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Clinical and Biological Effects and Quality of Life After Parathyroidectomy in Patients with Hyperparathyroidism Secondary to Chronic Renal Failure

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Abstract: Surgical treatment of hyperparathyroidism secondary to chronic renal failure still finds its place despite advances in dialysis and medical treatment. After a certain period of development, surgical management takes place on forms that are particularly symptomatic and resistant to medical treatment. The aim of our study is to evaluate the clinical and biological effects of parathyroidectomy and to correlate the results with a questionnaire on the quality of life. Through a retrospective study of 32 patients, operated over a period of 10 years in the Department of Surgery "A" of Ibn Sina Hospital in Rabat. We evaluated the clinical and biological effects of parathyroidectomy at the 3-year followup. The gesture achieved consists of parathyroidectomy 7/8e in the majority of cases after research and identification of the parathyroid glands. Postoperative hypocalcaemia was present in 22 cases (68.75%), and was symptomatic in 04 cases. Medium and long-term outcomes were satisfactory for the majority of patients clinically and biologically. The clinical improvement evaluated by a PAS (Parathyroidectomy Assessment of Symptoms) questionnaire before and one year after parathyroidectomy was statistically significant. Biologically, hematocrit improvement, decreased parathyroid hormone and alkaline phosphatase were statistically significant between 3 months and 3 years after parathyroidectomy.

Keywords: Chronic Renal Failure, Secondary Hyperparathyroidism, Surgical Treatment, Quality of Life

1. Introduction

Secondary hyperparathyroidism (HPT II) is a common consequence of Chronic Kidney Disease and End Stage Renal Disease (ESRD). The development of secondary HPT is the result of many factors including: calcitriol deficiency, phosphate retention, calcium-sensing receptor (CaR) reduction in the parathyroid glands; and skeletal resistance to the calcemic action of parathormone [1].

As the kidney function declines, so does the phosphate excretion; causing a rise of the serum inorganic phosphate level above range while the calcium and the calcitriol levels decrease. The reduction in the calcitriol level cause subsequently a reduction in the intestinal calcium absorption. All of to these factors contribute to the development of hypocalcemia, which is the catalyst of high production of intact parathyroid hormone (PTHi) [2].

The conventional medical treatment of HPT of a renal origin includes dietery phosphate restriction; active vitamin D sterol, calcium supplement and calcimimetics [3]. The calcimimetics directly inhibit the PTH secretion by activating the CaR in the parathyroid glands. This unique mechanism of action leads to a simultaneous decrease of PTH, calcium, phosphate, and calcium× phosphate product serum levels [4].

The parathyroidectomy remains an important part in the

treatment of patients with refractory renal HPT [5] as well as improving the quality of life in chronic dialysis patients.

The ESRD exerts a great negative impact on the patient's quality of life, on one hand complications specifically related to the renal disease, and on the other hand issues related to dialysis that requires many visits to the dialysis center at least 3 times a week and therefore a drastic change of their normal lifestyle.

The assessment of health-related quality of life is a predictive indicator of the progression of the disease as well as a valuable research tool to assess the effectiveness of the therapeutic intervention, and the quality of life in patients.

The objective of this study is to evaluate the effect of parathyroidectomy clinically with a survey questioning the quality of life before and after surgery, and biologically with biological analysis.

2. Subjects and Methods

We retrospectively reviewed the data from 36 hemodialysis patients who had parathyroidectomy from January 2005 to July 2015 in surgical department "A" at university hospital "Ibn Sina" in Rabat.

Parathyroidectomy was performed for ESRD patient with symptomatic secondary HPT: PTHi level > 1000pg/ml; uncontrollable clinical signs even under medical treatment: bone or joint pain, pruritis, brown tumor or radiological signs of renal osteodystrohy, and calciphylaxis.

The following data were recorded from hospital files: age, gender, during of dialysis, preoperative serum calcium, phosphate, alkaline phosphatase (ALP), iPTH, haemoglobin level, haematocrit. The postoperative data were recorded from differents dialysis centers (respectively 3 and 6 months after parathyroidectomy then at 1, 2 and 3 years after).

