

Measurement of Quality of Life after Total Parathyroidectomy in Patients with Secondary Hyperparathyroidism and End Stage Renal Disease

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Rezumat

Instrument de măsurare a calității vieții după paratiroidectomie totală la pacienții cu hiperparatiroidism secundar și boală renală în stadiul final

Introducere: Paratiroidectomia reprezintă tratamentul definitiv pentru pacienții cu hiperparatiroidism secundar (2HPT) și boală renală stadiul final. Scopul studiului este de a cuantifica impactul intervenției chirurgicale asupra evoluției calității vieții (QoL) pacienților cu 2HPT și de a identifica variabilele care influențează această evoluție.

Material și metodă: O serie de 85 pacienți consecutivi au urmat paratiroidectomie totală pentru 2HPT. QoL a fost măsurată folosind Chestionarul SF-36, iar ameliorarea simptomatologiei a fost cuantificată utilizând un instrument specific (scorul PAS), bazat pe scala analog vizuală, preoperator, postoperator și la 6 luni.

Rezultate: Preoperator, pacienții au prezentat scoruri SF-36 mai mici decât populația generală în cele 10 scale, cu o scădere semnificativă în scalele sănătății fizice ($p < 0.0001$). Scorurile s-au îmbunătățit în toate cele 10 scale la 6 luni postoperator,

cele mai semnificative creșteri fiind obținute în Durere (45.02 ± 5.52 vs 33.12 ± 8.82 , $p < 0.0001$), Rol-fizic (41.00 ± 7.43 vs 33.46 ± 8.54 , $p < 0.0001$), Funcție-fizică (40.06 ± 7.77 vs 33.36 ± 10.84 , $p < 0.0001$). Scorul PAS a scăzut de la nivelul preoperator de 569.99 ± 136.45 la 372.20 ± 104.62 la 7 zile post-operator și la 292.64 ± 85.16 la consultul de 6 luni ($p < 0.0001$). **Concluzii:** Nu am găsit nicio corelație între nivelul preoperator al Parathormonului sau al calcemiei și simptomatologia clinică. Paratiroidectomia ameliorează semnificativ simptomatologia și crește calitatea vieții acestor pacienți, cu un efect durabil la 6 luni.

Cuvinte cheie: calitatea vieții, hiperparatiroidism secundar, paratiroidectomie totală, 2HPT

Abstract

Background: Surgery is the definitive treatment of secondary hyperparathyroidism (2HPT) and end stage renal disease patients. The aim of this study to assess the impact of surgery on the evolution of quality of life (QoL) in patients with 2HPT, and to identify the variables that influence this evolution.

Methods: A series of 85 consecutive unselected patients underwent total parathyroidectomy for 2HPT in our clinic. QoL was measured using the Short-Form Health Survey(SF-36) and alleviation of symptoms was documented using an outcome tool (PAS score), based on visual analog scales, preoperatively, postoperatively and at 6 months.

Results: Preoperatively, patients had lower SF-36 scores than

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the general population in all 8 individual and 2 component summary scales, with significant decrease in the physical health scales ($p < 0.0001$). Patients improved in all ten scales at 6 months follow-up, most significant being: Body Pain (45.02 ± 5.52 vs 33.12 ± 8.82 , $p < 0.0001$), Role-physical (41.00 ± 7.43 vs 33.46 ± 8.54 , $p < 0.0001$), Physical functioning (40.06 ± 7.77 vs 33.36 ± 10.84 , $p < 0.0001$). PAS Scores decreased from preoperative levels of 569.99 ± 136.45 to 372.20 ± 104.62 at 7 days after surgery and furthermore at 292.64 ± 85.16 at 6 months follow-up ($p < 0.0001$).

Conclusions: We found no correlation between preoperative PTH or Calcium levels and clinical symptoms. Parathyroidectomy clearly alleviates symptomatology and improves QoL in 2HPT patients, with durable effect at 6 months.

