



DOI: 10.2478/rmlm-2014-0028

Parathyroidectomy in the treatment of secondary hyperparathyroidism. Clinical and laboratory outcomes

Paratiroidectomia în tratamentul hiperparatiroidismului secundar. Aspecte clinice și de laborator

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Abstract

Background. Secondary hyperparathyroidism (sHPT) is frequently encountered in patients on hemodialysis (HD) for end stage renal disease (ESRD). In spite of improved medical therapy, parathyroidectomy is still frequently indicated for patients with medically refractory secondary and tertiary hyperparathyroidism. The aim of this study is to analyse the impact of parathyroidectomy, regardless of the surgical procedure, on perioperative and follow-up clinical symptoms and biochemistry tests. **Material and method.** We studied 29 patients who underwent parathyroidectomy for sHPT due to ESRD, at the Second Department of Surgery, Emergency Mures County Hospital, between February 2010 and May 2013. Outcome parameters included symptoms relieving (bone pains, pruritus, etc) and laboratory data (intact parathyroid hormone (iPTH), total calcium and phosphorus, serum alkaline phosphatase (AlkPhos), hematocrit and hemoglobin), assessed before, shortly after and then at short-medium term follow-up. **Results.** The majority of our patients had significant improvement of the symptoms during the follow-up period. The iPTH values considerably decreased after the operation. The postoperative calcemia mean value decreased and we have identified statistically significant differences between the monthly calcemia average values ($p=0.008$). The mean phosphorus level in the first 2 postoperative months decreased significantly ($p=0.001$) and we recorded statistically significant decreases ($p=0.0007$) in AlkPhos level after the operation. Both hematocrit and hemoglobin levels experienced a statistical significant growth in the follow-up period. Persistent HPT was encountered in two patients (6.89%), and we had 8 patients who developed mild hypocalcaemia in the first month after the operation (“hungry bones” syndrome). We had few minor and transient postoperative complications and we did not encounter postoperative mortality in our series. **Conclusions.** Parathyroidectomy, regardless of the technical procedure, is feasible, safe and effective for patients with refractory secondary and tertiary hyperparathyroidism.

Keywords: hyperparathyroidism, parathyroidectomy, clinical and biochemical follow-up

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Rezumat

Introducere. Hiperparatiroidismul secundar este frecvent întâlnit la pacienții dializați. Paratiroidectomia rămâne o soluție terapeutică în cazul hiperparatiroidismului secundar refractar și a celui terțiar. Scopul acestui studiu este de a urmări impactul paratiroidectomiei, indiferent de tehnica chirurgicală utilizată, asupra simptomatologiei și principalelor constante biologice. **Material și metodă.** Am studiat 29 de pacienți la care s-a efectuat paratiroidectomie pentru hiperparatiroidism secundar și terțiar, la Clinica Chirurgie II, Spitalul Clinic Județean de Urgență Mureș, în perioada februarie 2010- mai 2013. Paramentrii urmăriți au fost clinici și de laborator (parathormonul, calciul total, fosforul și fosfataza alcalină serică, hemoglobina și hematocritul) determinați preoperator, imediat postoperator și pe termen scurt și mediu de urmărire. **Rezultate.** Simptomele clinice s-au ameliorat la majoritatea pacienților incluși. Valorile parathormonului seric s-au redus semnificativ, rămânând scăzute pe întreaga perioadă de urmărire; valorile medii ale calcemiei, fosfatemiei, fosfatazei alcaline s-au redus semnificativ statistic în perioada de urmărire după paratiroidectomie. Hemoglobina și hematocritul au prezentat creșteri semnificativ statistice atât pe termen scurt cât și mediu de urmărire. Am întâlnit două cazuri de hiperparatiroidism persistent după prima intervenție (6,89%); 8 pacienți au prezentat hipocalcemii în prima lună postoperator (sindrom "hungry bones"). Nu am întâlnit mortalitate în seria studiată. **Concluzii.** Paratiroidectomia, indiferent de tehnica chirurgicală utilizată, rămâne o soluție fezabilă în tratamentul hiperparatiroidismului secundar și terțiar.

Cuvinte cheie: hiperparatiroidism, paratiroidectomie, urmărire postoperatorie

Received: 2nd January 2014; **Accepted:** 22nd July 2014; **Published:** 11th September 2014.

Introduction

Secondary hyperparathyroidism (sHPT) is frequently encountered in patients on hemodialysis (HD) for end stage renal disease (ESRD) and is characterized by abnormalities in serum calcium, phosphorus and intact parathyroid hormone levels (iPTH), high-turnover bone disease with associated musculoskeletal pain, bone changes and elevated serum alkaline phosphatase level (AlkPhos), symptomatic pruritus, vascular and soft-tissue calcification in advanced stages of the disease (1).

