SUBTOTAL PARATHYROIDECTOMY IN THE TREATMENT OF RENAL HYPERPARATHYROIDISM – SINGLE CENTER INITIAL EXPERIENCE

R.M. Neagoe\textsuperscript{1,*}, D.T. Sala\textsuperscript{1}, V. Roman\textsuperscript{2}, S. Voidazan\textsuperscript{3}, I. Pascanu\textsuperscript{4}

\textsuperscript{1}Second Department of Surgery, \textsuperscript{2}Nephrology Department, Emergency Mures County Hospital, \textsuperscript{3}Epidemiology Department, \textsuperscript{4}Endocrinology Department, University of Medicine and Pharmacy Targu Mures, Romania

Abstract

Objective. We analyse our initial experience regarding the first 24 patients diagnosed with refractory secondary and/or tertiary hyperparathyroidism (HPT) who underwent subtotal parathyroidectomy (sPTx) in our clinic between 2010 and 2012.

Methods. Data were retrospectively retrieved from a prospectively maintained database. We included patients diagnosed with refractory secondary and/or tertiary HPT who underwent sPTx; we excluded patients who underwent total parathyroidectomy (tPTx) and patients followed-up for less than six months.

Results. We analyzed 24 patients, 16 women (66.7\%) and 8 men (33.3\%) who were evaluated in a prospective manner in a short (1-6 months)/medium (6-18 months) term follow-up. Preoperative intact parathyroid hormone level (iPTH) was characterized by a median of 2131 pg/mL (range: 1141-10000); in the first month after surgery the median iPTH level was 28 pg/mL (range: 3-1263). We found a statistically significant difference (p<0.01: Student test) in calcium level between preoperative values and values in the first month after surgery. Postoperative serum phosphorus (nv: 2.7-4.5 mg/dL) normalized in 19 patients (79.16\%) and serum alkaline phosphatase values decreased significantly in the interval 2-6 months postoperative versus preoperative levels (p=0.002). We tried to establish a correlation between preoperative alkaline phosphatase (Alk Phos) and postoperative calcium level in the first month postoperatively. The overall clinical response to sPTx was good and we did not encounter postoperative mortality in our series.

Conclusion. We believe that subtotal parathyroidectomy is feasible, safe and effective for patients with refractory secondary and tertiary hyperparathyroidism.

Key words: subtotal parathyroidectomy, renal hyperparathyroidism, short/medium term follow-up.

INTRODUCTION

The chronic renal failure (CRF) is constantly associated with a profound alteration of calcium homeostasis due to parathormone stimulation, secondary hyperparathyroidism (sHPT) being a...
common complication of end stage renal disease (ESRD). Although the pathogenic mechanism implicated is unsettled, there are complex aspects involved which include abnormalities in vitamin D action on intestinal mucosal function, phosphate retention, negative feedback dysfunction between calcium plasmatic level and parathyroid gland activity, elevated levels of the phosphatonin fibroblast growth factor 23 (FGF-23) and end organ susceptibility to parathyroid hormone (1, 2). Hyperparathyroidism (HPT) is a major contributor to renal osteodystrophy and it has been put forward as a cause of joint and muscle pains, soft tissue calcification, pruritus and anaemia in patients with chronic renal failure (1). Medical management of the disease includes dietary measures, phosphate binders, vitamin D analogs, calcimimetics which all may provide an adequate control of hyperparathyroidism in most cases. However, in spite of improved medical management, 0.7-1.45 % of dialysis dependent patients require parathyroidectomy annually, this procedure being indicated for patients with medically refractory secondary and tertiary HPT. (3, 4). Medically refractory hyperparathyroidism is a state in which excessive PTH secretion no longer responds to standard medical therapy. Some of these patients, if they develop irreversible hypercalcemia, are said to have tertiary hyperparathyroidism (5), but the latter term is generally defined as persistent hyperparathyroidism occurring post-transplantation, despite normalized renal function.

