THE PLACE OF SURGICAL TREATMENT IN HYPERPARATHYROIDISM SECONDARY TO CHRONIC RENAL FAILURE: REPORT OF 51 PATIENTS

PLACE DU TRAITEMENT CHIRURGICAL DANS L'HYPERPARATHYROÏDIE SECONDAIRE À L'INSUFFISANCE RÉNALE CHRONIQUE: A PROPOS DE 51 PATIENTS

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ABSTRACT

Background: Secondary hyperparathyroidism (SHPT) affects a majority of patients with chronic kidney disease (CKD) of stage 3. Despite the development of calcimimetics and their effectiveness in treating SHPT, many patients continue to fail medical management and should be referred to a parathyroid surgeon.
Aim: In this paper, we summarize indications for surgical management of SHPT, preoperative planning, and postoperative management.
Material and method: We performed a retrospective descriptive study of patients operated for SHPT, during 10-years long period (from January 2010 to December 2019).
Results: A total of 51 patients, 33 (64,7%) of whom were males, with a mean age of 41 years old were assessed in this study. All our patients present CKD and 96,1% of them were in end-stage renal disease (ESRD). The main clinical manifestations were bone pain and asthenia. All patients were evaluated by 99Tc-sestamibi scintigraphy. Parathyroidectomy (PT) was performed in open surgery under general anesthesia. The following types of interventions have been performed: PT type ¾ (13,7%), PT type 7/8 (84,3%), total PT with autotransplantation (2%). In patients with associated thyroid disease, thyroidectomies were done (5,9%). Postoperatively, forty-four patients (85,7%) had hypocalcemia immediately postoperatively, corrected by intravenous calcium supplementation.
Conclusions: Management of SHPT can be extremely challenging. PT remains the most effective treatment and would lead to a better quality of life and improved overall survival.
Keywords: Secondary hyperparathyroidism, End-stage renal disease, Scintigraphy, Parathyroidectomy, Hypoparathyroidism

RÉSUMÉ

Introduction: L'hyperparathyroïdie secondaire (HPTS) touche la majorité des patients atteints d'insuffisance rénale chronique (IRC) de stade 3. Malgré le développement des calcimimétiques et leur efficacité dans le traitement de l'HPTS, de nombreux patients continuent d'échouer face à la prise en charge médicale et doivent être adressés pour chirurgie parathyroïdienne.
Objectif: Dans cet article, nous résumons les indications chirurgicales de l'HPTS, la planification préopératoire et la prise en charge postopératoire.
Matériel et méthode: Nous avons réalisé une étude rétrospective descriptive de patients opérés pour HPTS, sur une période de 10 ans (de janvier 2010 à décembre 2019).
Résultats: Cinquante et un patients ont été inclus, dont 33 (64,7 %) étaient des hommes, âgés en moyenne de 41 ans. Tous nos patients présentent une IRC et 96,1% d'entre eux sont en insuffisance rénale chronique terminale. Les principales manifestations cliniques étaient des douleurs osseuses et l'asthénie. Tous les patients ont été évalués par scintigraphie au 99Tc-sestamibi. La parathyroïdectomie (PT) a été réalisée en chirurgie ouverte sous anesthésie générale. Les types d'interventions suivants ont été réalisés : PT type ¾ (13,7%), PT type 7/8 (84,3%), PT totale avec autotransplantation (2%). Chez les patients présentant une maladie thyroïdienne associée, des thyroïdectomies ont été réalisées (5,9 %). En post opératoire, quarante-quatre patients (85,7 %) présentaient une hypocalcémie immédiatement postopératoire, corrigée par une supplémentation intraveineuse en calcium.
Conclusion: La prise en charge de l'HPTS peut être extrêmement difficile. La PT reste le traitement le plus efficace et entraînerait une meilleure qualité de vie et une survie globale améliorée.
Mots clés: Hyperparathyroïdie secondaire, I*nsuffisance rénale chronique terminale*, Scintigraphie, Parathyroïdectomie, Hypoparathyroïdie