A dietary regimen and medical treatment can control sHPT in the majority of ESRD patients. In the past 2 decades numerous therapeutic agents and regimens have been introduced i.e. new low phosphorus diet, nonaluminum phosphate binders, and, most recently, calcimimetics, which modulate the calcium-sensing receptor with consequent lowering of serum calcium level and iPTH secretion (2,3).

However, in spite of improved medical management, 0.7-1.45 % of dialysis dependent

patients require parathyroidectomy annually, the procedure being indicated for patients with medically refractory secondary and tertiary hyperparathyroidism (4,5).

Medically refractory hyperparathyroidism is a state in which excessive parathyroid hormone secretion no longer responds to standard medical therapy. Some of these patients, if they develop irreversible hypercalcemia, are said to have tertiary hyperparathyroidism (tHPT), but the latter term is generally defined as persistent hyperparathyroidism occurring post-transplantation, despite normalized renal function (6,7).

The aim of this study is to analyze the impact of parathyroidectomy, regardless of the surgical procedure, on perioperative and follow-up clinical symptoms and biochemistry tests.

Material and method

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.

Between February 2010 and May 2013, a total of 33 consecutive patients underwent parathyroidectomy for sHPT due to ESRD, at the Second Department of Surgery, Emergency Mures County Hospital.

We have included in our study patients diagnosed with medically refractory secondary and/or tertiary HPT who were submitted to parathyroidectomy and followed up for at least 6 months after the surgery. We excluded 4 patients operated on in the last period who did not comply with the follow-up criteria imposed by the present study.

After exclusions 29 patients remained eligible for our investigation (87.8%) for whom 31 surgeries have been performed. The majority of them have been submitted to subtotal parathyroidectomy (sPTx: 24 patients, 82.75%) whereas the others underwent total parathyroidectomy with autotransplantation (tPTx +AT: 3 patients, 10.34%) and total parathyroidectomy without AT (tPTx: 2 cases, 6.89%); we also included in our analysis 2 re-interventions for persistent HPT.

The diagnosis was established on laboratory and imagistic data. Imagistics consisted of ultrasonography, performed by an endocrinologist with expertise in all our cases; preoperative 99 Tc-MIBI scintigraphy and CT were not routinely used.

As a preoperative treatment, all patients were loaded with vitamin D and were dialyzed the day before the operation, the next dialysis being performed in the first postoperative day. All patients have signed an informed written consent form, the study being done with the consent of the Hospital Ethics Committee.

Surgical technique

The treatment options were subtotal parathyroidectomy, total parathyroidectomy with

autotransplantation and total parathyroidectomy without autotransplantation, depending on surgeon's preference.

The operation was performed under general anesthesia. Parathyroids were first sought for 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. Thymectomy was not performed routinely if four glands have been confidently identified. Subtotal parathyroidectomy was performed in 24 cases, leaving one third-one fourth of a quasinormal well vascularized inferior gland with its neopeticle (small mediastinal and thymic vessels) and bringing it in a subcutaneous position just above the sternal notch. In 3 cases we performed tPTx+AT of 9-12 small non-nodular glandular tissue in 3-4 muscular pockets of sternocleidomastoid muscle. Total parathyroidectomy without autotransplantation was performed in 2 cases, on patients who were not expected to receive a renal transplant for various reasons.

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 four situations we needed frozen section to confirm the parathyroid tissue.

Postoperative management and follow-up

All our patients were followed-up in the intensive care unit for the next day after surgery; first postoperative dialysis was performed in day 1, with extra attention to the heparinization. Serum calcium level was 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. Outcome parameters included symptoms relieving (bone pains, pruritus, etc.) and laboratory data (iPth, total calcium and phosphorus, serum AlkPhos, hematocrit and hemoglobin), assessed before, shortly after and then at short-medium term follow-up. For plasma iPth, an immunoradiometric assay was used [normal value (nv): 20-65 pg/ml]; hemoglobin and hematocrit were determined with Sysmexxt 4000 analyzer, spectrophotometrically and directly, respectively. A Cobas 6000 analyzer was used for serum calcium (o-cresolphthalein colorimetric method), phosphate (molybdate UV) and alkaline phosphatase [colorimetric assay in accordance with the recommended reference method of the International Federation of Clinical Chemistry (IFCC)] determination.