A cervical ultrasonography had been performed to explore the parathyroid glands (number, size and location) and evaluate the structure of the thyroid parenchyma. The Sesta-MIBI scintigraphy is not performed systematically. It is only required when there is a persistence or a recurrence of HPT II even after surgery, its purpose is to visualize if there is ectopic or supernumerary glands.

A questionnaire on the quality of life of patients (PAS=parathyroidectomy assessment of symptoms) is administered before and after parathyroidectomy. This questionnaire assesses the specific symptoms of HPT [6, 7].

A score for questions means that the patient did not experiencing any symptoms at all; on the other hand a score of 100 means the patient is experiencing the most extreme aspect of the symptoms [6, 7].

All patients were operated by the same senior surgeon. The interventions were performed under general anesthesia. The cervical incision is madepreferably in a skin crease. The subcutaneous and the musculoaponeurotic tissues were dissected layer by layer until the thyroid gland was exposed. After that the middle thyroid veins were controlled to be able to turn over medially each thyroid lobe. In the case where the parathyroid glands have not been identified during exploration of the posterior wall of each lobe, we practice a meticulous dissection of the para-tracheal space with the utmost attention towards the recurrent nerve. It is common to find a parathyroid gland posterior to the nerve. It's commonlythe privileged site for superior parathyroids.

Two surgical techniques were adopted: Subtotal excision of the parathyroids or Total parathyroidectomy with or without auto-implantation.

The thymectomy was not performed routinely if the four parathyroid glands have been throughtfully identified. For the thyroidectomy, it was only performed if the cervical ultrasound showed a multinodular goiteror a thyroid nodule. The samples are sent to the laboratory pathology to confirm the parathyroid nature and type the tissue proliferation.

The main goal of surgery is to achieve a level of PTHibelow 300 pg/ml within six month of surgery [8]. A PTHi level above 300 pg/ml with or without persistent clinical symptoms defines persistent HPT. The appearance of clinical manifestations or an increase of PTH normal range beyond this period was considered as recurrent hyperparathyroidism.

Data is presented as means and standard derivation when the distribution is normal or median and interquartile if the distribution is not homogeneous. The student's t-test was used to compare the averages and the Mann Whitney U test to compare the medians. The difference was considered significant from a P value less than 0,05. The stastical software used was SPSS, IBM, version13.

3. Results

A total of 32 hemodialysis patients with secondary HPT were included in this study. The exclusion criteria included reoperation for recurrent HPT, renal transplantation or incomplete medical records (figure 1).

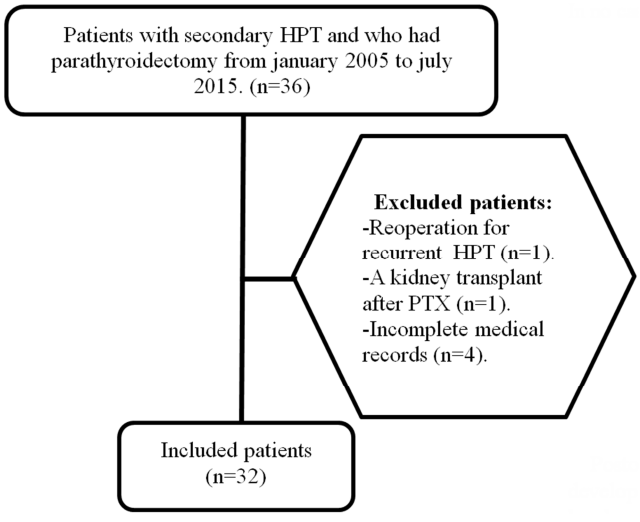

Figure 1. *Flow diagram of study inclusion.*

There were 18 men and 14 women with a mean age of 44,03±14,87 years old and mean hemodialysis duration of 8,38±5,14 years.