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INTRODUCTION:

Secondary hyperparathyroidism (SHPT) encompasses the biochemical abnormalities of chronic kidney disease-mineral and bone disorders and develops in most patients with end-stage renal disease (ESRD) who require dialysis [1]. It is the major cause of morbidity, such as cardiovascular mortality, ectopic calcifications, renal osteodystrophy, insomnia and depression in patients with ESRD [2]. Medical treatment is based on the administration of phosphorus binders, calcium salts, native vitamin D derivatives and calcitriol analogues [3]. Referral to a surgeon is considered when patients have failed medical management. Symptoms including bone pain and severe pruritis have been shown to improve significantly after parathyroidectomy (PT). The demand for PT increases significantly with dialysis period and proved to enhance survival rate in ESRD patients, for whom the surgical options are subtotal or total PT with auto-transplantation [4].

The objective of this study was to evaluate our experience in the surgical management of SHPT and to assess the short- and long-term results of this treatment.

METHODS:

This is a retrospective monocentric descriptive study of patients operated on in the Department of Ear, Nose and Throat (ENT) and Cervical-Facial Surgery at Fattouma Bourguiba University Hospital in Monastir between 2010 and 2019. In this study, all patients operated for SHPT were included. Patients with primary or tertiary hyperparathyroidism were excluded.

The positive diagnosis is confirmed by biological data: association of hyperphosphatemia (N: 0,6-1,62 mmol/L) and hypo- or normal calcemia (N: 2,2-2,6 mmol/L) with elevation of parathyroid hormone level (PTH) to 2-3 times normal (N: 11-54 ng/L).

The instrumental pre-operative procedures were as follows: high resolution neck ultrasound, in order to assess thyroid morphology and look for possible nodules and technetium 99m sestamibi scintigraphy of the neck and mediastinum or scintigraphy combined with computed tomography (SPECT/CT), useful in identifying supernumerary or ectopic parathyroid glands, that is the exact number of glands or their precise location.

Haemodialysis treatment was carried out without use of anticoagulant agents one day before surgery and the first day after surgery.

Surgical treatment has been indicated for patients who had clinically symptomatic HPT such as bone pain, pruritis, and generalized weakness, or complications attributable to SHPT with pathological PTH values. Parathyroidectomy (PT) was performed in open surgery under general anesthesia, the preferred approach being the anterior cervical Köcher incision. Surgery consisted of PT type 3/4 (removal of 3 glands while retaining the least hyperplastic/normal parathyroid gland), PT type 7/8 (removal of 3 glands and more than half of the 4th least hyperplastic/normal gland) or total PT with parathyroid tissue autotransplantation. In our department, the exploration of the four parathyroid sites is systematic for the surgical strategy. Intraoperative PTH assessment was not performed due to lack of the necessary technical facilities.

We analysed the immediate and long-term results of PT. The day after surgery, PTH and calcemia were measured. Hypocalcemia is defined as a drop in serum calcium to <2.1 mmol/L. Symptoms of severe hypocalcemia include perioral paresthesias, tingling in the extremities, carpopedal spasm, severe muscle cramps, and/ or positive Chvostek or Trousseau sign. All patients should be educated on these symptoms as they can develop after discharge if home calcium supplementation is insufficient. Treatment involves aggressive repletion with intravenous calcium. Usually, on the fourth day, patients were discharged for home with medical treatment.

Regarding postoperative evolution, the treatment success criteria were:

- PTH levels that fall into a normal range,
- Regression or even disappearance of the clinical signs of hyperparathyroidism (HPT),
- Absence of postoperative complications.

We defined the medium-term follow-up period as the period from one month postoperatively to one year after the operation. The long term is the period up to 5 years of evolution. In our practice, we defined persistence of SHPT by recurrence of symptoms and/or elevated PTH levels immediately postoperatively or in the medium term ranging from one month postoperatively to 1 year. While we defined recurrence by reappearance of clinical signs of HPT with the rise of calcium and PTH levels after at least 1 year.