Statistical analysis

All statistical calculations were performed using Graph Pad Software, San Diego, California, USA. We tested the normal distribution for continuous variable using Kolmogorov-Smirnov test. We characterized them as mean and standard error of the mean (SEM), for variables with normal distribution, or as median and 25-75 percentiles, for variables with abnormal distribution, respectively. We chose adequate statistical tests according to data distribution. Differences between mean age values were determined by Student t-test. Differences between compared preoperative and postoperative variables value (1-6 months and 7-18 months, respectively) were determined by Kruskal Wallis test (associated with the Dunns multiple comparison test) and ANOVA test, respectively (associated with the Bonferroni multiple comparison test. Graphs were plotted using Medcalc Software. In a Box-and-Whisker plot, the central box represents the values from the lower to upper quartile (25 to 75 percentile). The middle line represents the median. A line extends from the minimum to the maximum value.

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

Patients characteristics

Our lot included 19 women (65.5%) and 10 men (34.5%), with a male to female ratio of 0.52 and with a median age of 52 years (range 31-69 years). In the women group the mean age was 53.2 ± 2.33 comparing with the male group where it was 47.3 ± 3.37 ($p=0.15$).

All patients included in this study have received long term renal replacement therapy, the average time of HD being 8.49 ± 1.5 years (range 5-11 years). The CRF causes were: chronic glomerulonephritis (12 cases), chronic pyelonephritis (5 cases), polycystic kidney disease (4 cases), hypertensive nephrosclerosis (4 cases) and unknown etiology (4 cases).

We noted one female patient who had previously received a renal graft followed by a chronic rejection reaction.

Regarding the clinical complains osteoarticular manifestation were the most frequent encountered (21 patients, 72.4%) and consisted of generalized bone pain, polyarthralgia, bone changes and pathological fractures. We also noted muscular weakness (18 patients, 62.1%), pruritus (12 patients, 41.4%), high blood pressure (12 patients, 41.4%), soft tissue calcification (4 patients, 13.8%).

The majority of our patients had significant improvement of these symptoms during the follow-up period, especially decrease in bone pains, polyarthralgias and pruritus.

iPTH evolution in 1-6 months, 7-18 months respectively

The preoperative iPth values were very high, reaching a median of 2500 pg/ml (range:

1141-10.000 pg/ml; nv: 20-65 pg/ml). In order to graphically identify the monthly values in the short post-operative interval, we have excluded the preoperative data, taking into consideration the 1-6 months and 7-18 months intervals. In the first interval, the iPTH values considerably decreased to a month 1 median of 27.7 pg/ml (range: 3-1263 pg/ml). In the months 2 to 6, the iPTH values were situated between 13-37 pg/ml, with a rather consistent distribution and with no significant differences ($p=0.49$). The iPTH values in month 7 were high, with a clear later tendency to decrease in the medium term (7-18 months), with median values varying insignificantly between 7-26.6 pg/ml (Figure 1).

Serum calcium level in 1-6 months, 7-18 months respectively

If the preoperative serum calcium mean value was at a level of 9.2 mg/dl (nv: 9-11 mg/dl), the postoperative mean value decreased to a constant level between 7.9-8.2 mg/dl. We have identified statistically significant differences be-

tween the monthly calcemia average values ($p=0.008$; the significant differences were recorded between the means of preoperative calcemia values and the means of the calcemia values 2, 3, and 4 months after the operation). In the medium term evolution (7 to 18 months), calcemia values varied between 8.4 and 9.2 mg/dl ($p=0.62$), (Figure 2).

Serum phosphate level in 1-6 months, 7-18 months respectively

If in the preoperative period we recorded a mean serum phosphorus level of 5.8 ± 0.23 mg/dl (nv: 2.7-4.5 mg/dl), in the first 2 postoperative months this level decreased significantly ($p=0.001$). In the following period up to 6 months after the operation, the serum phosphorus level gradually grew to a value of 4.8 mg/dl. For the 7-18 months interval, we have not obtained statistical significance ($p=0.64$), with a variation of mean values in excess of 5 mg/dl, between 5.1-5.9 mg/dl (Figure 3).