Key words: quality of life, secondary hyperparathyroidism, total parathyroidectomy, 2HPT

Introduction

Secondary hyperparathyroidism (2HPT) is a common development in end stage renal disease (ESRD) patients but the pathogenesis is complex and incompletely understood. Impaired urinary phosphate excretion and hyperphosphatemia, along with low vitamin D levels occurring in chronic kidney disease (CKD) lead to hypocalcemia and continuous overstimulation of the parathyroid glands that further lead to a diffuse hyperplasia with monoclonal cell growths and hypersecretion of parathyroid hormone (PTH). (1,2) As many as 90% of CKD patients will develop 2HPT by the time they reach ESRD. (3)

Elevated PTH levels are associated with many complications, such as psychological and neurological disorders, mineral bone disorder, ectopic calcifications in the cardiovascular system, malnutrition, and inflammation. (4) Calciphylaxis, the calcification of small arterial vessels results in ischemic skin necrosis, and uremic pruritus. Also, 2HPT has been linked to higher cardiovascular morbidity and mortality in patients with ESRD. (5,6)

These complications can severely compromise the quality of life (QoL) of the already impaired ESRD patients. (7)

In the great majority of patients, 2HPT can be successfully managed by intensified dialysis, kidney transplantation, or medical treatment with phosphate binders and supplementation of calcium and vitamin D, vitamin D analogs, or calcimimetics (8). However, over time, changes in the expression of calcium and vitamin D receptors promote nodular hyperplasia and potentiate adenomatous changes within the parathyroid glands, thus becoming autonomous and difficult to control through conservative treatment (9,10).

The beneficial effects of Parathyroidectomy (PTX) for 2HPT have been reported by quite a few of retrospective, observational studies. After PTX, serum Ca and P have generally easily achieved recommended target values (11). Bone

metabolism (12), and diastolic cardiomyopathy (13) are markedly improved and also reduced incidence of major cardiovascular events and overall mortality was found (14). Other studies have demonstrated that bone pain, malaise, pruritus or calciphylaxis is likely to improve after PTX (15,16)

However the studies that assessed the QoL improvement and alleviation of symptoms in patients with 2HPT enrolled only small numbers of patients (less than 50), or were retrospective, thus suffering from obvious limitations. (17) An important contribution to this field has been the development of a surgical outcome tool designed specifically for HPT symptoms validated by Pasieka and coworkers, both on primary and secondary HPT patients (18-20)

The aim of this study is to assess the evolution of QoL in patients with 2HPT and ESRD that received surgical treatment and to identify the different clinical, biological or pathological variables that influence this evolution. The results may serve as a basis for future clinical decision making.

Patients and Methods

Subjects

During a 1 year period, beginning in January 2014, a series of 85 consecutive unselected patients with ESRD underwent total parathyroidectomy for 2HPT by a single surgical team.

All patients had been on peritoneal dialysis or hemodialysis for more than three months, they were > 18 years of age, had no mental disorders, were able to speak clearly, and had no evidence of malignancy. During hospital admission, we explained the research purposes to potential subjects and their families, and obtained informed consent.

Demographic, biochemical, radiological, operative, and histological details were recorded in a prospective database. Demographic data included age, gender, education, occupation, primary disease that resulted in ESRD, dialysis modality (hemodialysis or peritoneal dialysis), dialysis frequency, total months of dialysis, presence of other chronic diseases. Routine blood biochemistry, blood cell counts, serum calcium, inorganic phosphate, and PTH were measured preoperatively, at 5-7 days postoperatively and at scheduled 6 months follow-up visit.

QoL and symptoms measurement tools

QoL was measured using the Medical Outcomes Study Short-Form Health Survey (SF-36) (21), adapted for the Romanian population. (22) This instrument was selected because it is practical, well suited for clinical use, inexpensive and has been validated in a variety of disease conditions in adults, including ESRD. (23) By means of 36 simple questions that are scored from 1 to 6, the SF-36 allows reproducible measures of patient-perceived wellness on eight dimensions: physical functioning (PF), social functioning (SF), role-functioning emotional (RE), role-functioning physical (RP), vitality (VT), pain (BP), mental health (MH) and general health (GH) perceptions. Scores range from 0 to 100; the higher the score, the better the QoL.