The aim of this study is to analyse our initial experience regarding the first 24 patients with renal HPT operated on in our clinic between 2010 and 2012. We hereby present the indications for surgery, describe the type of operation performed and review the short and medium term results.

**CLINICAL MATERIALS**

**Study design**

This is a retrospective review of prospectively collected data on a cohort of patients treated at a single university referral center, all the surgical procedures being performed by the same surgical team (RN, DS).

**Patients and methods**

We studied 24 patients with refractory secondary or tertiary renal HPT (rHPT) due to ESRD, included in hemodialysis program and submitted to subtotal parathyroidectomy (sPTx) between February 2010 and December 2012 at the Second Department of Surgery, Emergency Mures County Hospital. We included in our study only patients diagnosed with medically refractory secondary and/or tertiary HPT who underwent sPTx; exclusion criteria were represented by patients with parathyroidectomy followed-up for less than six months; furthermore, in the scope of group homogeneity we also excluded patients with total parathyroidectomy with or without autotransplantation (5 cases) operated on in the same period of time.

The diagnosis was established on laboratory and imagistic data.

Imagistics consists of ultrasonography, done by an endocrinologist with expertise, this investigation being
performed in all our cases; preoperative 99 Tc-MIBI scintigraphy and CT were not routinely used.

All patients received medical treatment during variable periods of time and the lack of response to this conservative approach was considered another indication for surgical treatment. As a preoperative treatment, all patients were loaded with vitamin D and were dialysed the day before the operation, the next dialysis being performed in the first postoperative day. All patients have signed an informed written consent form.

**Surgical technique**

The operation was performed under general anaesthesia. A standard collar incision was used with lateral retraction of the strap muscles. Parathyroids were sought firstly in their normal position and then in the common known ectopic positions, visually identifying the recurrent laryngeal nerves which were routinely dissected at the beginning of the procedure. We constantly sought the inferior parathyroid glands under the sternal manubrium when we encountered difficulties in finding them. Thymectomy was not performed routinely if four glands have been confidently identified. Subtotal parathyroidectomy was performed, leaving one third-one fourth of a cvasinormal well vascularised inferior gland with its neopedicle (small mediastinal and thymic vessels) and bringing it in a subcutaneous position just above the sternal notch.

In four cases we encountered associated thyroid pathology requiring a total thyroidectomy. Two of these cases revealed a papillary thyroid carcinoma and a micro carcinoma, respectively. All glands were histologically verified and in three situations we needed frozen section to confirm the parathyroid tissue.

**Postoperative management**

All our patients were followed-up in the ICU for the next day after surgery; first postoperative dialysis was performed in day 1, with extra attention to the heparinisation. Serum calcium levels were monitored three times a day during the first 3-4 postoperative days when we administered calcium gluconate infusion along with alphacalcidolum orally as required. After this period calcium infusions were gradually reduced and replaced with oral calcium medication, patients being discharged or transferred to the endocrinology clinic. Nevertheless, they should be kept in close observation during the first two-three postoperative weeks while the parathyroid grafts begin their function and the “hungry bones” syndrome might be severe.

**Statistical analysis**

All statistical calculations were performed using Graph Pad Software, San Diego, California, USA. Differences between compared preoperative and postoperative variables value were determined by Student t-tests, Wilcoxon test and ANOVA respectively.

Analysis of the correlation link and strength of this connection was performed with the Pearson correlation coefficient. All the tests were interpreted relative to the significance threshold \( p = 0.05 \), and statistical significance was considered for p-values below the significance threshold value.
RESULTS

We included 24 patients in our study, 16 women (66.7%) and 8 men (33.3%). The mean age was 50 ± 10.6 years, ranging between 31 and 69 years. All patients included in this study have received long term renal replacement therapy, the average time of hemodialysis being 8.35 years (range 5-11 years). The CRF causes are stipulated in Fig.1. We had one female patient who had previously received a renal graft followed by a chronic rejection reaction. The main complaints related to renal HPT were osteoarticular pains (15 patients), bone changes and pathological fractures (11 patients), pruritus (8 patients), muscular weakness (14 patients), soft tissue calcification (2 patients).