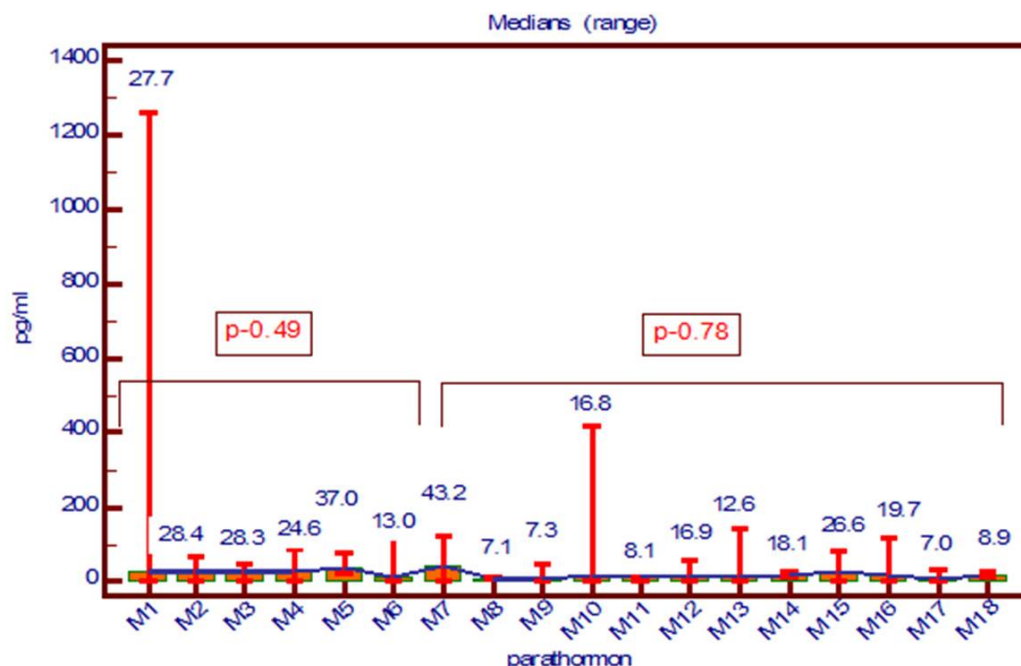


Figure 1. iPTH values evolution during the 1-18 months postoperative interval

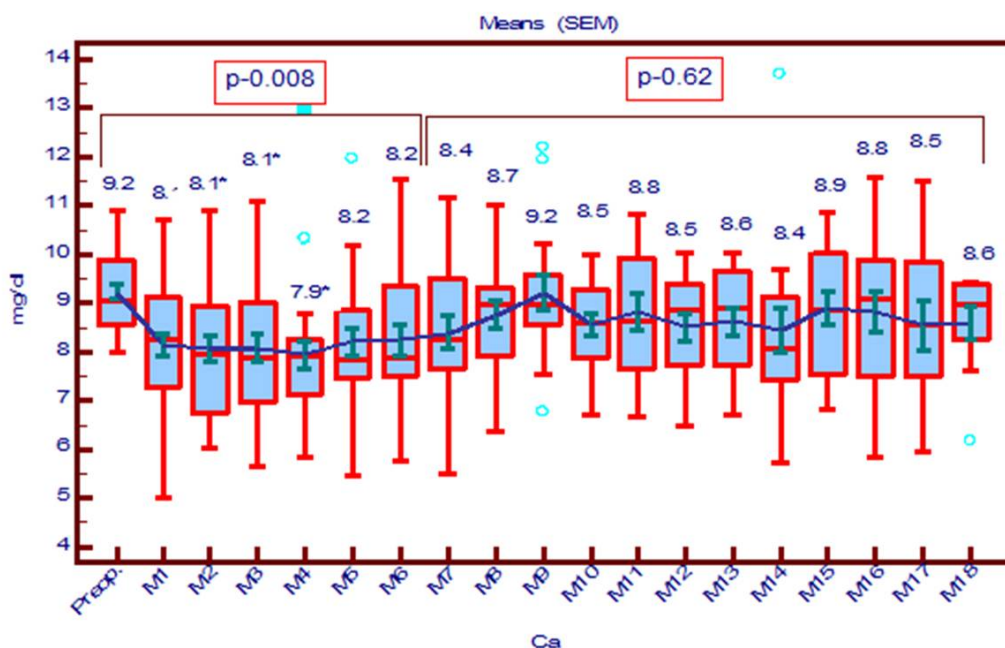


Figure 2. The evolution of preoperative calcemia values compared with the 1-18 months postoperative interval

Serum AlkPhos level in 1- 6 months

The median preoperative serum AlkPhos

value was 489.2 UI (range:175-2636 UI; nv: 98-278 U/L). After the operation, we recorded statistically significant decreases (p=0.0007), with

