3. Distribution of the P mean values and their respective 95% CI throughout the surgical periods in patients undergoing PTxT+AT and PTxST.

Figure 4 shows the distribution of the PTH median values and their respective interquartile ranges (Q1-Q3) throughout the surgical periods in patients undergoing PTxT+AT and PTxST. The parametric Kruskal-Wallis test showed statistically significant difference (*p*<0.0001), with difference between all periods in the multiple comparisons of the Dunn's post hoc test for each group separately; however, no statistically significant difference (*p*>0.05) was

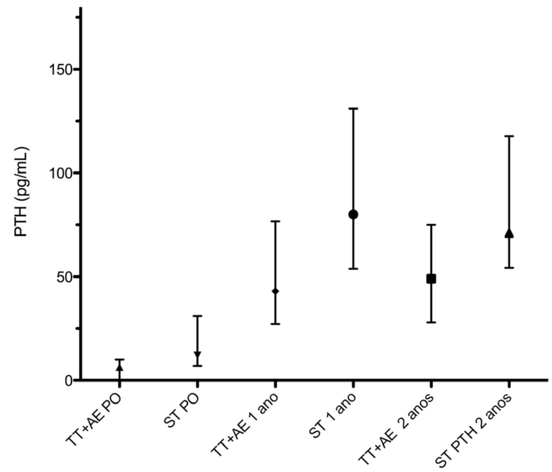

Figure 4. Distribution of the PTH median values and their respective interquartile ranges (Q1-Q3) throughout the surgical periods in patients undergoing PTxT+AT and PTxST.

observed between groups. An exception was found in the comparative analysis between preoperative PTH and systemic PTH one year after surgery for the PTxST group, which did not present a statistically significant result ($p>0.05$).

Figure 5 shows the distribution of the Creatinine median values and their respective interquartile ranges (Q1-Q3) throughout the surgical periods in patients undergoing PTxT+AT and PTxST. The non-parametric Kruskal-Wallis test did not show statistically significant difference ($p=0.12$), with no difference between all periods in the multiple comparisons of the Dunn's post hoc test both for each group separately and between groups. However, when the non-parametric Wilcoxon test was applied, that is, comparing the pre- and post-operative results of the same patient, statistically significant difference was found between the creatinine values before and immediately after surgery both in the PTxT+AT ($p=0.0004$) group and PTxST ($p=0.028$) group.

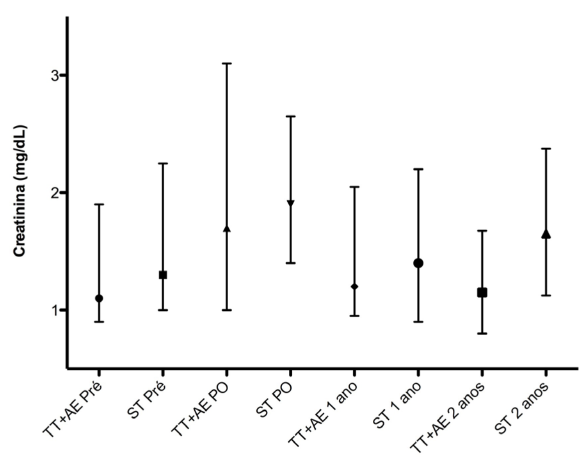

Figure 5. Distribution of the Creatinine median values and their respective interquartile ranges (Q1-Q3) throughout the surgical periods in patients undergoing PTxT+AT and PTxST.

Renal graft loss was observed in 4 (19%) patients in the PTxT+AT group and in 2 (11.7%) patients in the PTxST group. No statistically significant difference was found after application of the Fisher's exact test (p=0.67).

One year after surgery, no patient had systemic PTH below the lower limit of normality. The lowest values found after PTxT+AT and PTxST were 18 and 35 pg/mL, respectively. Two years postoperatively, minimum PTH values of 23 and 21 pg/mL were verified for patients submitted to PTxT+AT and PTxST, respectively. Therefore, considering only the minimum systemic PTH level, there would be no hypoparathyroidism in either group one year after surgery.