For the statistical analysis, it was carried out using SPSS version 21 software. Quantitative variables were expressed as mean, qualitative variables as number and percentage.

RESULTS:

This study analysed 51 cases of patients operated for SHPT. All our patients present CKD and 49 patients (96,1%) were in ESRD. The medium duration of dialysis was 7 years. In 14 cases (27,5%), patients suffered from coexisting thyroid nodules. The main clinical manifestations in our study were bone pain found in 36 patients (70,6%) and general syndrome made of asthenia and weight loss found in 15 patients (29,4%). Biologically, hyperparathormonemia was found in all our patients with a mean rate of 1391 pg/ml and extremes ranging from 334 to 3236 pg/ml. Hypocalcemia was found in 27 patients (52,9%) and normocalcemia in 24 patients (47,1%), with a mean calcemic rate at 2,23 mmol/l. Phosphoremia was only done in 25 patients (49%), 20 (39,2%) of whom had hyperphosphatemia, while the other five had normal levels. Whereas vitamin D was only measured in 14 patients (27,4%), three of whom had severe hypovitaminosis D (<20 *ng/ml)*. Free

T4 (FT4) and Thyroid Stimulating Hormone (TSH) were requested in all case of associated thyroid nodules and were normal in 13 patients (93%) and pathological (hypothyroidism) in a single patient (7%).
Neck ultrasound was performed in 49 patients (96,1%) and technetium 99m sestamibi scintigraphy of the neck and mediastinum in all cases. Scintigraphy combined with computed tomography (SPECT/CT) was only performed for three patients (6%) (figure 1). Moreover, two patients (3,9%) had brown tumours whose origin was linked to hyperparathyroidism (on histological evidence following biopsies). Epidemiological data of patients are summarized in Table I.

Figure 1: Subtraction parathyroid scintigraphy coupled to CT (SPECT-CT) showing parathyroid fixation of the right upper and lower parathyroid and upper left parathyroid (arrow)

Table I: Epidemiological data of patients with SHPT in our series (n = 51)

Characteristics	n (%)	Mean	Range
Age (Y)		41	26-72
Males	33 (64,7)		
CKD	51 (100)		
ESRD	49 (96,1)		
Duration of dialysis (Y)		7	1-25
Thyroid nodules	14 (27,5)		
Arterial hypertension	18 (35,3)		
Diabetes	5 (9,8)		

CKD: Chronic kidney disease; ESRD: End-stage renal disease; Y: Years

Regarding treatment of SHPT, the preoperative medical treatment included calcium supplementation was prescribed for 21 patients (41,2%), Vitamin D for 4 patients (7,8%), a combination of calcium and vitamin D supplementation for 26 patients (51%). No patient has had treatment with calcimimetics by default of availability. All our patients underwent surgical treatment. The approach was the anterior cervical incision of Köcher in all cases. Surgery consisted of subtotal PT type 7/8 in 43 patients (84,3%) (Figure 2). An associated thyroid surgery was done in three cases (5,9%) for patients with thyroid nodules. It was a thyroid lobectomy in all cases. The table II summary different surgical procedures in our series.

Table II: Surgical procedures for patients with SHPT in our series (n = 51)

Surgical procedure	n (%)
PT type 7/8	43 (84,3)
PT type ¾	7 (13,7)
PT with auto transplantation	1 (2)
Thyroid lobectomy	3 (5,9)