Two summary scores were calculated: (1) the physical component summary score (PCS), as the mean of physical functioning, role-functioning physical, vitality, pain and general health perceptions scores and (2) the mental component summary score (MCS), as the mean of social functioning, role-functioning, emotional, mental health, vitality and general health perception scores.

The obtained scores for each questionnaire suffered a norm-based transformation with the 1998 U.S.A. population that has a mean of 50 and a standard deviation of 10 on every scale, using the commercially available SF Health Outcomes TM Scoring Software (QualityMetric Inc., Lincoln, USA). Thus, scores above or below are better or worse with respect to the general population. The purpose of this was twofold: first, to aid graphic display and interpretation of the data across the 10 scales; and second, to facilitate comparisons to population norm-based scoring.

Patients completed the SF-36 questionnaire at 2 distinct times: after admission, prior to surgery and at 6 months follow-up.

The alleviation of symptoms was documented using parathyroid assessment of symptoms score (PAS), a standardized questionnaire developed by Pasieka et al (18-20). The 13 items explored included: bone pain, feeling tired easily, mood swings, feeling "blue" or depressed, pain in the abdomen, feeling weak, feeling irritable, pain in the joints, being forgetful, difficulty getting out of a chair or car, headaches, itchy skin, and being thirsty. Each item was scored according to the response on a 100-mm visual analogue scale. PAS was calculated as the sum of all 13 answers, with a maximum PAS possible of 1300.

The patients filled out the PAS questionnaire pre-operatively, postoperatively at 5 to 7 days, and at 6 months follow-up.

The responderate was 100%.

Statistical analysis

Data analysis was performed by SPSS software, version 12 (SPSS, Chicago, IL). Nonskewed data are presented as means $\pm$ standard deviation (SD). Skewed data were analyzed by using the Anderson-Darling Normality Test, and presented as median values. As appropriate to the presented data, Wilcoxon Matched-Pairs Signed-Ranks Test for paired observations, independent sample t-test, paired sample t-test, and Pearson chi² were used to identify any correlations between clinical data, laboratory values, PAS scores,

Table 1. Patient preoperative characteristics

Variables	No. of pts.	Percentage %	Mean $\pm$ SD
Sex (male/female)	39/46		
Age (years)			51 $\pm$ 12
Duration of dialysis (years)			8 $\pm$ 3
Hemodialysis	81	95.3	
Peritoneal dialysis	4	4.7	
Diabetes	21	24.7	
Hypertension	65	76.5	
Coronary heart disease history	24	28.2	
Stroke history	9	10.6	
Renal transplant history	1	1.2	
Anemia	25	29.4	
Atrial fibrillation	8	9.4	
Chronic Hepatitis Virus B/C	14	16.5	

SF-36 scores and the response to surgery. A conservative alpha for any correlation was set at $p < 0.001$.

Results

Between January 2014 and December 2014, 85 patients with 2HPT and ESRD were prospectively enrolled in the study. All patients were enrolled in a dialysis protocol at admission.

Patient history and demographic data are listed in Table 1. The male/female ratio was similar, and the patient distribution by age was normal ($p=0.0569$, Anderson-Darling Normality Test). The great majority of patients (82/85) had had dialysis for at least 3 years with a maximum of dialysis duration of 17 years. Comorbidities, except ESRD were significant, the most common being hypertension, coronary heart disease, anemia, diabetes and chronic viral hepatitis. One patient suffered a kidney transplant in 2007, but was back on dialysis 3 years later.

The most common indication for parathyroidectomy was failure to control PTH levels, 73 patients (85.9%) having pre-operative PTH > 800 pg/ml. The median value of preoperative PTH was 1379pg/ml, with a maximum value of 3345pg/ml. (Table 2) Preoperative hypercalcemia was observed in 62 patients (72.9%).