The diagnosis was established on laboratory and imagistic data. All our patients had markedly elevated preoperative serum iPTH; we also frequently noted hyperphosphatemia and high levels of alkaline phosphatase (Alk Phos). Not all of our patients had elevated preoperative serum calcium level. As regarding preoperative imaging study both cervical ultrasonography and MIBI scintigraphy failed to identify all the parathyroids, but the largest glands were always visualized.

Our patients were evaluated in a prospective manner in a short (1-6 months)/ medium (6-18 months) term follow-up. Serum iPTH, calcium, phosphate, and alkaline phosphatase were determined by standard methods. (Table 1).

Preoperative intact parathyroid hormone level (iPTH) was characterized by a median of 2131 pg/mL (range: 1141-10000). This level decreased postoperatively by 150.1 times on average, in the first month after surgery the median iPTH level being 28 pg / mL (range: 3-1263); the median ratio iPTH levels preoperatively / postoperatively, in the first month after the operation, was 71.85 (range 1.3-826.3). In the months following surgery, iPTH levels decreased

![Figure 1. Chronic renal failure causes in our study.](image)
significant from preoperative levels at 2-6 months (p=0.0001), respectively at 7-18 months (p=0.0001) (Table 2).

Definitive hypoparathyroidism, defined as serum iPTH levels below 10 pg/mL one year after the surgery under proper calcium – alphacalcidol supplementation, was observed in 2 cases (8.3%). Persistent HPT was encountered in two patients (8.3%), both with only three parathyroids resected at the time of the initial operation.

Table 1. Pre- and postoperative biochemical modifications in patients under study

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<th>Serum P (mg/dL)</th>
<th>AlkPhos (u/L)</th>
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Subtotal parathyroidectomy in secondary renal hyperparathyroidism

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in all months followed a Gaussian distribution. We found a statistically significant difference (p<0.01: Student test) between preoperative values and values in the first month after surgery, the difference between the means being 0.73 ± 0.29 mg/dL. The average of the ratio preoperative/postoperative serum calcium level in the first month was 1.12.

In the first month after surgery (range 2-35 days), 7 patients (29.16%) developed mild hypocalcaemia under calcium infusions, due to “hungry bones” syndrome. The average level of calcium in the first 6 months after surgery ranged from 7.9-8.4 mg/dL, and between 7-18 months we found average values between 8.4-9.2 mg/dL.

Postoperative serum phosphorus (nv: 2.7-4.5 mg/dL) normalized in 19 patients (79.16 %), the other 5 patients (20.84%) remaining slightly hyperphosphatemic.

We found a statistically significant difference between pre- and postoperative phosphate levels in the first month (p=0.0001 Student test). The difference between the averages was 1.9 ± 0.42 mg/dL with a mean of 5.86 ± 1.31 mg/dL preoperatively and of 3.9 ± 1.6 mg/dL in the first postoperative month.

Blood phosphorus values decreased postoperatively in the first month by 1.5 times versus the preoperative level. In the interval 2-7 months after the operation we found average values ranging from 3.7 to 4.8 mg/dL, significantly lower (p<0.0004) compared to the preoperative level while in the interval 7-18 months averages ranged between 4.9-5.9 mg/dL, but they were not significantly different (p=0.38) compared to the preoperative levels.

