

Published: July 31, 2023

Citation: Rosano M, Das Neves MC, et al., 2023. Subtotal Resection of Parathyroids Preserving an Intact Parathyroid in Patients with Tertiary Hyperparathyroidism, Medical Research Archives, [online] 11(7).
<https://doi.org/10.18103/mra.v11i7.2.4109>

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DOI
<https://doi.org/10.18103/mra.v11i7.2.4109>

ISSN: 2375-1924

RESEARCH ARTICLE

Subtotal Resection of Parathyroids Preserving an Intact Parathyroid in Patients with Tertiary Hyperparathyroidism

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ABSTRACT

Introduction: Parathyroid hormone, is one the controllers of calcium homeostasis, is synthesized and secreted by the parathyroid glands. They can become hyper functioning, generate excessive amounts of PTH, and determine the clinical-laboratory picture called hyperparathyroidism. When hyperparathyroidism is a consequence of a pre-existing metabolic

imbalance, it is called secondary. Secondary hyperparathyroidism is thus an acquired disorder represented by parathyroid hypersecretion in response to calcium homeostasis disorders.

Chronic kidney disease is a condition often associated with secondary hyperparathyroidism. It is a heterogeneous disorder characterized by varying degrees of stimulation and suppression of PTH, being associated with hyperplasia of the parathyroid glands.

Material and Method: The present study is a historic prospective cohort analysis of patients undergoing subtotal parathyroidectomy, keeping a parathyroid gland intact in its bed, by tertiary hyperparathyroidism.

Result: 44 patients between 30 and 75 years of age were selected, with a median of 49.5 years for the group, divided equally between men and women. Conservative treatment time was 36.75 months and hemodialysis time was 67.33 months. Renal transplantation time was 42.64 months, with PTH value on the day of renal transplantation of 822.03 pg/mL. On the day of surgery, the PTH value was 170.9 pg/mL, reaching an average value of 77.2 after 5 years. The initial value of ionic calcium was 1.477 mmol/L and a final value of 1.299 mmol/L after 5 years.

Conclusion: The evaluation of the present study allows us to conclude that subtotal parathyroidectomy, keeping a parathyroid gland intact in its bed, is a safe and effective technical option in the surgical treatment of patients with tertiary hyperparathyroidism.

Introduction

Parathyroid hormone (PTH) is one of the controllers of calcium homeostasis, synthesized and secreted by the parathyroid glands. Secondary hyperparathyroidism (SHPT) is thus an acquired disorder represented by hypersecretion of parathyroids in response to disturbances of calcium homeostasis.

Patients with kidney disease may have several different clinical presentations. Some patients have symptoms directly linked to the kidneys, such as hematuria, low back pain, and infections. In other cases, we have symptoms called extrarenal, such as edema, hypertension, and uremia. Despite this, many are asymptomatic and only diagnosed in laboratory evaluations.

The persistence of abnormalities in mineral metabolism may result in the evolution of SHPT to a state of gland autonomy¹ with PTH hypersecretion followed by hypercalcemia.

Tertiary hyperparathyroidism (THPT) is the persistence of excess parathyroid hormone secretion (PTH) with hypercalcemia², that occurs after kidney transplantation in patients with secondary hyperparathyroidism³. Most patients present improvement of hypersecretion within one year⁴, however, approximately 8% of them persist with the autonomy of the glands, maintaining the status of the disease in its natural course⁵.

Parathyroid resection (PTX) is the most important intervention for the control of secondary hyperparathyroidism when clinical measures fail, and patients in stage 5 of chronic kidney disease have great benefit with this modality of therapy⁶.

The choice of the parathyroidectomy technique should be based basically on the following pillars: risks of recurrence of hyperparathyroidism versus risk of definitive hypoparathyroidism and, if recurrence occurs, the surgeon should know how to identify it and how to treat it.

The most common surgical technique of subtotal resection of the parathyroids consists in the maintenance of tissue of one of the parathyroid glands in its anatomical bed, through the maintenance of a parathyroid fragment estimated between two and three times the size of a normal parathyroid (12mm), made by section of part of the gland chosen to remain.