The established causes of end stage renal disease were: hight blood pressure (n=5; 15,6%), diabetes (n=3; 9,4%);

hereditary nephropathy (n=4; 12,5%); and unknown causes (n=20; 62,5%).

Preoperative symptoms are reported in table 1, included bone pain (93,8%), joint pain (87,8%), muscular pain and cramps (54,4%), pruritus (68,75%) and pathological fracture (3%).

The quality of life questionnaire (PAS) was administered to 28 patients. The mean score before surgery was 483.44±113.86.

Thirty patients had a subtotal parathyroidectomy (94%). A total parathyroidectomy with auto-implantationwas performed in 1 patient (3%) and without auto-implantation in another patient (3%).

Eleven patients underwent an ismolobectomy or total thyroidectomy (34.37%) when the ultrasound or intraoperative exploration found thyroid nodule or multinodular goiter. Seven patients had cervical thymectomie (21.8%).

In 2 patients, a cervical lymphadenectomy was performed when the lymphadenopathies were intimately connected to the parathyroid gland.

All patients (32) have nodular or diffuse hyperplasia glandular parenchyma. In patients who have had a cervical thymectomy, the analysis histology of the thymus showed the presence of remnants of thymic tissuehistologically normal or adipose involution in the 7 cases, no case intrathymic parathyroid glands in hyperplasia.

For the 11 parts of the thyroidectomy, the histological analysis showed a benign nodular hyperplasia of the thyroid in 8 patients. In no case intrathyroid hyperplasia is not observed.

Postoperative hypocalcemia in the first 24 hours were developed in 22 patients (68,75%). The Serum Calcium levels were equal or less than 80mg/l in these patients and higher than 80mg/l in 10 patients. Thirteen patients from the hypocalcemia group (54,54%) had an age< 45 years.

We found a statistically significant decrease in PTH and PAL between 3 months and 3 years (table 3), this explains the improvement in pain and joint symptoms assessed by the PAS score.

Blood transfusion requirements decreased after subtotal parathyroidectomy (2 patients after parathyroidectomy received daily transfusion versus 18 prior patients).

The PAS questionnaire was administered for a second time 1 year after parathyroidectomy in the 28 patients (Figure 2). The average PAS score of our participants decreased from 483.44±113.86 to 246.20±100.85 after 1 year of the PTX with a statistically significant improvement of 50.92% (P<0.05).

Table 1. *Characteristics and serum biochimical of 32 patients with secondary hyperparathyroidism.*

Number of patients	32	
Age of surgey (years)		44,03±14,87
Female/male	14/18	
Duration of dialysis (years)		8,38±5,14
Clinical symptoms (n):		
Bone pain	30 (93,8%)	
Joint pain	29 (87,8%)	
Pruritis	22 (68,75%)	
Muscle weakness	18 (54,4%)	
Pathological fracture	01 (3%)	
Analysis preoperative:		
Hemoglobin (g/dl)		10,54±1,83
Hematocrite (%)		31,59±6,65
Calcim (mg/l)		98,58±9,30
Phosphate (mg/l)		62,78±17,96
Parathormone (pg/ml)		1908 [1318,75; 3164,75]
Alkaline phosphatase (UI/L)		433 [246; 588,25]
Surgical technique:		
PTX total with autotransplantation	01 (3%)	
PTX total without auto transplantation	01 (3%)	
PTX subtotal:	30 (94%)	
7/8	24	
6/8	03	
4/8	03	
Thyroid surgey:	11	
Isthmolobectomy	06	
Thyroïdectomy totale	05	
Thymectomy:	07	