82 patients underwent total parathyroidectomy without autotransplantation. 2 young patients who were candidates for renal transplantation underwent subtotal parathyroidectomy. In one case, total parathyroidectomy was incomplete, only 3

Table 2. Laboratory Data before and after surgery

Variables	Preoperative	Postoperative	6 months
Calcium (mg/dl)	10.3 $\pm$ 1 *	7.5 $\pm$ 1.6 *	8.8 $\pm$ 1.2 *
Phosphorus (mg/dl)	5.2 $\pm$ 1.1 *	4.2 $\pm$ 1.3 *	4.3 $\pm$ 1.3 *
ALP (U/l)	204 (75 - 1220) **	168 (80 - 280) **	178 (85 - 302) **
PTH (pg/ml)	1379 (414-3345) **	20.9 (3 - 303) **	18.8 (2.5 - 110) **

ALP : Alkaline Phosphatase, PTH : Parathyroid Hormone; * Data is presented as Mean $\pm$ Standard Deviation; ** Data is presented as Median (Range)

Table 3. *Sf-36 Health Survey Results*

SF-36 Scale	Preoperative	Postoperative 6 months	p*
Physical functioning (PF)	33.36 ± 10.84	40.06 ± 7.77	<0.0001
Role-physical (RP)	33.46 ± 8.54	41.00 ± 7.43	<0.0001
Pain (BP)	33.12 ± 8.82	45.02 ± 5.52	<0.0001
General Health (GH)	38.15 ± 9.61	41.23 ± 7.30	<0.0001
Role-emotional (RE)	41.38 ± 14.82	46.79 ± 10.81	<0.0001
Social function (SF)	37.21 ± 12.77	42.90 ± 9.36	<0.0001
Vitality (VT)	43.87 ± 7.57	48.29 ± 6.14	<0.0001
Emotional well-being (MH)	40.11 ± 10.80	42.32 ± 9.06	0.0091
Physical component summary (PCS)	29.96 ± 8.11	38.50 ± 5.36	<0.0001
Mental component summary (MCS)	45.06 ± 11.37	47.28 ± 9.30	0.0149

Data is presented as Mean ± Standard Deviation. * paired student t-test

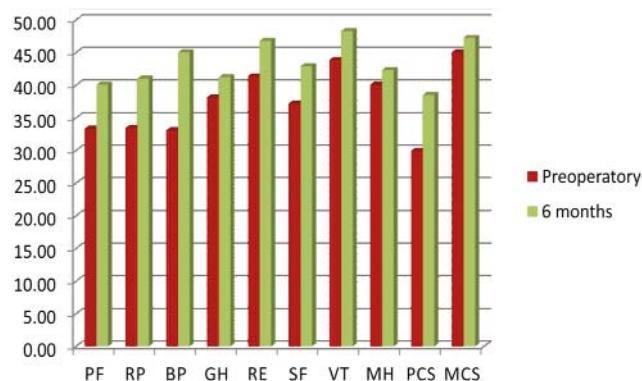
out of 4 glands being excised. However, in this case, PTH levels dropped to normal at 7 days postoperatively and there was a significant alleviation of symptoms. The patient is currently under observation.

As expected, PTH levels dropped significantly after surgery to a median of 20.9 pg/ml, 68 patients having PTH levels within normal limits at 7 days postoperatively and 78 patients at 6 months. (Table 2). All patients required calcium supplementation after surgery, normalization occurring in 2 to 7 days.

There were no postoperative complications reported, including bleeding, recurrent laryngeal nerve injury. No HPT recurrence was documented.

The responses to the Sf-36 Health Survey are shown in Table 3. The surveys completed prior to surgery showed that 2HPT patients had lower scores than the general population in all 8 individual and 2 component summary scales, with a more significant decrease in the physical health scales.

6 months after surgery, patients improved significantly in all ten scales: Physical Functioning Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, Physical component summary ($p < 0.0001$), Emotional well-being ($p = 0.0091$), Mental Component Summary ($p = 0.0149$), however the results were still lower than the general population. These data are represented graphically in Fig. 1.