Material and methods

The present study is a historical prospective cohort analysis of patients undergoing subtotal parathyroid resection with maintenance of an intact parathyroid gland in its bed, for THPT in tertiary hospital from Brazil, from 2013 to 2015. The objective is to provide a better surgical strategy for patients with hyperparathyroidism after renal transplantation. The results of this study are significant as they may lead to a safer and easier surgical option for patients, potentially changing the form of treatment. The study was approved by the Ethics Committee for Analysis of Research Projects. All patients in this study protocol were instructed and included as study participants after signing the Free and Informed Consent Form. Persistent hypercalcemia was the only indication for all patients, and there were no cases of other indications such as hyperphosphatemia, pruritus,

calciophylaxis or ectopic calcifications. We emphasize that PTH levels, in isolation, are not considered as a factor for indication of surgery. It is very important to emphasize that the time of chronic kidney disease is calculated from the moment of diagnosis of the drop-in glomerular filtration rate, regardless of the clinical stage in which the patient is or even the therapy instituted (conservative treatment, hemodialysis, peritoneal dialysis or even kidney transplantation). Patients with renal transplantation time of less than one year and already hypercalcemic were not considered for the sample. The standard treatment used by the surgical team and by the group of Parathyroid Diseases of the Department of Otorhinolaryngology and Head and Neck Surgery of the Federal University of São Paulo is PTXT+AE

in the pre-sternal muscle bed, a technique already described and established in the literature⁷.

In this study, however, the technique employed was PTXST with maintenance of an intact parathyroid in its bed. In this study we chose to keep the gland intact, without violating its anatomical bed and without performing biopsies or other interventions on the remaining tissue, avoiding manipulation of the gland, reducing the risk of injury to the vascular pedicle or inadvertent rupture of the gland. The gland chosen to remain intact in its bed was properly identified, recorded in a standardized surgical description, and marked with nonabsorbable thread (figure 1) or metal clip so that it remains as identification in a future surgical reapproach.