However, the use of calcium and calcitriol was different between the two groups. Tables 2 to 5 describe supplementation with calcium ($CaCO_3$) and/or calcitriol one and two years after surgery in both groups. Of the 21 patients undergoing PTxT+AT, 11 received $CaCO_3$ supplementation after one year, whereas none of the patients undergoing PTxST did. The Fisher's exact test showed no statistically significant difference (p=0.0003) regarding $CaCO_3$ supplementation one year after surgery between the groups. In the same period, calcitriol was used by 7 patients submitted to PTxT+AT and only 2 patients undergoing PTxST (p=0.25; Fisher's exact test). Analysis of $CaCO_3$ supplementation between groups by the same statistical test also showed statistically significant difference (p=0.01), with 9 patients undergoing PTxT+AT

Table 2. Distribution of the number of patients in the different $CaCO_3$ and/or calcitriol supplementation regimens one year after surgery in the PTxT+AT group.

N		Calcitriol (µg)					Total
		0	**0.25**	**0.5**	**0.75**	**1.0**	
$CaCO_3$ (mg)	**0**	7	2	0	0	0	**9**
	500	2	0	1	0	0	**3**
	1,000	2	0	1	0	1	**4**
	1,500	2	0	2	0	0	**4**
Total		**13**	**2**	**4**	**0**	**1**	**20**

Table 3. Distribution of the number of patients in the different $CaCO_3$ and/or calcitriol supplementation regimens one year after surgery in the PTxST group.

N		Calcitriol (µg)					Total
		0	**0.25**	**0.5**	**0.75**	**1.0**	
$CaCO_3$ (mg)	**0**	15	2	0	0	0	**17**
	500	0	0	0	0	0	**0**
	1,000	0	0	0	0	0	**0**
	1,500	0	0	0	0	0	**0**
Total		**15**	**2**	**0**	**0**	**0**	**17**

Table 4. Distribution of the number of patients in the different $CaCO_3$ and/or calcitriol supplementation regimens two years after surgery in the PTxT+AT group.

N		Calcitriol (μg)			Total
		0	0.25	0.5	
$CaCO_3$ (mg)	0	11	0	1	**12**
	500	3	0	1	**4**
	1,000	3	0	0	**3**
	1,500	1	0	0	**1**
	2,000	0	0	0	**0**
	2,500	0	0	0	**0**
	3,000	0	0	0	**0**
	3,500	0	0	0	**0**
	4,000	0	0	0	**0**
	4,500	0	1	0	**1**
Total		**18**	**1**	**2**	**21**

Table 5. Distribution of the number of patients in the different $CaCO_3$ and/or calcitriol supplementation regimens two years after surgery in the PTxST group.

N		Calcitriol (μg)			Total
		0	0.25	0.5	
$CaCO_3$ (mg)	0	14	2	0	**17**
	500	0	0	0	**0**
	1,000	1	0	0	**0**
	1,500	0	0	0	**0**
	2,000	0	0	0	**0**
	2,500	0	0	0	**0**
	3,000	0	0	0	**0**
	3,500	0	0	0	**0**
	4,000	0	0	0	**0**
	4,500	0	0	0	**0**
Total		**15**	**2**	**0**	**17**

and only 1 patient submitted to PTxST. However, 4 patients in the PTxT+AT group and 2 patients in the PTxST group received calcitriol supplementation two years after surgery (p=0.67, Fisher's exact test).

The tables show that the doses of calcium and calcitriol used were relatively low. As for calcium, the highest daily dose was 1,500 mg one year after surgery (taken by four patients); however, two years after surgery, one patient in the

PTxT+AT group used a maximum of 4.5 g/day of $CaCO_3$, even with systemic PTH and creatinine values of 23 pg/mL and 1.4 mg/dL, respectively. In the PTxST group, only one patient used maximum daily doses of 1,000 mg calcium and 0.25 mcg calcitriol two years after surgery.

Using the criterion of calcium and/or calcitriol supplementation one year after PTx, 6 patients would be using only $CaCO_3$, 5 patients would be using calcium and calcitriol, and 2 patients would be using only calcitriol (total of 13), that is, 61.9% of the patients, whereas 2 (11.8%) of the 17 patients in the PTxST group would present hypoparathyroidism. This is a statistically significant difference, with p=0.0025 according to the Fisher's exact test. Nevertheless, it should be noted that all patients presented normal systemic PTH levels.