PT: Parathyroidectomy

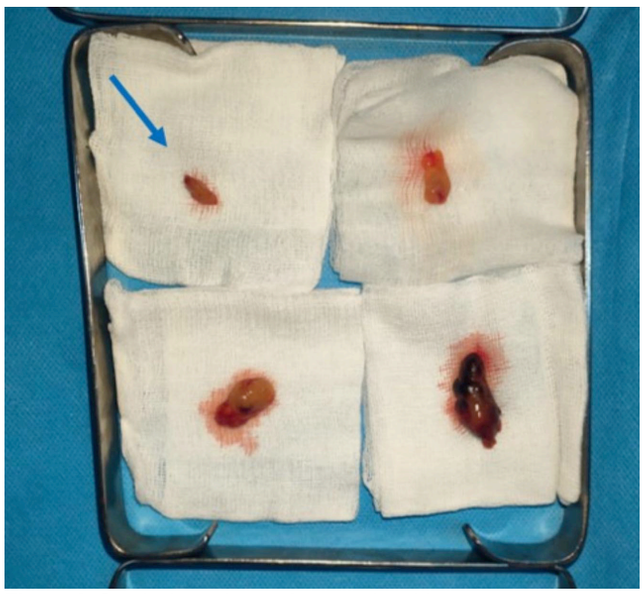

Figure 2: Surgical specimen after parathyroidectomy type 7/8, removing the left lower and upper parathyroid, lower right parathyroid and more than half of the upper right parathyroid gland (arrow)

The extemporaneous examination was performed in 3 patients (5,9%) when there was an anatomic or histological doubt intraoperatively. The result of this examination was the presence of parathyroid parenchyma in 2 cases and adipose *tissue in one case. In the last case, we have identified parathyroid gland after dissection*. The final histological examination confirmed the hyperplasia of all removed glands. It was a diffuse hyperplasia in 94,1%, a diffuse and nodular hyperplasia in 3,9% and a nodular hyperplasia in 2%.
Concerning the postoperative course, the majority of patients (85,7%) required intravenous administration of calcium due to immediate and transient hypocalcaemia. The average postoperative hospitalisation stay was 4,4 days.
Postoperatively, we have observed a cure rate of 78,4%. Persistent HPT was found for 8 patients (15,7%). One case was related to a vitamin D deficiency requiring supplementation. The persistence was related to ectopic parathyroid gland for 3 patients. Combined SPECT/CT was requested in these cases a few months after the first surgery (Figure 3). Hyperfunctioning parathyroid glands previously undiscovered were found in the mediastinum. Patients were referred to thoracic surgery department for second operation.

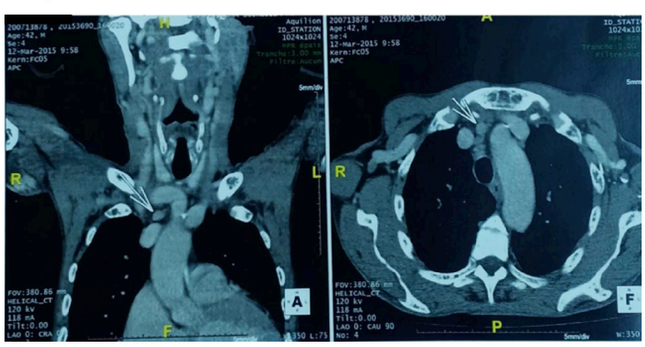

Figure 3: Computed tomography scan shows a persistent right mediastinal parathyroid gland (arrow).

Persistent HPT was due to incomplete resection of pathological parathyroid tissue in the first operation for one patient and secondary hyperplasia of the parathyroid gland left in place for 3 patients. These patients have had successful reoperations compared with the initial operation after re-exploration.

We reported recurrence in 2 cases (3,9%). The first case was related to a carcinoma of the parathyroid gland. The initial operation performed was PT type ¾ and on histological examination, it was a diffuse hyperplasia of all removed glands. In this patient, a revision surgery for removal of the right parathyroid initially left in place was done associated to thyroid surgery and central lymph nodes removal. The other case was in relation to the development of a parathyroid adenoma on the right upper parathyroid left in place. The patient was subsequently was re-operated. He underwent a PT with parathyroid tissue autotransplantation with normalisation of postoperative calcium and PTH figures at one-year follow-up. The two cases have progressed well after treatment, and we did not notice persistent or recurrent HPT.

We did not have operative mortality in our series.