**Figure 1.** *Sf-36 Health Survey Result Comparison before and 6 months after surgery*

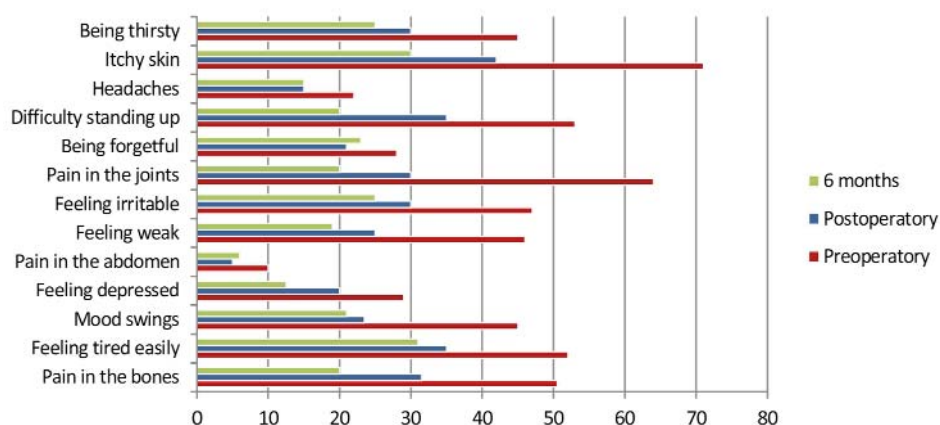
PF - Physical functioning; RP - Role-physical; BP - Pain, GH - General health; RE - Role-emotional; SF - Social function; VT - Vitality; MH - Emotional well-being; PCS - Physical component summary; MCS - Mental component summary

The most significant progress at 6 months follow-up was obtained in the following Sf-36 scales: Body Pain (45.02 ± 5.52 vs 33.12 ± 8.82 , $p < 0.0001$), Role-physical (41.00 ± 7.43 vs 33.46 ± 8.54 , $p < 0.0001$), Physical functioning (40.06 ± 7.77 vs 33.36 ± 10.84 , $p < 0.0001$) and Physical component summary (38.50 ± 5.36 vs 29.96 ± 8.11 , $p < 0.0001$) and also Vitality (48.29 ± 6.14 vs 43.87 ± 7.57 , $p < 0.0001$).

The most commonly reported symptoms preoperatively were: joint pain, bone pain, pruritus, feeling weak, difficulty standing up, but also feeling depressed or irritable. Compared to preoperative values there was a significant decrease in all individual symptom scores at 7 days postoperatively ($p < 0.001$, Wilcoxon Matched-Pairs Signed-Ranks Test), and with exception of headaches, being forgetful, and abdominal pains the decrease continued at 6 months postoperatively. (Fig. 2)

PAS score ranged from 302 to 854 of a potential maximum score of 1300. No patients in our series had scores lower than 200, a cutoff considered nonspecific according to Pasieka et al (27-29).

PAS Scores decreased from preoperative levels of 569.99 ± 136.45 to 372.20 ± 104.62 at 7 days after surgery and further-

Figure 2. *Parathyroidectomy Assessment of Symptoms as recorded on a Visual Analog Scale at specific moments. Data are presented as median values*

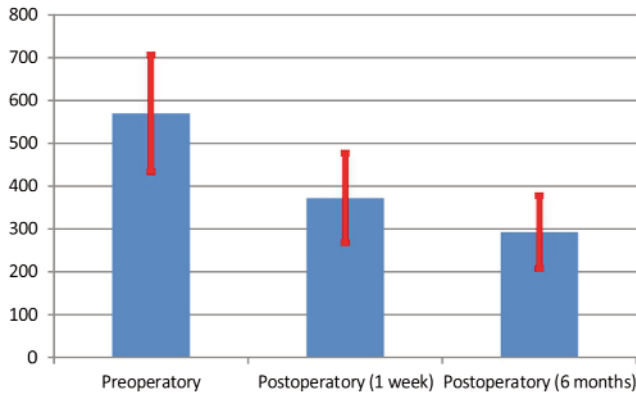


Figure 3. Postoperative changes in Pasieka's Parathyroid Symptom Score. Columns express mean values. Red Lines express Standard Deviation