Discussion

In HPT-RT, PTx should be considered when there is failure, even if transient, in the normalization of serum calcium levels[19]. Post-transplant PTH levels decline in a biphasic pattern: a sharp drop (approximately 50%) in the first 3 to 6 months after surgery, attributed to reduction in functional parathyroid mass, followed by a more gradual decline. Possibly, the long half-life of a parathyroid cell (approximately 20 years) contributes to the slow involution of hyperplastic glands after renal transplantation. However, structural and molecular changes determined by the disease mechanism are not fully understood, and other mechanisms may occur. As a result, in over 25% of kidney transplant recipients, elevated PTH levels may persist for up to one year after surgery despite patients presenting normal renal function[5]. In these patients, referral to surgery should be based on clinical or anatomical criteria determined by imaging (glandular volume) and metabolic (such as hypercalcemia) methods[5].

Choice of the surgical technique should consider a balance between promoting adequate excision of neoplastic parathyroid tissue to prevent disease persistence and minimizing risks, especially postoperative hypoparathyroidism[19].

Transient hypocalcemia is the most frequent surgical complication in the control of HPT-RT, varying between less than 10% in PTxST and 100% in PTxT+AT[5]. In patients undergoing PTxT+AT, the grafted tissue usually regains its function a few months after surgery[5]. Definitive hypoparathyroidism can range from 0 to 10% of cases, and it is more often associated with PTxT+AT than with PTxST[5].

In addition, hypoparathyroidism or hypocalcemia alone is capable of triggering several other complications potentially related to the surgical procedure[5]. These patients can develop significant and difficult-to-manage morbidities[20]; however, most of them can be controlled with calcium and/or vitamin D (occasionally magnesium) supplementation and require periodic laboratory monitoring[20].

In general, PTx is a safe surgical procedure that presents very low complication rates; however, many of the patients undergoing PTx due to HPT-RT have numerous comorbidities[5,19].

To define whether PTx was successful, most studies have used biochemical and laboratory criteria, such as normalization of serum calcium or decline of PTH levels[5]. However, observation of laboratory parameters separately may not be the most reliable way to predict whether the surgery was successful or not. Perhaps the clinical repercussion of these patients is a more important parameter in this analysis than serum calcium or PTH levels. For instance, the patient may have PTH levels within normality but present hypocalcemia, thus requiring oral calcium supplementation. Stack et al.[20] postulated that postoperative hypoparathyroidism should be defined by a biochemical character accompanied by symptoms related to hypocalcemia, and further demonstrated that, even if generally related, hypocalcemia can occur regardless of hypoparathyroidism; however, the latter will ultimately lead to hypocalcemia. Therefore, relative hypoparathyroidism or parathyroid insufficiency are better defined as clinical signs of hypoparathyroidism that require drug treatment despite normal laboratory values.

Based on laboratory measurements, a success rate ranging from 70 to 100% was found in the literature[5,19]. However, in many patients, serum calcium levels decreased below normality usually due, in the short term, to an intense inversion of their blood flow to bone tissue, as well as to an imbalance between bone formation and resorption - also known as hungry bone syndrome[5,19].

Florescu et al.[21] demonstrated that, in PTx following HPT-RT, serum PTH and calcium levels were reduced by 147 ng/L and 1.5 mg/dL, respectively, in the same group, and that the P level was reduced by 0.13 mg/dL, and no patient developed hypophosphatemia.

There is still a lack of studies that directly compare the effectiveness of PTxST or PTxT+AT in cases of HPT-RT. Retrospective studies have suggested a similarity of results[5]. In cases of primary multiglandular or secondary HPT, some surgeons prefer PTxST in order to avoid postoperative hypoparathyroidism[20]. Recently, there has also been a tendency to perform PTxST in HPT-RT.

A certain similarity in the behavior of patients in both groups could be observed in the present study. There was no statistically significant difference between them in the analysis of laboratory results. Difference was found only when the calcium, phosphorus and PTH laboratory results were compared in the pre- and immediate post-operative periods in each group separately, suggesting a biochemical improvement in both techniques. One year after surgery, an apparent stability of calcium levels was observed in both groups, with similar profiles.

Regarding the target PTH values, there is still little information and much disagreement in the literature. Some studies recommend following the National Kidney Foundation (NKF KDOQI) guidelines[5], while others simply suggest maintaining levels of PTH >50 pg/mL[19], or that hypoparathyroidism be characterized, among other factors, by PTH <12 pg/mL[20].

This study showed that serum PTH and calcium levels tended to be higher in the PTxST group two years after surgery. Although no statistically significant difference was observed between the groups, this trend should not be disregarded, given that HPT recurrence causes several damages to kidney transplant recipients. Thus, a longer follow-up, such as five years after surgery, could provide more solid and secure information regarding recurrence.

