SURGERY OUTCOMES IN PATIENTS WITH SECONDARY HYPERPARATHYROIDISM AND IMPACT OF INTRA-OPERATIVE PTH MEASUREMENT

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Abstract

Context. The current therapeutical management of secondary hyperparathyroidism (S-HPTH) is difficult to obtain due to the lack of kidney donors. Surgical intervention on the pathologic parathyroid tissue has been suggested as a method to alleviate symptoms in patients with chronic kidney disease (CKD).

Objective. The aim of our study was to evaluate the outcomes of parathyroid surgery in patients with S-HPTH and the advantages of intraoperative quick PTH (iqPTH) to improve surgical results.

Material and methods. In a real-life study, we compared one group of S-HPTH with iqPTH performed after removing all suspected glands and before wound suture (Group 1) and one group in that iqPTH was not assessed (Group 2). When iqPTH dropped less than 50%, additional exploration followed.

Results. Eight out of the 34 patients from Group 1, who underwent subtotal parathyroidectomy, showed elevated levels of serum PTH and calcium, which remained elevated during follow-up, thus, suggesting disease persistence. From the 21 patients in Group 2, none showed early postoperative disease persistence. Serum calcium, but not PTH was increased in one patient from the iqPTH group but normalized after one month. Overall, iqPTH allowed detection of a supplementary parathyroid gland in one case, thereby increasing early post-surgery remission to 100% in Group 2 compared to 76.47% in Group 1. Late postoperative remission of hyperparathyroidism with no further increase in the rate of hypoparathyroidism was obtained in Group 2.

Conclusions. Assessment of intra-operative PTH levels proved to be a useful tool in augmenting the outcome of S-HPTH surgery. In patients which are eligible for renal transplantation who undergo a subtotal resection, iqPTH can enhance the post-operative quality of life by lowering disease recurrence rates until the kidney transplant procedure.

Key words: secondary hyperparathyroidism, quick intra-operative PTH, total parathyroidectomy, surgery, chronic kidney disease, persistent S-HPTH.

INTRODUCTION

Chronic kidney disease (CKD), the main cause of secondary hyperparathyroidism (S-HPTH) in humans, results in imbalanced phosphor-calcium metabolism, which, on the parathyroid glands, acts like a systemic stimulus. Persistently high circulating parathyroid hormone (PTH) levels further aggravate biochemical and morphological changes, particularly contributing to the development of CKD-mineral and bone disorders (CKD-MBD) (1). A functional kidney transplant, prior to structural changes of the parathyroid glands in patients with CKD remains the ideal therapeutic choice, however, it is difficult to be accomplished (2).

A milestone in the management of S-HPTH is the surgical approach, with the goal of reducing hyperplastic parathyroid tissue, resulting in immediate and sustained favorable effects. The absence of an efficient long-term medical treatment of the disorder highlights the importance of surgical treatment; at least 1% of patients on hemodialysis within one year and 15% within 10 years will eventually require parathyroidectomy (3). There is compelling evidence that surgery in patients with S-HPTH decreases bone pain, ameliorates calciphylaxis, improves wound healing and may improve cardiac function (4).

It has been shown that the surgical management of S-HPTH reduces symptoms like bone pain and pruritus in patients who undergo chronic hemodialysis, at the same time improving the clinical outcome of renal osteopathy, cardiac function and the quality of life (4).

Nonetheless, the decision on surgical therapy is controversial due to lack of consensus concerning which type of parathyroidectomy has to be performed in order to avoid recurrence and at the same time permanent hypoparathyroidism, which compels the

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surgeon to decide based on personal experience (5). A prospective randomized trial described by the group of Rothmund *et al.* showed that the clinical outcome improved significantly in total parathyroidectomy and auto-transplantation patients with S-HPTH compared to a subtotal parathyroidectomy. A parathyroidectomy followed by an auto transplantation resulted in the decrease of the percentage of patients in whom surgical reintervention was needed as well as the decreased serum calcium levels as compared to the subtotal parathyroidectomy group (6). On the other hand, significantly higher recurrence rate was reported in patients with autografts in the forearm tissue in comparison to subjects in whom auto transplantation was not performed (7, 8).