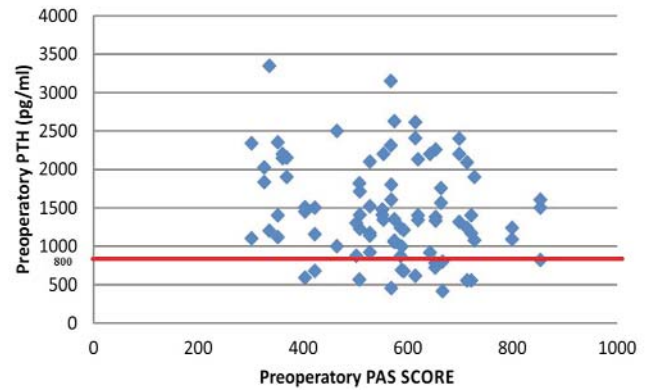


Figure 4. Relationship between preoperative PTH levels and PAS Scores in 85 patients with 2HPT PTH: Parathyroid Hormone; PAS: parathyroid assessment of symptoms

more at 292.64 ± 85.16 at 6 months follow-up, parathyroidectomy generating a more than significant alleviation of symptoms ($p < 0.0001$, paired student t-test for each comparison) – Fig. 3.

There was no correlation between PTH and preoperative PAS scores. In fact, when comparing PAS scores from the 12 patients with $PTH < 800 \text{ pg/ml}$ with the 73 patients with $PTH \geq 800 \text{ pg/ml}$, we found a higher mean PAS score for the first group (592.5 ± 103.08 vs 558.48 ± 141.19 , $p = 0.4268$ student t test), but without statistical meaning. The abnormal distribution of PTH levels in function of the PAS scores is seen in the scatter chart in Fig. 4.

In addition, the postoperative improvements were not correlated with the serum levels of calcium or phosphorus.

By using a Pearson product moment correlation, we found no other significant correlations between preoperative laboratory values and the presenting symptoms, SF-36 Health Survey Results or PAS scores.

Discussion

The definitive treatment of 2HPT is surgery. Parathyroidectomy (PTX) is required in about 15% of patients after 10 years and 38% of patients after 20 years of ongoing dialysis (24). Subtotal PTX (3.5 glands resected), total PTX with autotransplantation (functioning parathyroid tissue is transplanted either into the forearm, thigh or sternocleidomastoid muscle), or total PTX without autotransplantation, each accompanied by a routine bilateral cervical thymectomy, are the validated surgical procedures (25-28). There is ongoing controversy on the advantages and setbacks of each surgical technique. Total PTX, has the one clear advantage of an almost inexistent risk of recurrence (0-4% vs 5-80%). (29,30) The disadvantage is that it carries a non-calculable risk of adynamic bone disease and permanent hypocalcemia that requires long-term calcium and vitamin D supplementation. However, even when all parathyroid glands are removed, PTH levels usually are measurable because nests of parathyroid cells remain, mainly in the thymus.

In our clinic, we perform total PTX without autotrans-

plantation in all ESRD patients with 2HPT, except for patients who are on a waiting list for kidney transplantation, because control of the serum Calcium level may be difficult after kidney transplantation, in which case, we prefer subtotal PTX. Our main argument is that any secondary intervention for recurrence carries greater risk in these fragile patients, adding to morbidity and mortality.

The indications for PTX are still not well established, although guidelines for the treatment have been proposed in the United States (31), Japan (32) and European countries. (33) These guidelines propose that PTX should be recommended in patients with severe 2HPT (persistent high serum level $PTH > 500\text{-}800 \text{ pg/ml}$), associated with hyperphosphatemia (serum $P > 6.0 \text{ mg/dl}$), and/or hypercalcemia (serum Calcium $> 10.0 \text{ mg/dl}$) refractory to at least 6 months of medical therapy. Moreover, in patients suffering from clinical symptoms (bone and joint pain, muscle weakness, irritability, pruritus, osteoporosis, pathologic bone fracture, anemia, dilated cardiomyopathy, calciphylaxis), PTX is absolutely indicated (31-33). Also, ultrasound detection of an enlarged parathyroid gland (with an estimated volume $> 500 \text{ mm}^3$ or diameter $> 1 \text{ cm}$) is strong indication for surgery. (34)

We believe that improving the quality of life and alleviating symptoms is crucial in the chronic treatment of ESRD patients that invariably will develop 2HPT. The present study represents an evaluation of the impact of surgical approach on patient-reported quality of life and symptoms after total parathyroidectomy without autotransplantation, using two validated measuring tools: the Sf-36 Health Survey and The PAS Score.