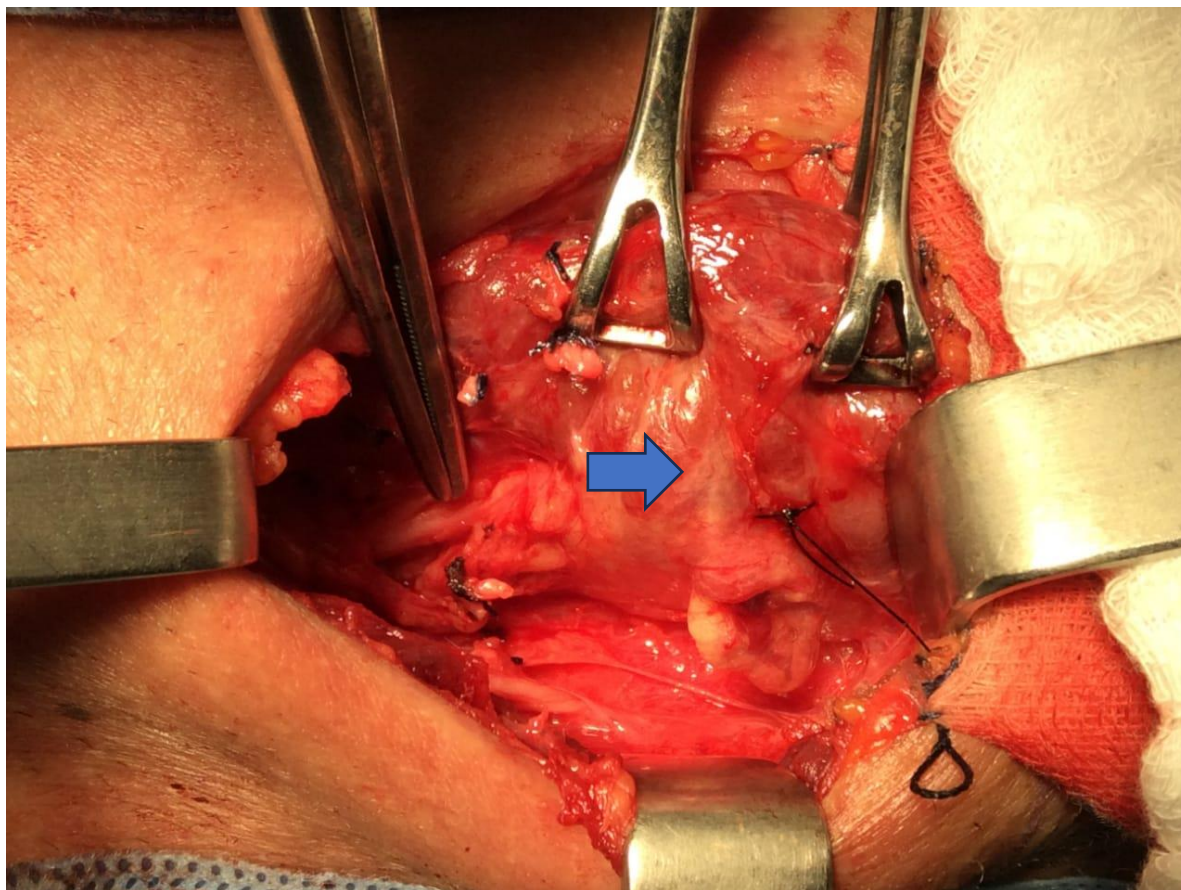


Figure 1: Identification of the remaining gland with nonabsorbable thread

Parathormone collections were performed during the surgical procedure following the protocol established internationally for patients with chronic kidney disease⁸, being the first collection at the time of anesthetic induction and the second collection after 20 minutes of removal of the third gland, always in the peripheral vein of the lower limbs. We characterized as failure patients who, after one year postoperatively, evolved with

hypocalcemia ($\text{Ca}_{\text{I}} < 1.15\text{mmol/L}$). Similarly, we characterized as recurrence patients who, after one year postoperatively, evolved with hypercalcemia ($\text{Ca}_{\text{I}} > 1.40\text{mmol/L}$). In short, we consider as success patients those who maintained adequate renal function and remained within the expected range of calcium in the next five years after surgery. Thus, the evolution of all parameters over time was analyzed. In many of them we will have the TO

(examination on the day of surgery) until the 5th year (fifth year after the procedure). In the paired analysis, the Friedman/Wilcoxon tests were used, and, in the independent analysis, we used the Kruskal-Wallis/Mann-Whitney tests.

Results

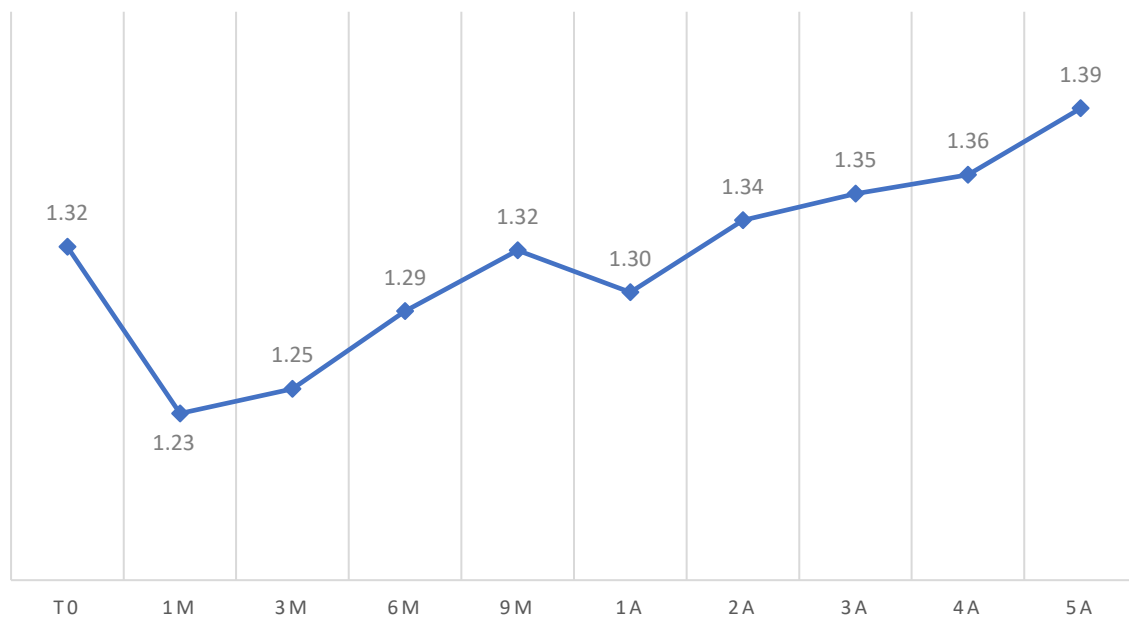
The age of the patients ranged from 30 to 75 years, with a median of 49.6 years for the whole group. As for gender we have an equal distribution of 18 men and 18 women, so with 50% in each group.