Preoperatively Alk Phos level was characterized by a median of 575.0 U/L, and in the first month after surgery, the average fell slightly to 452.0 U/L.
Subtotal parathyroidectomy in secondary renal hyperparathyroidism

In 6 patients, Alk Phos values were increased in the first month after surgery compared with preoperative values. Alkaline phosphatase values decreased significantly in the interval 2-6 months postoperative versus preoperative levels (p<0.002), continuing to decline between 7-18 months (p<0.01) (Table 2). We tried to establish a correlation between preoperative serum AlkPhos and postoperative calcium level in the first month postoperatively, where there is a strong negative and statistically significant correlation (Pearson correlation coefficient r=-0.49) with p<0.01.

This means that a high value for the preoperative Alk Phos variable predicts a small postoperative Calcium value (Fig. 2).

Functional statistically significant dependence for a confidence level of 0.05 between preoperative Alk Phos and postoperative calcium is given by the equation $\text{Ca} = 9.2100 + (-0.001108 \times \text{Alk Phos})$. This equation allows the theoretical calculation of Ca on the basis of Alk Phos parameter.

Bone pain, pruritus and muscular weakness were usually relieved early after the operation (2-4 weeks) and no pathological fractures reoccurred. We did not encounter postoperative mortality in our series; no patient suffered permanent recurrent laryngeal injury but we had two patients who developed temporarily disphonia after the operation. One patient developed a cervical hematoma after the

![Figure 2. Correlation between preoperative AlkPhos and Ca level in the first postoperative month.](image-url)
first postoperative dialysis, requiring surgical evacuation.

With regard to the weight of the excised parathyroids we observed that in our series the average weight was 3789±1897 mg.

Definitive histological examinations showed diffuse hyperplasia (7 cases), nodular hyperplasia (14 cases) or a mixed pattern (3 cases) in all excised glands. As we previously mentioned we encountered 4 patients with associated thyroid diseases.

**DISCUSSION**

Secondary and tertiary hyperparathyroidism is common in patients with replacement therapy for CRF, being one of the most common complications that influence mortality and quality of life; 40% of ESRD patients die from cardiovascular events and the mortality risk is increased by 25% with iPTH levels higher than 495 pg/mL and with phosphorus levels higher than 6.5 mg/dL (1, 2).

The indications for surgery in renal HPT are still debated in the literature but the following are accepted by the majority of endocrine surgeons: 1). Plasma iPTH-values >700 pg/mL combined with hypercalcemia or hyperphosphatemia 2). Size of at least one parathyroid gland bigger than 0.5 cm³ in volume or 1 cm in diameter at ultrasonography 3). Radiological or biochemical signs of osteoclastic bone resorption or clinical signs of HPT like pruritus, calciphylaxis, nontraumatic bone fractures or rupture of tendons (6). Apart from these biochemical and imagistic findings, failure to respond to medical therapy is another recognised indication for surgery (3, 7-9).

In our group of patients the operatory indication has been established mainly on the basis of clinical and laboratory data. One particular aspect refers to the preoperative iPTH values which were very high in our series, with a median of 2131 pg/mL (range 1141-10000 pg/mL). These markedly increased preoperative iPTH values, recorded even after the recent preoperative interruption of calcimimetics, along with the severity of rHPT clinical manifestations (mainly osteoarticular) and the almost constant intraoperative discovery of nodular parathyroids, betrays the long evolution of rHPT, its “tertialization” and maybe even surgery delays. We did not frequently encounter hypercalcemia in our series, the preoperative calcium level expressed as average ± SD being 9.2 ± 0.84 mg/dL (nv:8.5-10.5 mg/dL). In spite of this we frequently noted hyperphosphatemia, with values expressed as average ± SD of 5.86 ± 1.31 mg/dL (nv:2.7-4.5 mg/dL).

We strongly agree with the authors who support the necessity of a full imagistic investigation prior to the parathyroid surgery, this being justified by its usefulness in detecting ectopically located or supranumerary glands (10-12). Unfortunately, we have not managed to investigate all patients through Tc 99m MIBI scintigraphy, the method recognized to have the highest diagnostic sensitivity (11). We have consistently benefited of US and, at times, of CT (18...
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cases). This is probably the explanation for the percentage of persistent HPT in the group of study (8.3%), along with the expected learning curve.