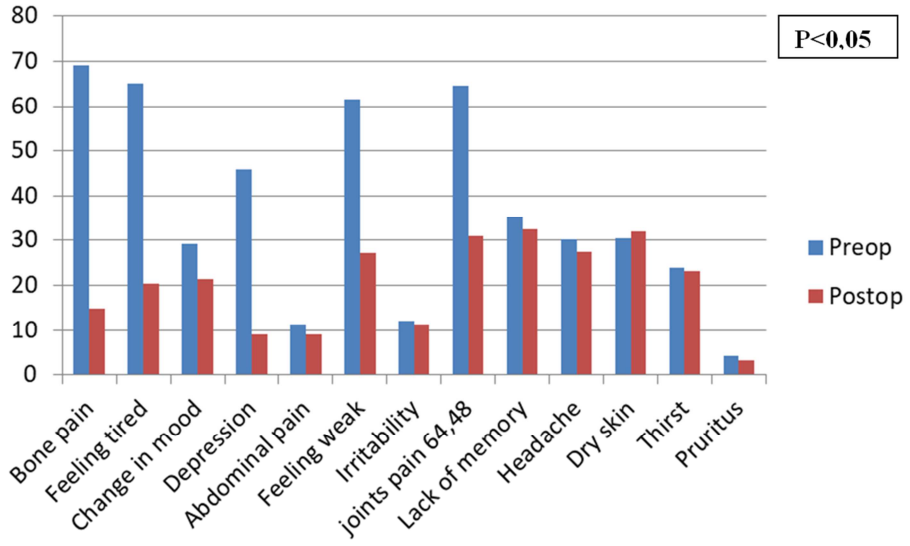

Figure 2. *Preoperative and postoperative parathyroidectomy assessment of symptoms (PAS) scores in 28 patients with secondary HPT.*

Table 2. *Hematologic and serum biochemical values after parathyroidectomy.*

	3 months	6 months	12 months	2 years	3 years
Hemoglobin (g/dl)	10,23±1,82	10,47±2,09	11,41±1,51	11,32±1,38	11,25±1,37
Hematocrite (%)	30,53±5,74	31,32±6,61	34,22±4,46	33,45±4,08	35,18±4,35
Calcium (mg/l)	81,03±15,38	81,58±12,40	83,23±9,75	86,59±12,20	84,18±10,04
Phosphate (mg/l)	31,58±15,15	35,56±18,06	35,22±16,25	39,23±16,61	43,26±18,9
PTH (pg/ml)	35 [16,9; 80]	59 [31,97; 119,25]	64 [24,5; 119,25]	66 [31,75; 137,25]	82 [27,5; 171,5]
ALP (UI/L)	143,5 [86; 182,5]	103 [68; 126,5]	87 [47,5; 141,5]	72 [43; 109]	87 [74,75; 114]

Table 3. *Comparison of biological results at 3 months and 3 years postoperatively.*

	3 months	3 years	P value
Hemoglobin (g/dl)	10, 35±1,74	11,25±1,37	0,10
Hematocrite (%)	30,93±5,8	35,18±4,35	0,026
Calcium (mg/l)	78,76±14,66	84,18±10,04	0,21
Phosphate (mg/l)	32,46±12,38	43,26±18,9	0,085
PTH (pg/ml)	35 [16,9; 80]	82 [27,5; 171,5]	0,028
ALP (U/L)	143,5 [86; 182,5]	87 [74,75; 114]	0,015

4. Discussion

Secondary hyperparathyroidism is a severe and frequent complication in patients with advanced chronic kidney disease, characterized by hyperaplasia of all parathyroid glands and high serum PTH levels [9].

Parathyroidectomy indication is practically unequivocal. According to our experience, the presence of extraskeletal calcification, calciphylaxis, debilitating bone disease, refractory pruritus, severe hypercalcemia, and PTHi >1000 pg/L are strong indications for surgical treatment.

In our study, the age of starting hemodialysis is 35.46 years old (under 45 years old) whichis considered relatively young. The period between starting dialysis and undergoing parathyroidectomy is 8,38±5,14 years old. It is estimated that parathyroidectomy is required in about 15% of patients after 10 years and in 38% of patients after 20 years of ongoing dialysis therapy [10].