Intact PTH consists of a polypeptide chain of 84 amino acids with a molecular weight of 9300 Daltons; structurally, it cleaves into an amino-terminal region, which is biologically active, a hydrophobic middle region and a carboxy-terminal region, with the intact hormone being the biologically active form (9). While the amino-terminal fragment of PTH has a short half-life of 3 to 4 minutes, the carboxy-terminal fragment has a half-life of several hours and is eliminated by glomerular filtration; thus depending on the renal function (10).

The elimination kinetics of PTH has been well studied in patients with primary hyperparathyroidism (P-HPTH) with normal renal function (13). Since 1991, several quick PTH assays have been developed to enable unilateral instead of bilateral neck exploration for surgery of P-HPTH (14-16).

The most frequently used criteria for interpreting iqPTH results are the Miami criteria: the PTH level has to drop below 50% of the initial value and has to be within the normal range after 10 minutes from resection (17). Additional measurements of iqPTH may be performed at 10, 20 and 30 minutes after excision; they increase sensitivity, but increase operating time and delay the diagnosis of hyperparathyroidism persistence (18).

In contrast to the quite large experience in patients with P-HPTH, the impact of iqPTH assay in surgery for S-HPTH is less validated and standardized. Therefore, we here aimed to evaluate the outcomes of parathyroidectomy in patients with CKD and S-HPTH under real-life circumstances and the role of iqPTH measurements to improve surgery results.

PATIENTS AND METHODS

A total of 55 patients with a biological diagnosis of S-HPTH, hospitalized in two academic medical centers, were prospectively enrolled in the study (Table 1). Group 1 consisted of 34 patients aged between 26 and 70 years and included 14 males (46.57 ± 14.72 years old) and 20 females (52.45 ± 9.48 years old), respectively. Patients from first group (Group 1) were subjected to surgical intervention without measuring iqPTH. A second group (Group 2) included 21 patients aged between 24 and 71 years, of whom 14 were males with a mean age of 54.79 ± 9.74 years and 7 females aged 45.43 ± 14.98 years. Group 2 patients were treated by parathyroidectomy and concomitant iqPTH assessment, as measured from internal jugular vein blood samples obtained at 10 minutes after the excision of hyperplastic glands and before wound closing. Halving of PTH values in the intra-operative assessment was considered to be an optimal indicator of surgical success (19), and it was aimed during the surgical procedure. An immunochemical method with detection by electrochemiluminescence (ECLIA) was employed for iqPTH quantitation, with two monoclonal antibodies reacting with epitopes from 26-32 and 37-42 aminoacids regions within the PTH molecule (20, 21). The IMMULITE 1000 Turbo Intact PTH Assay system (Siemens Healthineers, USA) was used for measurements of iqPTH levels in EDTA plasma samples. Miami criteria of cure were applied for evaluation, i.e. a decrease in PTH serum levels of at least 50% as compared to pre-operative PTH was targeted. When the criterion was not fulfilled, further

Table 1. General characteristics of patients with secondary hyperparathyroidism (S-HPTH) enrolled in the study

	Secondary Hyperparathyroidism (S-HPTH)		
	All (Groups 1 and 2)	Patients without iqPTH assessment (Group 1)	Patients with iqPTH assessment (Group 2)
Number (N)	55	34	21
Age (years)	50.65 ± 9.81	50.02 ± 9.61	51.66 ± 10.15
Years of hemodialysis (HD)	8.56 ± 2.86 (2 – 21)	7.7 ± 2.54 (2 – 12)	9.92 ± 3.18 (5 – 21)
% Total parathyroidectomy	50.9	35.29	76.19
% Reintervention after ≥ 6 months	16.36	26.47	-

surgical exploration continued. In addition to PTH measurements, calcium levels were assessed before and one day after the operation.

Both groups were included in a follow-up study and serum PTH was re-assessed the first day after surgery and after six months. Persistent S-HPTH was defined as PTH concentration above 300 pg/mL the first day after surgery, while disease relapse was considered in patients in whom PTH levels rose from normal to pathologic levels at any point during follow-up.

Study approval was obtained from the University Ethics Committee and patients signed informed consent.

All patients were examined by cervical ultrasonography, while preoperative parathyroid scintigraphy, to detect ectopic parathyroid glands, was available in 40% of the patients.