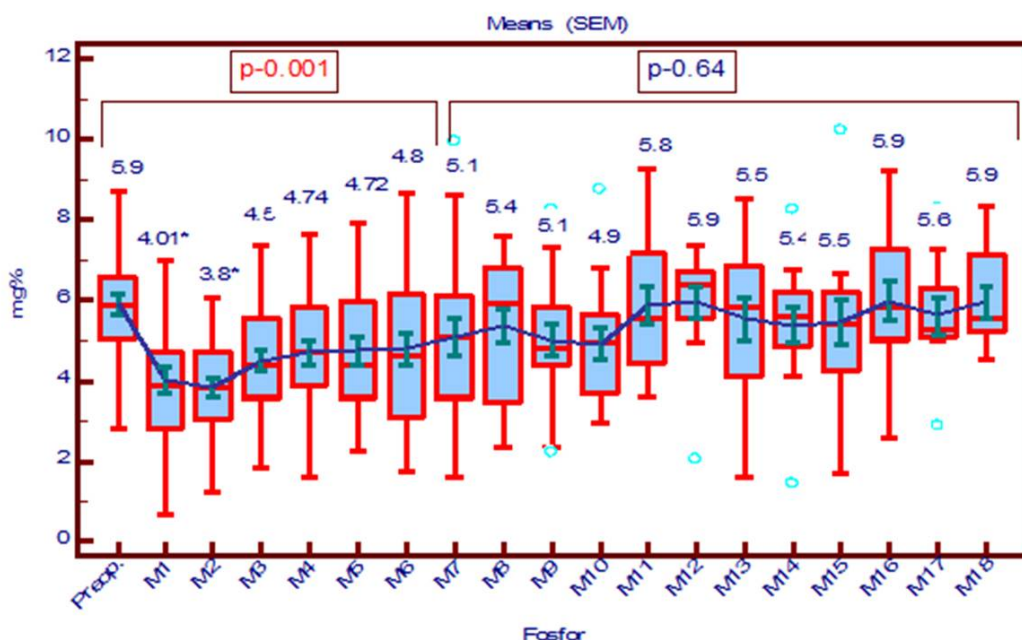


Figure 3. Evolution of preoperative serum phosphorus values compared with the 1-18 months postoperative interval *-the statistical significance is between the preoperative level and the mean values in the first and second month after the operation

median values in the first postoperative month decreasing to 399.5 UI and with even lower values in postoperative months 2-6 with intervals, of 182.2-269.8 UI. In the medium term, the insufficient AlkPhos data made it impossible to undergo a statistical analysis (Figure 4).

Hematocrit level in 1-6 months, 7-18 months respectively

The mean preoperative hematocrit value was $30.6 \pm 0.53\%$ (nv: male: 42-54%; woman: 35-45%). In the short term follow-up period (1-6 months), the hematocrit experienced a growth, with values between 32.9-35.7% with statistical significance ($p=0.0001$). In the medium term (7-18 months), the Hct values are significantly higher compared with the preoperative level ($p=0.0001$), range between 36.93-41.0 % (Figure 5).

Hemoglobin level in 1-6 months, 7-18 months respectively

The mean short term hemoglobin (Hgb) values vary between 10.7-11.5 g/dl (nv: male

13.5-17.0 g/dl; woman 12.0-15.5 g/dl) with statistical significance ($p=0.0001$). Similar results are obtained for the medium term ($p=0.0001$), with values varying between 11.4-12.2 g/dl (Figure 6).

Persistent HPT was encountered in two patients (6.89%), both with only three parathyroids resected at the time of the initial operation; they were re-operated on with good clinical and laboratory outcome.

We had 8 patients who developed mild hypocalcemia in the first month after the operation ("hungry bones" syndrome); 2 of them (6.89%) required long-term oral calcium and alphacalcidol supplementation, probably due to definitive hypoparathyroidism.

We did not encounter postoperative mortality in our series; no patient suffered permanent recurrent laryngeal injury but we had two patients who developed temporarily dysphonia after the operation. One patient developed a cervical hematoma after the first postoperative dialysis, re-