At initial evaluation, patients reported a conservative treatment time prior to renal replacement therapy of 36.75 months on average. The duration of hemodialysis until kidney transplantation was 67.33 months on average.

Regarding the time of renal transplantation, we had a mean time of 42.64 months, with a PTH value of 822.03 pg/ml.

In the evaluation of creatinine, we have an initial mean value of 1.326 mg/dl, reaching after 5 years, a mean value of 1.399 mg/dl with significant values ($p < 0.004$) as shown in figure 2.

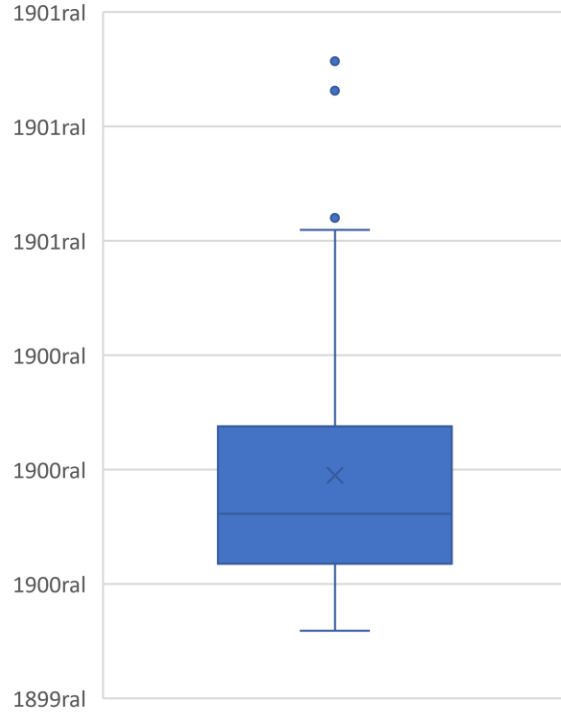
Figure 2: Evolution of mean creatinine values (mg/dl)



The PTH value on the day of surgery is shown in figure 3. In its analysis, we have a maximum value of 557 pg/mL, but most of the values were concentrated in a narrow range between 117 and 237 pg/mL, still above the normal values for the method. It is important to point

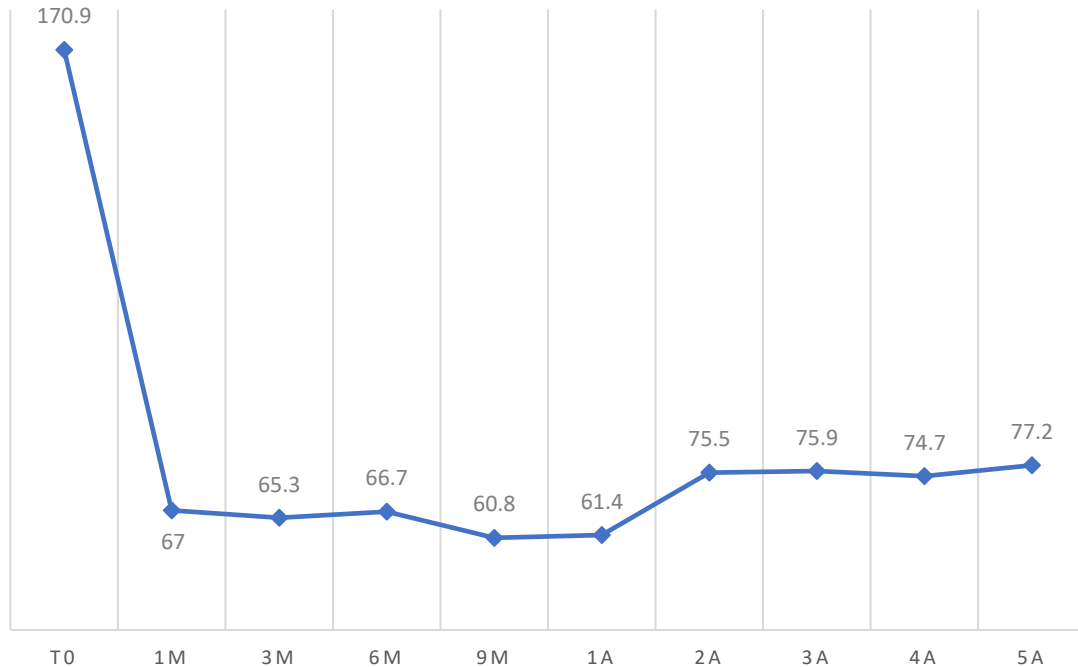
out that the indicative factor of surgery was hypercalcemia and not the isolated PTH value for this studied group. The studied group presented an initial (preoperative) mean PTH value of 170.9 pg/mL, reaching a mean value of 77.2 after 5 years ($p < 0.001$).