Surgical procedure

The surgical procedure implemented in patients with S-HPTH was the standard bilateral neck exploration procedure with excision of enlarged parathyroid glands suspected of having hyperplastic modifications. The techniques used were either total parathyroidectomy without auto-transplantation or subtotal parathyroidectomy, based on the surgeon's operatory experience and the recommendations of the nephrologist (i.e. subtotal parathyroidectomy for patients who were enrolled on renal transplant list).

Statistical analysis

Statistical analysis was performed using GraphPad Prism 6.0 (GraphPad Inc. USA), the statistical significance being assigned to a p-value equal to or less than 0.05. A receiver operating characteristic (ROC) curve was constructed with the tabulated data. Sensitivity was plotted against the false positive rates (FPR) at each PTH value to construct the curve. Using the Chi-square test, the incidence of surgical failure was compared between groups.

RESULTS

Histopathology confirmed S-HPTH in all patients. Overall, total parathyroidectomy was achieved in 28 of 55 patients (50.9%), with 12/34 (35.29%) in Group 1 and 16/21 (76.19%) patients in Group 2 ($p = 0.0007$). The surgical treatment procedure was based on an inter-disciplinary decision taken jointly with other physicians such as nephrologists and endocrinologists; the patients who were subjected to a

subtotal parathyroidectomy being eventually scheduled for a renal transplantation.

Eight out of the 34 patients from Group 1 who underwent subtotal parathyroidectomy showed elevated levels of serum PTH (above 300pg/mL) with normal or slightly lowered levels of ionic and total calcium (ionic calcium 3.53 ± 0.24 mg/dL; total calcium 7.28 ± 0.19 mg/dL) the next day after surgery. PTH remained elevated during follow-up, while ionic calcium levels raised to around 4.20 ± 0.07 mg/dL and total calcium levels to 8.58 ± 0.11 , thus, suggesting disease persistence. We should mention that although the surgeons' intention was to perform total parathyroidectomy in these patients, from the 4 pieces that went to pathology only three were hyperplastic glands, the fourth one being a lymph node.

Six patients from the same group were enrolled at follow-up for a second surgical intervention; all of them showed signs of persistent S-HPTH, thus raising the total number of patients with persistent S-HPTH in Group 1 to fourteen. Eventually, 6 months later second surgical intervention was performed in 9 patients.

From the 21 patients in Group 2, none showed early postoperative disease persistence. Serum calcium, but not PTH was increased in one patient from the iqPTH group but normalized after one month and remained normal during follow-up. Intraoperative PTH decreased more than 50% of the preoperative value in 18 out of 21 patients, but remained slightly over 50% in 3 patients. For the 3 patients, not fulfilling the Miami criterion, additional exploration followed and one more hyperplastic gland was identified in one case, which was excised. No other intraoperative findings were reported in the other two cases. However, the PTH value one day after surgery normalized in all patients; 4 of them showing values below 20 pg/dL.

Five patients from both groups, 2/21 (9.52%) in Group 2 and 3/34 in Group 1 (8.88%), ($p = 0.17$) respectively, showed clinical signs of hypoparathyroidism after total parathyroidectomy, 4 of them remaining with low levels of PTH and hypocalcaemia during follow-up; one was having normal calcium levels early postoperative but presented with hypocalcemia at 6- and 12 months follow-up, potentially requiring long term treatment with active vitamin D and calcium.

Mild transitory hypocalcemia was encountered after surgery in 28 patients, i.e. 9/21 (42.8%) of Group 2 and 19 (55.88%) of Group 1, ($p < 0.0001$), however, calcium levels normalized during follow-up.

Overall, the evaluation of iqPTH allowed

detection of a supplementary parathyroid gland in one case, thereby increasing the early post-surgery remission to 100% in Group 2 comparing to 76.47% in Group 1. Furthermore, late postoperative remission of hyperparathyroidism with no further increase in the rate of hypoparathyroidism was obtained in Group 2.

A ROC curve was constructed using the raw data obtained from the two patient groups. The curve was constructed in a nonparametric fashion, plotting the FPR - specificity (x-axis) against sensitivity (y-axis) to test the ability of intraoperative PTH levels in predicting the clinical outcome of the parathyroidectomy, plotting the values according to the PTH levels 6 months after the surgical procedure.