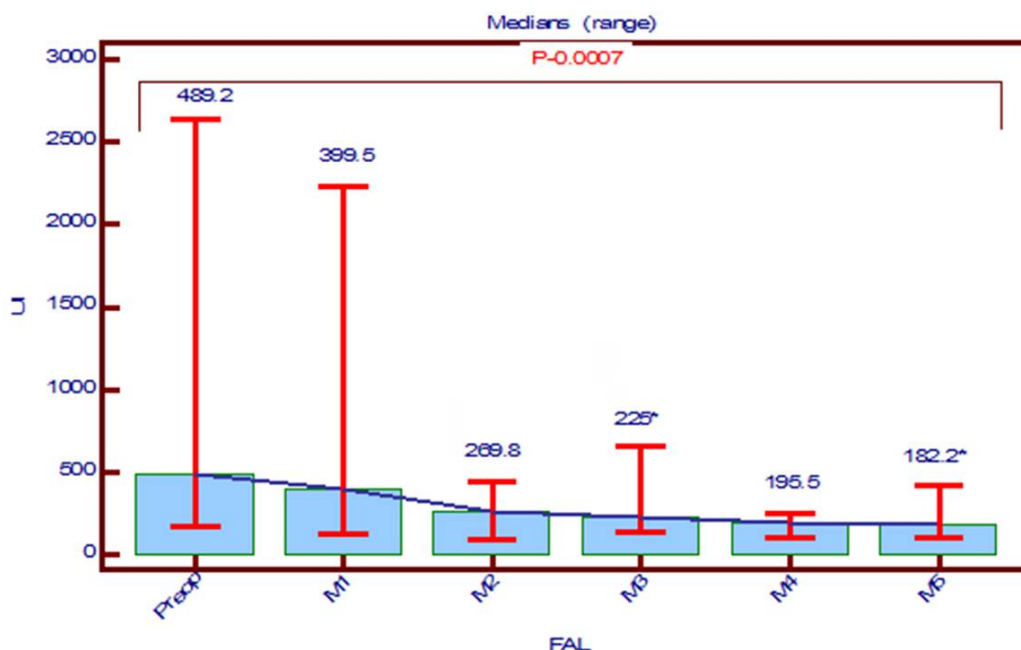


Figure 4. Preoperative AlkPhos values evolution compared with the 1-5 months postoperative interval

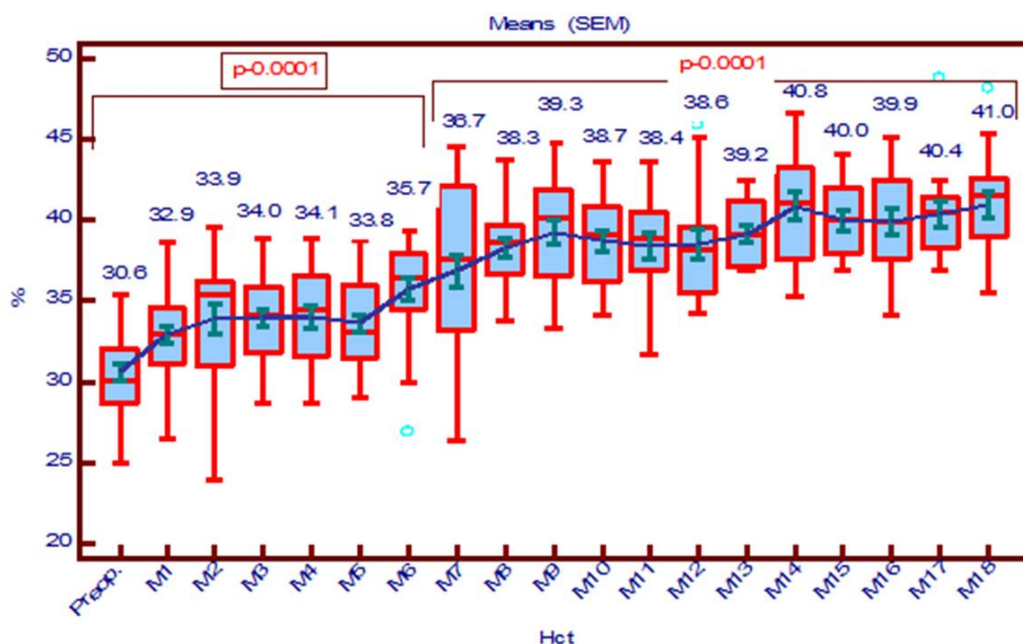


Figure 5. Preoperative hematocrit values evolution compared with the 1-18 months postoperative interval

*-the statistical significance derives from the fact that the postoperative values are higher compared with the preoperative results