Figure 3: PTH value (pg/mL) at hospital admission



In figure 4 we have the evolution of PTH values, with a tendency to stability, which was not

significant in the comparative analysis with the increase in calcium and phosphorus.



As for the direct laboratory parameters of PTX indication, we have an initial ionic calcium value of 1.477 mmol/L (figure 5) compared to a mean final value over five years of 1.299 mmol/L,

graphically shown in figure 6. Most of these patients were within the normal range for the method, even 5 years after surgery.

Figure 5: Ionic calcium values (mmol/L)

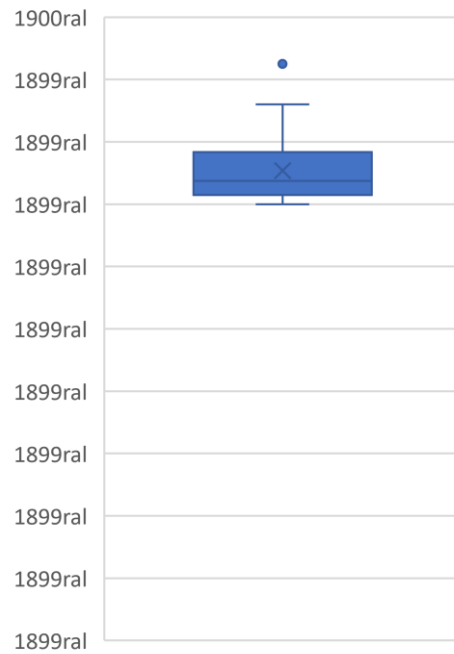
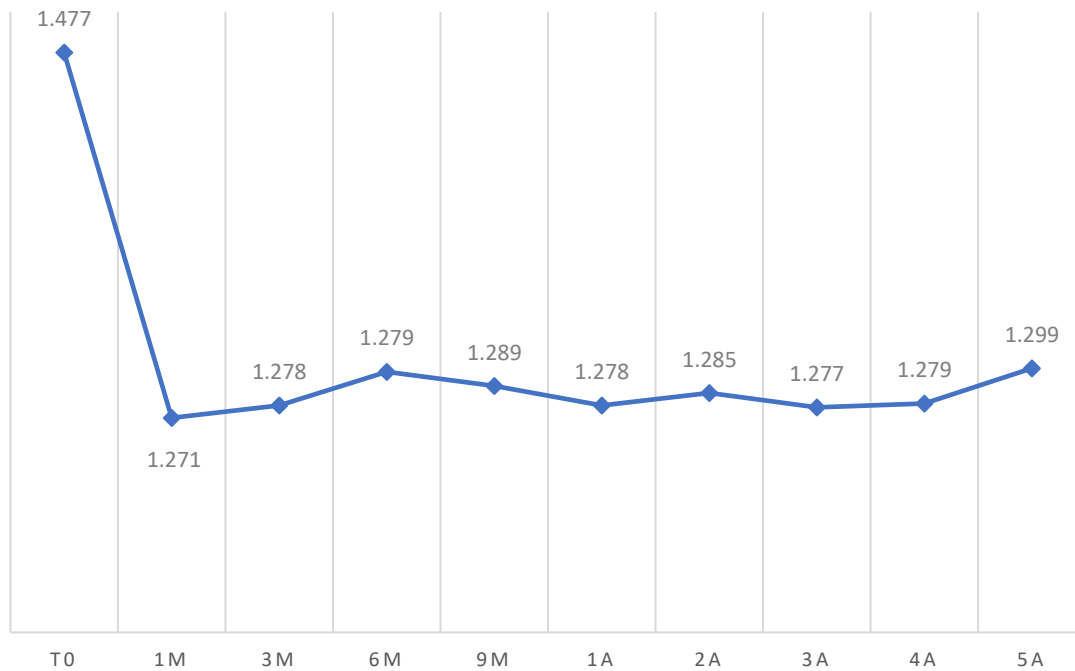