This ROC curve allows to select any point on the curve of the PTH values and determine the corresponding sensitivity and FPR (1 - Specificity). Three curves were constructed (Fig. 1) – Group 1 – PTH pre-op / 6 months later (dash dot line), Group 2 – PTH levels pre-op / 6 months-later (dash line) and one ROC curve for iqPTH levels plotted against the 6 month PTH levels after the surgical procedure (continuous line), and the area under the curve (AUC) was determined. With use of the ROC curve, an AUC of 1.0 indicates a perfect test, with 100% sensitivity and a 0% FPR. The AUC for Group 1 was 0.534, whereas the AUC for Group 2 was 0.704, indicating that the clinical outcome of Group 2 was superior due to surgical approach and the fact that PTH levels indicated a lack of disease recurrence. The AUC of the iqPTH ROC was 0.972, validating the data obtained in Group 2 by confirming the fact that low iqPTH levels correspond with a better outcome 6 months after surgical intervention. Using the obtained ROC curve, representative PTH values were selected from both groups and the associated sensitivity and FPR were calculated to show the variation in the

statistical measures with different PTH level limits (data not shown). The use of the ROC curve indicates the fact that the PTH limit value of 4 pg/mL correlates with 1.0 sensitivity but a FPR of 0.022 and a likelihood ratio of 1.030. Similarly, a PTH value of 1259 pg/mL has a 0.029 sensitivity and a 0.882 specificity and a likelihood ratio of 0.25 (Fig. 1).

We found 7 pg/mL to be the statistically significant lower limit value for predicting PTH levels 6 months after resection. In the current study, patients with a recovery room PTH level of more than 141 pg/mL were again significantly more likely to experience disease recurrence.

The statistical analysis of the obtained PTH data from both groups showed marked differences between individuals from both groups. Group 1 showed a number of 14 patients which presented disease recurrence, 9 out of which were eventually subjected to another surgical resection procedure. In the case of the other 5 patients, surgical intervention was postponed due to comorbidities that hindered such a medical procedure. The other 20 patients showed normal PTH values (<300pg/mL) suggesting secondary hyperparathyroidism remission. The Chi-squared test of Group 1 showed a value of 22719, suggesting a significant difference between the expected frequencies and the observed frequencies (Chi-square = 22719; df = 66; $p < 0.0001$). Group 2 showed a constant decrease in PTH to levels lower than 50% of the preoperative value starting with the intra-operative PTH assessment. No disease recurrences and relapses were identified 6 months after the initial intervention. As in the case of the first group, the differences between the individuals at each time points of the PTH evaluation were statistically significant, with a chi-square value of 3199 (df = 60, $p < 0.0001$) (Fig. 2).

Figure 1. Receiver operating characteristic curve (ROC) for Group 1, Group 2 and iqPTH levels plotted against the 6 months PTH levels after the surgical procedure.

Figure 2. Changes in serum PTH levels at different time points in both groups; Group 1 – 14 patients maintained an elevated serum PTH level in the post-surgical and the 6 month follow-up; Group 2 - shows the decrease of 6-month follow-up of PTH to baseline levels in all patients.

In Group 1, a Pearson's correlation coefficient showed that ionic calcium levels maintained a constant level pre-operatively vs. post-operatively; at the same time no correlation to post-operative PTH is shown (Fig. 3). For Group 2, although a rapid decrease of serum PTH was followed post-surgically by a drop in ionic calcium levels as compared to the pre-operative levels (Fig. 4), the differences in calcium were not statistically relevant and failed to relate to post-operative PTH according to the Pearson's correlation coefficient.

DISCUSSION

Although surgical resection of afflicted parathyroid glands in therapeutically refractory S-HPTH by experienced surgeons was associated with good results, as we have shown in this study, a significant number of these patients may need surgical re-intervention due to disease persistence or recurrence. This is in agreement to reports indicating subtotal- or total parathyroidectomy with auto transplantation having higher rates of recurrence in S-HPTH (ranges 5-80%) in comparison to patients undergoing total parathyroidectomy without auto transplantation (ranges 0-4%) (22, 8) and might contribute, at least in part, to differences in outcomes between groups in the present study. In fact, early disease persistence was observed in 23.5% of patients from Group 1 in whom subtotal parathyroidectomy was more prevalent. Moreover, iqPTH measurement triggered in 3 out of 21 (14.28%) patients further neck exploration for suspected disease persistence. The occult presence of supernumerary glands, inadequate surgical technique in addition to a continuous hyperplasia of the remnant tissue are all factors that contribute to disease relapse (23).