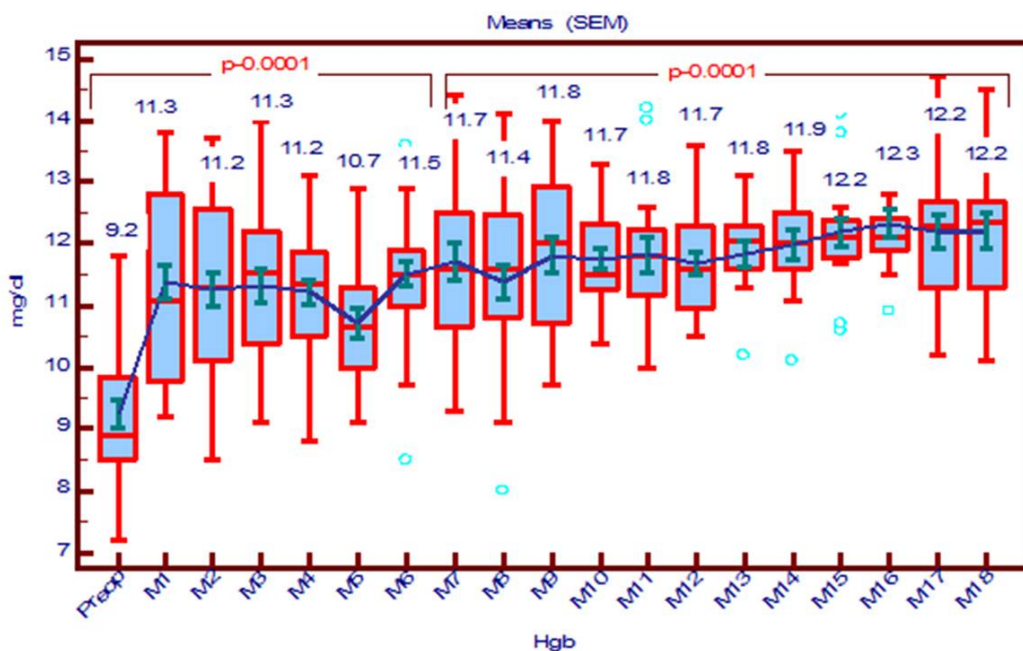


Figure 6. Preoperative Hgb values evolution compared with 1-18 months postoperative interval

*-the statistical significance derives from the fact that the postoperative values are higher compared with the preoperative results

quiring surgical evacuation. Definitive histological examinations revealed diffuse hyperplasia (9 cases), nodular hyperplasia (16 cases) or a mixed pattern (4 cases) in all excised glands.

Discussions

Secondary hyperparathyroidism (sHPT) is frequently encountered in patients on hemodialysis (HD) for ESRD, strongly influencing mortality and quality of life (7-9).

The average prevalence of renal replacement therapy (including HD) in the European countries, according to the ERA-EDTA Registry 2007, is around 695 per million people (pmp) with an average incidence rate of renal transplantation of 28.7 pmp (10). With regards to this issue there are still major differences between Eastern and Western Europe; Eastern European countries (including Romania) present a lower prevalence (450 vs.910 pmp) of renal replacement therapy with similar results concerning average incident of renal transplants (16 vs 38 pmp) (11). Therefore an important number of ESRD patients are recorded with long term dialysis (over 10 years); many authors have shown that 15 -38 % of the patients in long term dialysis present a parathyroidectomy indication due to refractory sHPT or tHPT (4,12). As far as we know the number of parathyroidectomies performed in Romania per annum is considerably lower than the one anticipated and consecutively there are few studies about surgical treatment of sHPT (5,7,13-17).

The indications for surgery in sHPT are still a matter of controversy but the following seems to be generally accepted: severe hypercalcemia or hyperphosphatemia in the context of high iPTH plasma levels, clinical signs of HPT, imagistic data suggesting enlarged parathyroid glands, clinical and radiological signs of osteoclastic bone resorption (18,19). Medically refractory and tHPT are other recognized indications for surgery (5-7).

Subtotal parathyroidectomy was the first procedure proposed in the literature for the surgical treatment of sHPT (Stanbury et al, 1960) (20); it was soon followed by tPTX without autotransplantation, performed by Fergusson and reported by Ogg in 1967(21) and tPtx+AT of parathyroid tissue in forearm muscle, also known as Wells method (22). For the past 50 years surgeons have debated the optimal surgical treatment for sHPT, every procedure having its own disadvantages and advantages (7). Regardless of the chosen surgical procedure, bilateral examination of all hyperplastic glands is mandatory in sHPT, bearing in mind possible atypical locations and the possibility of supernumerary parathyroid glands (23).

In the majority of our cases we performed sPTx with a particularity regarding the position of the remaining parathyroid tissue and its vascularization, as we previously described it (7). As others authors mentioned, this technique has some advantages such as low local spreading, by preserving the blood supply and partially the gland capsule, easy operative access in case of recurrent HPT (24). In our group we also had 5 patients with total parathyroidectomies with or without autotransplantation; since the number of these patients were too small we did not performed a comparative analysis with the sPTx group.

All the clinical complaints were markedly relieved or disappeared after surgery; we have noted significant improvement in the first year following parathyroidectomy especially as regarding bone pains, polyarthralgias, pruritus and incidence of pathologic fractures.

With respect to the effect of parathyroidectomy on biochemistry tests we have analyzed in a prospective manner the changes in serum iPTH, total calcium and phosphorus, AlkPhos and hemoglobin-hematocrit level in the short-medium follow-up period.