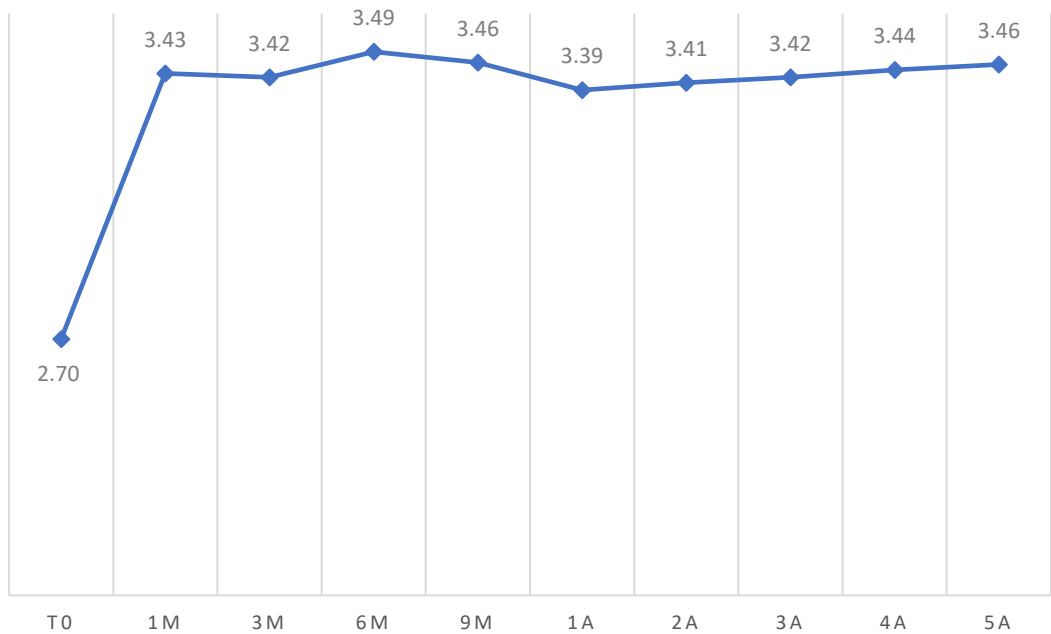
Figure 6: Evolution of the mean values of Ionic Calcium (mmol/L)



For phosphorus, the difference occurs between T0 (lowest value) and all other times. In the paired analysis, the mean at T0 was 2.705 mg/dL and, in

the first month, it rose to 4.435 mg/dL (figure 7) and remained stabilized around this value.