The main types of surgical procedures for parathyroidectomy currently performed in patients with renal HPT are subtotal parathyroidectomy (sPtX) and total parathyroidectomy (tPtX) with or without autotransplant (13-15). For the past 50 years, surgeons have debated the optimal operative management, every procedure having its own disadvantages and advantages. Subtotal PtX, first described by Stanbury in 1958, was for many years accepted as a standard surgical operation and is still, probably, one of the most often performed (16). We performed subtotal PtX with a particularity regarding the position of the remaining parathyroid tissue and its vascularisation, as we previously described it. As other authors mentioned, this technique has some advantages such as low local spreading, by preserving the blood supply and partially the gland capsule, as well as easy operative access in case of recurrent HPT (17). We constantly performed a superior mediastinal exploration and cervical thymectomy when we failed to identify four parathyroid glands.

Why have we chosen sPtX? Of course that we cannot enter a debate on the permanent controversy between sPtX and PtX with or without autotransplant. Besides any scientific argument discussed and debated in literature, sPtX – in the form we use and describe in this paper – is the procedure we have learned in the first instance and which we considered, at the beginning of our experience curve, as being simple and reproducible.

We did not encounter mortality in our series; we had two patients who developed temporarily disphonia after the operation and one patient who developed a cervical hematoma after the first postoperative dialysis, requiring surgical evacuation.

All the clinical complaints related to renal hyperparathyroidism were markedly relieved or disappeared after surgery. Persistent HPT was encountered in two patients (8.3 %), both with only three parathyroids resected at the time of the initial operation. Postoperatively, we performed a thorough imagistic examination in these cases, including Tc-99m sestaMIBI scintigraphy. We reoperated one patient with good postoperative result (postoperative iPTH value=25.6 pg/mL); at the reintervention we found the left inferior parathyroid gland in the anterior mediastinum. The other patient is scheduled for reintervention.

We have not noticed a recurrence of HPT in our series until now, but this observation is not pertinent due to the short time follow-up period.

In the first month after surgery 7 patients developed mild hypocalcaemia under treatment with calcium infusions and alphacalcidol, due to “hungry bones” syndrome. After this period calcium infusions were gradually reduced and replaced with oral calcium medication; we had 2 patients who required oral calcium supplementation for a long period after PtX, probably due to a small parathyroid graft left in place or hypovascularisation of the graft.
(definitive hypoparathyroidism).

We established a correlation between preoperative serum Alk Phos and postoperative calcium level in the first month postoperatively, showing that a high value for the preoperative Alk Phos variable predicts a small postoperative calcium value. Our findings correspond to those of other authors: the increased preoperative level of the alkaline phosphatase and parathormone, along with the large dimension of the parathyroids and patient’s age, could be regarded as predictive factors of the hungry bones syndrome’s severity (18, 19).

The most frequent pathology diagnosis in our series was nodular hyperplasia, a pattern which is considered to be involved in a higher disease recurrence rate (20, 21); the short/medium time follow-up period did not allow us to draw any conclusion regarding this issue. Among our patients four (16.6%) were found to have unexpected thyroid pathology at the time of PTx, including two with differentiated thyroid carcinoma. Even if the association between rHPT and DTC is a rare event, there is some evidence that CRF may predispose to malignancy (22, 23), so any incidental thyroid pathology should be treated adequately, preferably during the initial operation.

This study represents the analysis of our initial experience with subtotal parathyroidectomy in the treatment of renal hyperparathyroidism and has several drawbacks such as the limited number of patients and the short/medium time follow-up period. However, we believe that subtotal PTx is feasible, safe and effective for patients with refractory secondary and tertiary hyperparathyroidism.

Conflict of interest
We declare that there is no conflict of interest.

References