As a particularity of our group, we constantly noted increased values of preoperative serum iPTH, with a median of 2500 pg/ml, values which have often been recorded even after the recent preoperative interruption of calcimimetics. These values along with the severity of sHPT clinical manifestations (mainly osteoarticular) and the almost constant intraoperative discovery of a significantly increased, even “macroscopically” nodular parathyroids betray the long evolution of the disease, its tertialization and maybe even surgery delays (7). After the surgery iPTH level decreased significantly and the average values remain low in both short and medium term period of follow-up. As we have previously mentioned we had 2 patients with persistent HPT, thus giving us a success rate of 93.1% after the first operation, somehow lower than the one reported in the literature (24-26).

Hypocalcemia is a common, expected and sometimes dangerous parathyroidectomy complication (25). Prolonged severe postoperative hypocalcemia (more than 4 days long) associated with hypophosphatemia define “hungry bones” syndrome, its severity being directly related with the degree of preoperative bone disease (24-26).

We did not frequently encounter preoperative hypercalcemia in our series; in spite of this we frequently noted hyperphosphatemia before the operation, with a mean preoperative phosphorus level of 5.8 mg/dl (nv:2.7-4.5mg/dl). After the surgery serum calcium level decreased, the differences between the averages recorded preoperatively and those from the first 4 months after the surgery being statistically significant. In the first month after surgery 8 patients developed mild hypocalcaemia under treatment with calcium infusions and alphacalcidolum, due to “hungry bones” syndrome. We had 2 patients who required oral calcium supplementation for a long period after parathyroidectomy, probably due to a small parathyroid graft left in place or hypo-

vascularization of the graft (definitive hypoparathyroidism). On medium term follow-up serum calcium level remained in normal range. With respect to serum phosphorus level we also noted a significant decrease in the values recorded preoperatively and postoperatively, respectively. As regarding the interval 7-18 months serum phosphorus averages values ranged between 5.1-5.9 mg / dl, and were not significantly different compared to the preoperative levels.

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 (24,27). In a previous research we established a correlation between preoperative serum AlkPhos and postoperative calcium level in the first month postoperatively, showing that a high value for the preoperative AlkPhos variable predicts a small postoperative calcium value (7). All our patients had high levels of preoperative AlkPhos; we recorded statistically significant decreases in the median levels in post-operative months 2-6 with intervals but in the medium term, the insufficient AlkPhos data made it impossible to undergo a statistical analysis.

Anemia is almost constant in patients with ESRD, especially in those who are on long-term hemodialysis (28,29). The severity of sHPT seems to be involved in the degree of anemia; it appears that the elevated levels of Pth determine bone marrow fibrosis, inhibit the erythropoietin formation (30) and, along with hemodialysis procedure itself, decrease red cells life expectancy (28-31). Patients with ESRD-related anemia are treated with erythropoiesis-stimulating agents (ESA) but adverse cardiovascular therapy-related events and drug tachyphylaxy has been described (28,31). Parathyroidectomy seems to improve endogenous erythropoiesis, improve anemia and reduce the need of ESA

(31-33). Given the fact that nearly all patients were registered with long-term hemodialysis, we also frequently encountered preoperative anemia in our lot. After the surgery we noticed a significant improvement of both hemoglobin and hematocrit levels, the values of which remained constant during the follow-up.

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 (34,35); the short/medium time follow-up period did not allow us to draw any conclusion regarding this issue. Among our patients four (13.79%) were found to have unexpected thyroid pathology at the time of PTx, including two with differentiated thyroid carcinoma. Even if the association between sHPT and differentiated thyroid carcinomas (DTC) is a rare event, there is some evidence that CRF may predispose to malignancy (36,37), so any incidental thyroid pathology should be treated adequately, preferably during the initial operation.

This study represents the analysis of our experience with parathyroidectomy in the treatment of secondary hyperparathyroidism and has several drawbacks such as the limited number of patients, the insufficient AlkPhos data which made it impossible to undergo a statistical analysis of this parameter in the medium term and of course, the short/medium time follow-up period. However, we believe that parathyroidectomy, regardless of the technical procedure, is feasible, safe and effective for patients with refractory secondary and tertiary hyperparathyroidism, markedly relieving the symptoms of the disease, steadily decreasing iPTH and serum calcium levels in both short and medium-term follow-up, decreasing AlkPhos level and serum phosphate level in the next few months after the surgery and improving both hemoglobin and hematocrit postoperative levels in dialyzed patients for ESRD.

List of abbreviations

HPT = hyperparathyroidism

sHPT = secondary hyperparathyroidism

tHPT = tertiary hyperparathyroidism

ESRD = end stage renal disease

HD = hemodialysis

iPTH = intact parathyroid hormone

AlkPhos = alkaline phosphatase

sPTx = subtotal parathyroidectomy

tPTx+At = total parathyroidectomy with autotransplant

tPTx = total parathyroidectomy

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