The mean PAS score for the 28 patients decreased from 483.44±113.86 to 246.20±100.85 after 1 year of parathyroidectomy with a statistically significant improvement of 50.92% (P <0.05). Comparing our results with another study from Taiwan [11], mean PAS score of participants dropped significantly (P <0.05) from 545 to 284 (with only 48% improvement) after the parathyroidectomy.

Bone symptoms related to HPT II (bone pain, brown tumor, debilitating bone fractures) are related to manifest increase in number and activity of osteoclasts. This leads to rapid bone remodeling and an increase in markers of bone resorption [12]. The resorbed bone trabeculae are replaced by fibrous tissue, which gives fibrous osteitis.

On the other hand, in response to this increased activity of osteoclasts, there is an increase in alkaline phosphatase and other markers of bone formation [13].

The fibrous osteitis becomes diffuse with the continuous increase of bone resorption mechanism along with a dreadful anemia of CKD by decreasing the spinal cord erythropoietin (EPO) level after parathyroidectomy. The biomarkers of bone formation increase rapidly after surgery and then decrease, whereas the markers of bone resorption decrease rapidly after surgery [13]. All of this explains the disappearance of the bone pain after the PTX. The decrease of ALP in the long term results in the return of the metabolic balance of the bone remodeling (between the bone formation and the bone resorption).

The anemia observed in renal failure is mainly due to the absence of renal production of erythropoietin along with a direct inhibitory effect of parathyroid hormone on erythropoiesis by the the fibrosis of bone marrow with worsen even more this anemia [14]. The decrease in PTHi after parathyroidectomy has a direct effect on increasing the response to erythropoietin and therefor improved the hemoglobin level in our patients.

The problems one can have during the dissection: to not identify all the parathyroid glands or to confuse them with other tissues.

In two patients, there was a discrepancy between the resected pieceand the anatomopathological analysis of it.

The surgical procedure, however, remains fraught with local complications, particularly palsy of the recurrent laryngeal nerve. The reported frequency of this complication varies widely (0–20%) [15]. In reoperations, this risk is much higher.

In our serie, only one case of transient recurrent paralysis (3.12%) with a full recovery in the first 2 months postoperative.

The Hungry Bone Syndrome (HBS**)** is a postoperative complication of parathyroidectomy that is due to severe hypocalcemia. The frequency of hypocalcemia in our study was 68.75%. Postoperative hypocalcemia is due to the bone tissue avidity for calcium and phosphate after parathyroidectomy.

Many studies have been published to evaluate the predictive factors of postoperative hypocalcemia in patients after parathyroidectomy [8, 16, 17]. In our study, young age was not associated with the occurrence of postoperative hypocalcemia. Between the 22 patients with postoperative serum calcemia level below 80mg/ l, only 12 patients were under 45 years oldversus 5 patients with a serum calcium level above 80mg/l. The difference was statistically insignificant (table 2). Unlike other studies the young age (<45 years old) was a risk factor for a postoperative Hungry bone Syndrome (HBS) with a P value<0.05 [8, 16, 17].

Serum PTH test was performed the first postoperative day. It was under 300 pg/ml in 30 cases (93.75%) and more than 300 pg in two cases (6.25%). These last corresponded to a persistent hyperparathyroidism and therefore a failure therapy requiring surgical reintervention.

A patient in whom a 6/8 parathyroidectomy was performed; the anatomopathological examination had shown that a parathyroid gland was confused with a cervical ganglion and the postoperative consequences were marked by a persistent bone pain and pruritus. This problem of identification of the glands may be implemented to the fact that the extemporaneous examination of resected tissue or the peroperative parathyroid hormone test was not carried out. The cervical scintigraphy we're not done systematically, but when the ultrasound were not able to identify all the parathyroid glands, the cervical scintigraphy find a place during the first management to search search ectopic glands.

5. Conclusion

Parathyroidectomy is an effective treatment of secondary hyperparathyroidism of the chronic dialysis refractory to medical treatment. Its major aim remains the control of phosphocalcic metabolism and the improvement of the patients' quality of life.

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