Results showed that before surgery, the 85 patients in our series had a much poorer quality of life compared to the general population. This was expected, given the dependency of dialysis, the comorbidities and the ESRD-related symptoms these patients have to endure. The negative effect that any other disease, including secondary hyperparathyroidism has on these patients is difficult to interpret. It is very difficult whether a symptom and its severity are related to 2HPT, to ESRD, or both. For instance, bone and joint pain, the most common

complaints in HPT can be a result of aluminum bone disease or adynamic bone disease in patients with renal failure. Skin itching, not at all a common symptom in primary HPT can be a consequence of uremia. Headaches can be accounted to hypertension. Muscle weakness and fatigue are also very common in ESRD patients, that often present with anemia, or associated with ageing.

However difficult to differentiate, the two validated tools showed a significant improvement of quality of life and alleviation of all 13 symptoms at only 7 days after surgery, an evolution that continued positively at 6 months follow-up. Patients in our series had an uneventful recovery, with no mortality, showing that total parathyroidectomy without auto-transplantation can be safely performed with minimal risk to the patient.

Despite the improvement, 2HPT patients continue to present mild to moderate symptoms at 6 months follow-up, lowering their perceived quality of life, that still remains below the general population average.

Our results are completely different than the ones in studies that assessed the impact of surgery in primary hyperparathyroidism. (35-37) In our opinion, 2HPT is entirely a different disease than primary HPT and clinicians should avoid applying the same principles of treatment. 2HPT patients are severely impaired patients, that indeed benefit from surgery, but that do not return to normal life afterwards. Unfortunately, not seldom, conservative treatment is prolonged awaiting the fulfillment of biologic criteria for referral to surgery, patients already experiencing severe symptoms and poor quality of life.

The fact that we couldn't find any significant statistical correlations between preoperative laboratory data, age, sex or duration of dialysis and symptomatology before and after surgery, shows how extremely variable this disease is. Therefore, neither the degree of hypercalcemia nor the PTH levels are predictive of the severity of symptoms from which a 2HPT patient can suffer.

This comes to strengthen our belief in the importance of objectively measuring quality of life and severity of symptoms as an indication to surgery, maybe more important than PTH or calcium levels.

There are some limitations of our study. First, there was no randomization, the study was performed on a series of consecutive patients, as they were referred to our clinic from the Nephrology department. Second, attributing improvements in quality of life to an operative procedure without a control population is problematic, especially in patients with ESRD and many comorbidities. Third, our findings rely on patient-reported symptoms, and this method is inherently subject to bias. Fourth, we transformed SF-36 responses to normalized data for the general population of the United States, that might not be applicable to Romanian population.

We considered that some of these issues have been addressed in previous studies and preferred to use each patient as his own control by comparing the preoperative answers with those at 7 days and 6 months postoperatively.

The SF-36 Health Survey has been extensively validated, and it has been previously used in the measurement of surgical outcomes of parathyroidectomy. Pasieka's score was also validated in assessing both primary and secondary hyperparathyroidism (18-20). Because PAS Score can be easily calculated and allows easier and faster analysis, it is more likely to be adopted into routine clinical practice.

Conclusions

We found no relevant statistical correlation between preparatory PTH or serum Calcium levels and clinical symptoms in patients with secondary hyperparathyroidism and end stage renal disease.

Parathyroidectomy clearly alleviates symptomatology and improves quality of life in these already suffering patients, with a durable effect at 6 months.

PAS Score and SF-36 questionnaires are both useful tools in identifying and measuring symptomatic changes that correlate with the quality of life of patients with secondary hyperparathyroidism and we advocate that they should be integrated into the decision making process of referring patients to surgery, whenever medical treatment is incapable of controlling hyperparathyroidism related symptoms. The decision to operate should not be limited by the severity of biochemical abnormalities.

Acknowledgement

This paper is supported by the Sectorial Operational Programme Human Resources Development (SOP HRD), financed from the European Social Fund and by the Romanian Government under the contract number POSDRU/159/1.5/S/132395

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