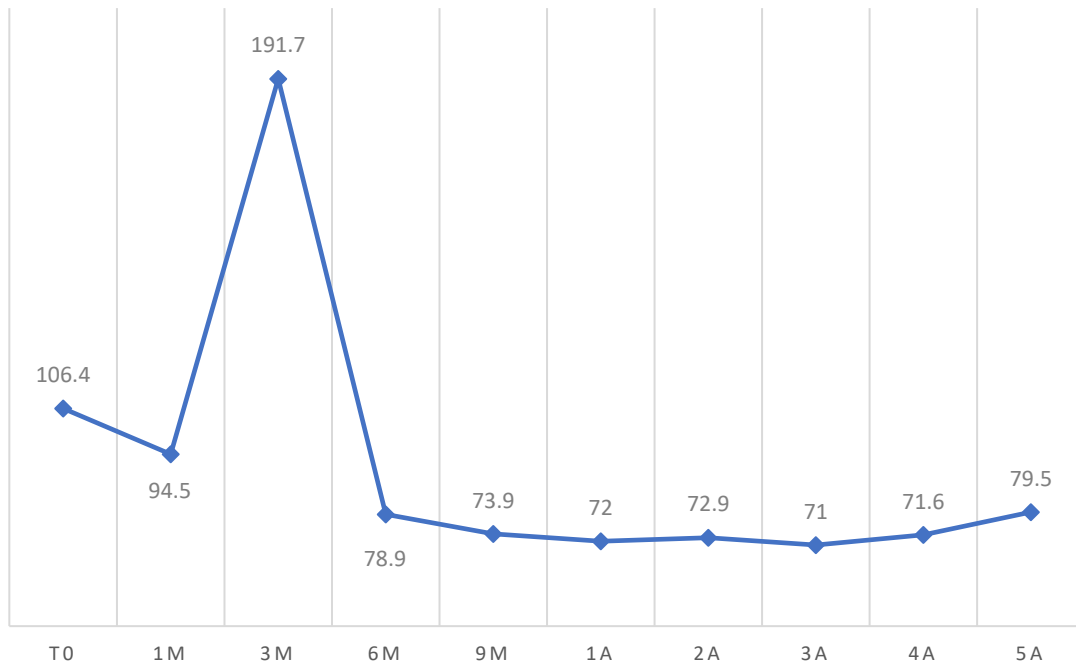
Figure 7: Evolution of mean phosphorus values (mg/dL)



All patients were receiving vitamin D in the preoperative period and maintained its use for the next five years, with dose adjustment pertinent to everyone. As for alkaline phosphatase, there was

stabilization of the mean values from six months (figure 8), remaining stable until the end of the time studied.

Figure 8: Evolution of mean alkaline phosphatase (U/L) values



We observed that from the fourth postoperative year on, no patient required calcium replacement. All patients received calcium

intravenously and orally in the immediate postoperative period, but 5 patients (13%) did not

need to receive calcium carbonate at hospital discharge.

Discussion

In our study, we tried to consider the time from the onset of kidney disease to transplantation. Thus, we consider that it would not be feasible to offer this surgical technique to patients with a long time since the loss of renal function, because we start from the premise that they would not have adequate glands against the criterion of selection of the technique, that is, glands of up to 12mm. This justifies the fact that our patients have only 3 years (on average) of conservative treatment and 5.5 years of dialysis until kidney transplantation, relatively short times compared to the Brazilian reality⁹.

This study aims to evaluate the use of subtotal resection of parathyroids with maintenance of an intact parathyroid in selected patients with TTPH, which brings an unprecedented contribution because this selection considers the time of previous hemodialysis and the time of renal transplantation¹⁰.

This work aims to evaluate the long-term outcomes of this specific type of surgical intervention, so it was only started after all patients had completed 5 years after the operation.

The preoperative calcium values found (1.477 mmol/L) confirm the indication for surgery, where all patients were hypercalcemic. At the end of the time studied, we had a value of 1.29 mmol/L, that is, all patients with levels below 1.40 mg/dl, considered as standard for calcemia¹¹. Regarding creatinine levels, we had a decrease in the value from 1.326 to 1.238mg/dl due to the improvement of the hypercalcemic environment. After 1 month (1.238mg/dl) we observed a slight upward trend until reaching its peak in 5 years (mean of 1.399mg/dl). In the long-term evaluation of this study, the glomerular filtration rates of the patients ranged on average from 64.57 to 53.54 mL/min/1.73m², which corresponds to an expected loss, without entering the range for renal replacement therapy¹².