DISCUSSION:

In this paper, we conducted a retrospective study of 51 patients operated for SHPT. The average age of our patients was 41 years. All our patients present CKD and 96,1% of them were in ESRD. In our series, the indication for parathyroid surgery was made in the presence of clinically symptomatic HPT, with pathological PTH values. The surgical approach was subtotal PT (type 7/8) in 43 cases (84,3%), PT type ¾ in 7 cases (13,7%) and total PT with autotransplantation in one case (2%). Postoperatively, persistent HPT was found in 8 patients (15,7%) and recurrent HPT in 2 patients (3,9%).

According to most series, the average age of patients treated surgically for SHPT varies between 40 and 50 years [3], which is congruent with our series. CKD is a very favourable factor for the occurrence of hyperparathyroidism [5]. Other factors are hypovitaminosis D, renal hypercalciuria, calcium deficiency, vitamin resistant rickets, medication and hypothyroidism [5-6]. Although being usually asymptomatic, severe secondary hyperparathyroidism can manifest as bone and joint pain, muscle weakness, refractory pruritus, progressive soft tissue calcification, cardiovascular calcifications (calciphylaxis), kidney stones, constipation, peptic ulcer, spontaneous long bone fracture and even psychiatric signs [7-8]. SHPT may also be revealed by single or multiple well-limited osteolytic lesions, suggestive of brown tumours. The incidence of these tumours in published SHPT series ranged from 1,5 to 1,7% [9].

In our series, hyperparathormonemia was found in all patients with a mean rate of 1391 pg/ml, which is close to that of the literature [10]. Vitamin D deficiency is usually observed in patients with ESRD [11]. Correction of hypovitaminosis D is recommended prior to SHPT surgery by multiple authors but should not be delayed if surgery is indicated [5].

Medical imaging plays an important role in the precise preoperative localization of the pathological parathyroid glands and the search for ectopic and/or supernumerary glands for a better surgical strategy. Parathyroid scintigraphy is most commonly performed using 99mTc-MIBI which is the radiopharmaceutical marker of choice in the diagnosis of HPT [12]. The use of CT scan remains as a second line indication, in case of white surgery or in case of discordance between the ultrasound and scintigraphy results [13,14]. The main advantage of SPECT/CT systems is to better localize ectopic positions of hyperplasic parathyroid glands and to make a differential diagnosis between benign and malignant lesions [15].

Concerning the management of SHPT, medical treatment is aimed at normalizing the phosphocalcic balance by administering phosphorus binders, calcium salts, native vitamin D derivatives and calcitriol analogues [16]. Actually, the revolutionary option is the calcimimetics, which act on calcium receptors on the main cells of the parathyroid glands by increasing their sensitivity to calcium [17]. According to the latest KDIGO (Kidney Disease Improving Global Outcome) recommendations, calcimimetics can be tried either as first-line therapy in SHPT or in case of recurrence after parathyroidectomy [18].

Although the place of surgery in the treatment of SHPT is no longer debatable today, it is still difficult to establish a clear-cut approach to its indications. According to literature, parathyroidectomy is indicated in cases of HPT not controlled by medical treatment, PTH values ≥ 500 pg/l, symptomatic SHPT, and resistant to medical treatment, SHPT with hypercalcaemia and/or hyperphosphatemia refractory to medical treatment, the existence of intractable bone pain, refractory pruritus, presence of calciphylaxis, radiological abnormalities of bone structure with or without fracture, the presence of significant vascular calcifications and transformation to tertiary hyperparathyroidism [19]. In our study, the indication for parathyroid surgery was symptomatic SHPT confirmed with isotopic imaging, and/or very high PTH values. Actually, there is no consensus on which parathyroidectomy techniques are associated with better outcomes [20]. Subtotal PT type ¾ or 7/8 preserves the residual parathyroid gland original blood supply and therefore has a lower risk of permanent postoperative hypocalcemia. Some authors opt for intraoperative angiography of the residual parathyroid gland using indocyanine green, which has shown great promise in helping the surgeon determine the viability and function of the parathyroid glands left in place. Conversely, total PT with autotransplantation is preferred for patients with compelling reasons to avoid a second surgery (contraindication to general anesthesia, history of repeated cervical surgery, known recurrent laryngeal nerve injury, significant medical co-