Overall, the patients in this study showed satisfactory outcomes with the measures implemented, including in terms of postoperative renal function. Unpaired analysis between the groups did not show statistical difference in the worsening of creatinine; however, paired analysis performed using the non-parametric Wilcoxon test showed statistical difference in the acute phase. Despite this, it was observed that, in both groups, the surgery led to acute worsening of renal function, with a tendency to improve over time. There was no significant difference in renal graft loss between the groups. In this aspect, the influence of hypoparathyroidism is not clear, and some authors have reported that less-than-subtotal parathyroidectomy would have less impact on the function of the transplanted kidney[22].

Many patients need intravenous calcium supplementation soon after PTx to maintain normal serum levels[5,19]. Oral calcium supplementation is started as soon as the patient regains the swallowing function, and the dose is adjusted as needed[5,19]. Oral supplementation is valid because oral calcium preparations have a low cost[20]. Typically, $CaCO_3$ and calcitriol are the drugs of choice, with the latter being a high-cost drug[20]. Stack et al.[20] reported that routine oral calcium supplementation reduced postoperative hypocalcemia by approximately 10%, and that addition of calcitriol, at doses of 0.5-1.0 µg/day, increased the effectiveness of oral calcium supplementation.

The main objective of long-term treatment of hypoparathyroidism is to maintain calcemic levels within an asymptomatic range and avoid fluctuations outside normal serum values[20]. For this, it is recommended that serum calcium levels remain close to the lower limit of normality, while phosphorus levels remain, at most, at the upper limit[20]. When serum calcium levels reach normality, the oral supplementation therapy can be suspended[5]. It is worth remembering that, in hypoparathyroidism, an increase in serum calcium may occur due to loss of the stimulation of tubular calcium reabsorption determined by PTH. This hypercalcemia can cause nephrolithiasis or nephrocalcinosis, resulting in damage to the transplanted kidney. Therefore, large calcium supplementation should be avoided and, when necessary, it should be optimized and accompanied by monitoring of renal excretion.

Stack et al.[20] also reported that most patients with hypoparathyroidism of various causes (mainly after PTxT+AT in patients without renal dysfunction or transplantation) required daily elemental calcium doses of 1,500 mg, and that there were cases requiring >9,450 mg/day. Calcitriol was almost always accurate, with doses ranging from 0.125 to 4.0 µg per day, with most patients taking 0.25 µg/day.

In this study, statistically significant difference between the groups regarding $CaCO_3$ supplementation was observed both one (p=0.0003) and two (p=0.01) years after surgery. Although the serum calcium level two years after surgery in both groups did not show statistically significant difference, the PTxST group needed smaller $CaCO_3$ doses. The same was not observed for calcitriol supplementation. One year after surgery, no patient in the PTxST group needed oral calcium supplementation. As for the PTxT+AT group, 55% of the patients required some dose of $CaCO_3$. Analysis of the supplementation profile two years after surgery showed that this difference was maintained: no patients in the PTxST group needed calcium supplementation while 48.8% of those in the PTxT+AT did. In this group, 23.8% of the patients needed daily $CaCO_3$ doses ≥1,000 mg, with one (4.7%) patient requiring 4,500 mg/day. Although more patients required significant calcium and calcitriol supplementation after PTxT+AT compared with that after PTxST, the biochemical parameters were very similar between the groups, and these patients seemed to present similar parameters two years after surgery. Nevertheless, using the criterion of calcium and/or calcitriol supplementation to define hypoparathyroidism, one year after surgery, 61.9% of the patients in PTxT+AT group would have this condition, whereas only 11.8% of the patients in the PTxST group presented this condition (p=0.0025). Despite this, all patients presented normal systemic PTH levels.

Limitations to the present study include the fact that this is a retrospective study, with a measurement bias; the lack of discrimination whether some tests were performed during acute health situations that could alter their results; the choice of surgery was not random, but based on the intraoperative decision of the surgical team responsible on the day; patient follow-up was carried out by different professionals, and there may not have been standardization regarding medication prescription; no symptoms of hypocalcemia were investigated in these patients; the type of immunosuppressive medication taken by the patients and its possible effects on bone metabolism, with impact on calcium management, were not assessed.