Multicenter studies have shown that in patients with TTPH, the timing of the parathyroid intervention had no impact on long-term renal function, and the decrease in PTH values (pre- and post-PTX value decay) did not influence renal graft deterioration¹³. The analysis of intraoperative PTH decay for this model of surgery does not present standardized values, but we can consider the mean value found of 73% as acceptable since in the long-term evaluation we did not have PTH values outside the recommended range for the study group^{14,15}. Another important factor to be discussed is that the

mean PTH value after surgery remained adequate, allowing most patients (83.34%) not to require the use of calcium carbonate in the long term, consequently reducing the use of medication and unwanted side effects, such as intestinal constipation and gastric disorders. None of the patients in the evaluated group presented insufficient PTH values (lowest value in 5 years of 37.5 pg/mL), therefore there weren't any case of definitive hypoparathyroidism¹⁵.

The moment when a transplanted patient should be submitted to a PTX should be carefully evaluated, considering laboratory values, symptom severity, possibility of loss of renal function and, finally, the general condition of the patient¹⁶. We believe that the joint decision of the multidisciplinary team brings more security and confidence to this indication^{17,18}. There is an understanding that performing PTX after kidney transplantation is effective and that all patients with levels below 1.40 mg/dl are considered as standard for calcemia^{19,20}.

Parathyroidectomy after kidney transplantation is effective, decreasing the risk of changes in other organs or the high cardiovascular risk¹³. In phosphorus values we had an increase from 2.70 to 3.46 mg/dL, which corresponds to an increase of 28% over five years. This value is compatible with the decrease in renal performance over the period, but still within the values considered acceptable for post-transplant kidney disease^{19,20}. Calcium presented a mean value of 1.29 mmol/L at the end of the period, emphasizing that the value used in this study was 1.40 mmol/L, which shows that all individuals in the sample are within the expected standard. This is an important fact in the long-term analysis since the maintenance of an adequate calcium value is the main predictive factor of disease control²¹. Alkaline phosphatase remained at the mean level of 79.5 U/L, a value considered adequate for the time and clinical condition of the patients. Regarding alkaline phosphatase, we have an initial increase in its values due to bone hunger syndrome that patients face soon after the procedure. The incidence of this can vary from 28% to 88% in patients undergoing surgical treatment of parathyroid^{22,23}. These values are still lower than those faced by patients undergoing PTX+AE due to the more controlled drop in PTH and absence of transient hypoparathyroidism until graft autonomization. These phosphatase values tend to decrease after a few months of adequate calcium replacement and normalization of bone cell activity²².

The surgeon is faced with the dilemma between hypoparathyroidism induced by the total procedure versus the imminent recurrence rate or

persistence of the subtotal procedure, which makes this decision complex and based solely on the surgeon's experience and habit²⁴. In the study, we were faced with a substantial drop in the PTH value during the procedure of 73%, a value that is important, but not as much as the values found during a total PTX, which are around 80% to be considered effective in the long term^{8,24}.

The analysis of PTH decay during surgery should be used as a complementary factor at the time of the operation since it can predict the presence of ectopic tissue or inadvertent removal of structures other than hyperplastic glands and should not be used as a predictor of long-term healing. The use of this parameter can influence up to 7% of cases, mainly due to the occurrence of hyperfunctioning supernumerary glands²⁵. The selected group presented a PTH value of 67.7 pg/mL in the first month after surgery, showing that this value is sufficient for a minimum maintenance of calcium and vitamin D homeostasis, unlike total PTX, which presents a period of temporary hypoparathyroidism until the autonomy of the grafted tissue²⁶. Over the five years evaluated, no patient required calcimimetics. The association between surgery and the use of calcimimetic is

important and has brought a synergy in the combination of these two therapeutic modalities since its use does not modify the indication of surgery but improves the functional status of the patient²⁷. The use of the subtotal technique with medication may open a new frontier in the treatment of this population, allowing a greater flexibility of PTH values for transplant patients²⁸. Providing a more assertive and effective form of treatment can increase the quality, benefits, and results of therapy, minimizing risks and complications. The search for better treatment options and for providing better quality of life to patients should be a constant in the life of a surgeon and a health professional. The search for better surgical techniques should be incessant, even if it is always challenging. Hyperplastic glands should not be used as a predictor of long-term healing.

Conclusion

The evaluation of the present study allows us to conclude that the subtotal resection of the parathyroids with maintenance of an intact parathyroid gland in its bed is a safe and effective technical option in the surgical treatment of patients with tertiary hyperparathyroidism.

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