morbidities), but it carries a higher risk of permanent hypocalcemia [18]. Albuquerque and al [21], in a study done in 2017, concluded that the two techniques were comparable in the short and medium term. In our series, the surgery was PT type ¾ in 7 patients and PT type 7/8 in 43 patients. Total PT with autotransplantation was performed in one patient. Nonetheless, measuring intraoperative PTH level assessment is very important in parathyroid surgery. Samples are taken gradually during the operation to assess the production of parathyroid tissue left in place, but also to eliminate a supernumerary gland [17].

Analysis of the results of series revealed that PT has been associated with a 26% reduction in the risk of all-cause mortality and a 41% reduction in the risk of cardiovascular mortality in contrast to calcimimetics in patients with severe, uncontrolled SHPT [22].

According to literature, hypocalcemia is the most common complication of surgery in SHPT [7]. Therefore, close monitoring of serum calcium postoperatively is essential because of the lack of clinical and biological parallelism [23]. For some series, low preoperative calcium concentration and high ALP (liver and bone iso-enzymes) as well as advanced age are risk factors for postoperative hypocalcemia [24]. However, the persistence or recurrence of HPT may be related to an incomplete initial parathyroidectomy, a presence of unnoticed supernumerary glands or a hyperplasia of the remaining stump [25]. According to the literature, the persistence rate in SHPT after surgery varied between 2,6% and 13,9% and the recurrence rate between 3,5% and 8% for all types of surgery combined [26,27]. These results are close to ours.

Finally, the review of the literature show that mortality specific to surgery is low, ranging from 0 to 7% [14,28]. Mortality after parathyroid surgery is mainly due to cardiovascular complications [27].

At this time, there are no universal, evidence based guidelines on the indications for PT in SHPT. Randomized, controlled trials are lacking but will be necessary to establish appropriate biochemical and clinical parameters for surgical referral and to define clinically significant persistence and recurrence of SHPT.

In recent years, various percutaneous ablation modalities have been developed, such as percutaneous ethanol injection, high-intensity focused ultrasound treatment, microwave ablation, radiofrequency and laser ablation, for patients with locally treatable causes of SHPT who refuse surgery or are non-operable [29].

This is a retrospective study based on medical charts. The main strengths of the present study lie in the homogeneous series of patients considered: the same surgical experience; and a standardized pre- and postoperative medical treatment. The main weakness of the study, on the other hand, concerns significative missing data. The only indication for parathyroid surgery was symptomatic HPT since medical treatment with calcimimetics is not available. Furthermore, more clinical investigations as measuring intraoperative PTH level and future prospective studies are needed to support our findings.

CONCLUSION:

Herein we have summarized the current evidence to guide the surgical management of SHPT. Despite advances in medical management, a significant number of patients have refractory disease and may benefit from surgical resection, particularly if there is a low likelihood of transplant. With the advent of new parathyroid surgical techniques, parathyroidectomy is the standard curative treatment for SHPT, recommended for patients who do not respond to medical therapy. PT decreases the mortality rate of refractory SHPT due to CKD. A consensus regarding which techniques of PT are associated with better outcomes is not available. Intraoperative PTH monitoring can help guide resection and avoid persistent hyperparathyroidism. In the immediate postoperative period, hypocalcemia is common and close monitoring is critical. Thus, the therapeutic management of SHPT is medical and surgical. It requires close collaboration between nephrologists, dialysis doctors, ENT surgeons, anesthetists, biologists and radiologists.

Ethical considerations: The ethics committee accord of our hospital was not necessary when conducting our work, due to the retrospective nature of the study, without experimental intervention with respect for the anonymity of the patients.

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