Conclusion

The behavior of patients in the PTxT+AT and PTxST groups presented some similarity. The laboratory results showed no differences between them. Biochemical improvement was observed from the preoperative to the immediate postoperative periods in each group separately. After one year of follow-up, an apparent stability of calcium levels could be noted in both groups. One year after surgery, there was stability in calcium levels in both groups. Serum PTH and calcium levels tended to be higher in the PTxST group two years after surgery. A longer follow-up period could have better clarified the chance of recurrence. Both techniques had satisfactory outcomes. Both groups presented transient deterioration of renal function. There was no significant difference in renal graft loss. The PTxST group needed less $CaCO_3$ supplementation one and two years after surgery; the same could not be observed regarding calcitriol. Although more patients required significant calcium and calcitriol supplementation after PTxT+AT, the biochemical parameters were very similar between groups. Using the criterion of oral calcium and/or calcitriol supplementation to define hypoparathyroidism, the PTxT+AT group presented a higher hypoparathyroidism rate.

Ethical matters

The present study was part of a line of research and a project that were submitted to and approved by the HC-FMUSP Research Ethics Committee, with Certificate of Presentation and Ethical Appraisal (CAAE) no. 0949.0.015.000.08.

The study was approved on 04 Feb 2009 and its electronic registration was obtained on 17 Feb 2009, through extension also approved under protocol no. 1072/08 on 16 Dec 2015.

References

1. Magnabosco FF, Tavares MR, Montenegro FLM. Tratamento cirúrgico do hiperparatireoidismo secundário: revisão sistematizada da literatura. Arq Bras Endocrinol Metabol. 2014;58(5):562-71. **http://dx.doi.org/10.1590/0004-2730000003372**. PMid:25166048.
2. Ianhez LE. Transplante Renal. Seguimento a longo prazo. São Paulo. Lemos Editorial; 2002. p. 36-8.
3. Evenepoel P. Recovery versus persistence of disordered mineral metabolism in kidney transplant recipients. Semin Nephrol. 2013;33(2):191-203. **http://dx.doi.org/10.1016/j.semnephrol.2012.12.019**. PMid:23465505.
4. Lewin E. Involution of the parathyroid glands after renal transplantation. Curr Opin Nephrol Hypertens. 2003;12(4):363-71. **http://dx.doi.org/10.1097/00041552-200307000-00004**. PMid:12815332.
5. Triponez F, Clark OH, Vanrenthergem Y, Evenepoel P. Surgical treatment of persistent hyperparathyroidism after renal transplantation. Ann Surg. 2008;248(1):18-30. **http://dx.doi.org/10.1097/SLA.0b013e3181728a2d**. PMid:18580203.
6. Torres A, Lorenzo V, Salido E. Calcium metabolism and skeletal problems after transplantation. J Am Soc Nephrol. 2002;13(2):551-8. **http://dx.doi.org/10.1681/ASN.V132551**. PMid:11805187.
7. Montenegro FLM. Paratireoidectomia total com autotransplante no tratamento do hiperparatireoidismo após transplante renal. [tese]. São Paulo: Faculdade de Medicina, Universidade de São Paulo; 2014.
8. Datasus. [Internet]. [cited 2014 July 21]. Available from: http://aplicacao.saude.gov.br/saude/transplante/Área_Especializada/relatorios_estatisticos/transplantes-realizados
9. Maass E, Mueller GA, Heller T, Koziolek MJ. Decrease in serum tacrolimus level and rise in serum creatinine under late addition of cinacalcet in a renal transplant recipient with hyperparathyroidism: a case report. Transplant Proc. 2007;39(10):3468-70. **http://dx.doi.org/10.1016/j.transproceed.2007.07.088**. PMid:18089410.
10. Cintin C, Karstrup S, Ladefoged SD, Joffe P. Tertiary hyperparathyroidism treated by ultrasonically guided percutaneous fine-needle ethanol injection. Nephron. 1994;68(2):217-20. **http://dx.doi.org/10.1159/000188260**. PMid:7830859.
11. Fletcher S, Kanagasundaram NS, Rayner HC, Irving HC, Fowler RC, Brownjohn AM, Turney JH, Will EJ, Davison AM. Assessment of ultrasound guided percutaneous ethanol injection and parathyroidectomy in patients with tertiary hyperparathyroidism. Nephrol Dial Transplant. 1998;13(12):3111-7. **http://dx.doi.org/10.1093/ndt/13.12.3111**. PMid:9870475.
12. de Barros Gueiros JE, Chammas MC, Gerhard R, da Silva Dias Boilesen CF, de Oliveira IR, Moysés RM, Jorgetti V. Percutaneous ethanol (PEIT) and calcitriol (PCIT) injection therapy are ineffective in treating severe secondary hyperparathyroidism. Nephrol Dial Transplant. 2004;19(3):657-63. **http://dx.doi.org/10.1093/ndt/gfg586**. PMid:14767023.

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13. Lou I, Schneider DF, Leverson G, Foley D, Sippel R, Chen H. Parathyroidectomy is underused in patients with tertiary hyperparathyroidism after renal transplantation. Surgery. 2016;159(1):172-9. **http://dx.doi.org/10.1016/j.surg.2015.08.039**. PMid:26603850.

14. Ferreira GF, Montenegro FL, Machado DJ, Ianhez LE, Nahas WC, David-Neto E. Parathyroidectomy after kidney transplantation: short- and long-term impact on renal function. Clinics (São Paulo). 2011;66(3):431-5. **http://dx.doi.org/10.1590/S1807-59322011000300012**. PMid:21552668.

15. Oliveira RB, Silva EN, Charpinel DMF, Gueiros JEB, Neves CL, Sampaio EA, Barreto FC, Karohl C, Ribeiro MC, Moysés RMA, Jorgetti V, Carvalho AB. Situação do hiperparatireoidismo secundário autônomo no Brasil: dados do censo brasileiro de paratireoidectomia. J Bras Nefrol. 2011;33(4):457-62. **http://dx.doi.org/10.1590/S0101-28002011000400011**. PMid:22189810.

16. Santos SRCL. Fatores preditivos da hipofunção do autoimplante de paratireoide em pacientes submetidos à paratireoidectomia total com autoimplante imediato por hiperparatireoidismo secundário à doença renal crônica. [tese]. São Paulo: Faculdade de Medicina, Universidade de São Paulo; 2012.

17. Ohe MN, Santos RO, Hojaij F, Neves MC, Kunii IS, Orlandi D, Valle L, Martins C, Janovsky C, Ferreira R, Delcelo R, Domingos AM, Abrahão M, Cervantes O, Lazaretti-Castro M, Vieira JG. Parathyroid carcinoma and hungry bone syndrome. Arq Bras Endocrinol Metabol. 2013;57(1):79-86. **http://dx.doi.org/10.1590/S0004-27302013000100011**. PMid:23440103.

18. Shoback DM, Bilezikian JP, Costa AG, Dempster D, Dralle H, Khan AA, Peacock M, Raffaelli M, Silva BC, Thakker RV, Vokes T, Bouillon R. Presentation of Hypoparathyroidism: Etiologies and Clinical Features. J Clin Endocrinol Metab. 2016;101(6):2300-12. **http://dx.doi.org/10.1210/jc.2015-3909**. PMid:26943721.

19. Shindo M, Lee JA, Lubitz CC, McCoy KL, Orloff LA, Tufano RP, Pasieka JL. The Changing Landscape of Primary, Secondary, and Tertiary Hyperparathyroidism: Highlights from the American College of Surgeons Panel, "What's New for the Surgeon Caring for Patients with Hyperparathyroidism. J Am Coll Surg. 2016;222(6):1240-50. **http://dx.doi.org/10.1016/j.jamcollsurg.2016.02.024**. PMid:27107975.

20. Stack BC Jr, Bimston DN, Bodenner DL, Brett EM, Dralle H, Orloff LA, Pallota J, Snyder SK, Wong RJ, Randolph GW. American Association of Clinical Endocrinologists and American College of Endocrinology Disease State Clinical Review: postoperative hypoparathyroidism – definitions and management. Endocr Pract. 2015;21(6):674-85. **http://dx.doi.org/10.4158/EP14462.DSC**. PMid:26135962.

21. Florescu M, Plumb T, Smith-Shull S, Nieman J, Mandalapu P, Islam KM. Calcium supplementation after parathyroidectomy in dialysis and renal transplant patients. Int J Nephrol Renovasc Dis. 2014;7:183-90. **http://dx.doi.org/10.2147/IJNRD.S56995**. PMid:24868170.

22. Jäger MD, Kaaden S, Emmanouilidis N, Lück R, Beckmann JH, Güner Z, Kespohl H, Glockzin K, Aselmann H, Kaudel CP, Schwarz A, Zapf A, Klempnauer J, Scheumann GF. Effect of incomplete parathyroidectomy preserving entire parathyroid glands on renal graft function. Arch Surg. 2011;146(6):704-10. **http://dx.doi.org/10.1001/archsurg.2011.138**. PMid:21690447.