The assessment of intraoperative serum PTH in the surgical management of parathyroid tissue pathology has been reported mainly in patients undergoing surgery for P-HPTH. A blunt unilateral cervical exploration based on imagistic data collected preoperatively (24) combined with iqPTH evaluations seem to be effective in reducing the possibility of omitting supplementary parathyroid tissue or multiple gland disease, while also benefiting the patient by decreasing operative time and potential post-operative morbidity (25).

In the present study, all patients experienced a dramatic decrease in PTH levels after parathyroidectomy. The significant decrease in mean PTH levels after surgery reached 91.07% and was associated with symptomatic improvements. Furthermore, resulted low PTH levels were maintained at the minimum up to one month after the surgical intervention; with the exception of the second group which was marked by a better clinical outcome as opposed to the first group in the 6 months follow-up. Our clinical observation that intraoperative PTH levels were affected by surgical manipulation of the glands is in accordance with previously published results (26).

The present study suggests that even though cervical ultrasound and parathyroid scintigraphy combined with SPECT-CT augmented pathological parathyroid gland identification in our patient groups, the use of intraoperative PTH measurements was a definitive measure which, albeit slightly, improved the clinical outcome in the second group. Therefore, quick PTH assessment during parathyroid surgery appears to provide valuable information regarding the success of pathological tissue resection in patients with S-HPTH.

In the time frame of 6 months after surgery, PTH values showed a slight increase in both groups.

Figure 3. Scatterplot for data correlation Group 1 (post-operative PTH vs. pre-operative ionic calcium: $r = 0.28$, $p = 0.09$ post-operative PTH vs. post-operative ionic calcium: $r = -0.07$, $p = 0.66$).

Figure 4. Scatterplot for data correlation Group 2 (post-operative PTH vs. pre-operative ionic calcium: $r = -0.14$, $p = 0.51$; post-operative PTH vs. post-operative ionic calcium: $r = -0.24$, $p = 0.29$).

However, patients identified with hypoparathyroidism immediately postoperatively maintained a questionable clinical outcome. In contrast, in patients with values > 150 pg/mL, PTH levels steadily increased over time, however no significant change in the patients' clinical state was recorded during that time.

Still, the clinical outcome in Group 2 was better as compared to Group 1. In spite of a steady increase in mean PTH levels during follow-up, none of the patients relapsed to secondary hyperparathyroidism. Similar results have been reported in previous studies (6).

In the analysis of a group of 77 patients in whom surgery for secondary hyperparathyroidism was performed, with follow-ups at 1, 3 and 5 years after the procedure, respectively, the group of authors led by Mazzaferro recorded decreases in all biochemical parameters immediately after surgery. Later on, calcium, phosphorus and PTH levels increased progressively, especially during first year, but these levels located below the normal average value (26). The average duration for the incidence of recurrence is 3 years (24). Patient-dependent factors need to be taken into account, including the organisms' susceptibility to the disease.

The present study had certain limitations such as mainly the modest size of patient samples and the limited time interval of the follow-up.

Nevertheless, based on the study outcome it can be concluded that intraoperative assessment of PTH represents a powerful tool to improve the surgical outcomes in patients with renal disease that develop secondary hyperparathyroidism. Overall, these will result in ameliorated quality of life of affected individuals.

In conclusion, despite the fact that at present times the gold standard for an optimal surgical outcome is considered to be the surgical skill of the physician responsible for the procedure, this study has shown that a quick intraoperative measurement of PTH levels can augment the surgical outcome of parathyroidectomy in secondary hyperparathyroidism. Moreover, in patients eligible for renal transplantation who undergo a subtotal resection (i.e. young patients or patients without comorbidities that make a renal transplant unfeasible) the measurement of intraoperative PTH levels can enhance the post-operative quality of life by lowering disease recurrence rates until the kidney transplant procedure.

Conflict of interest

The authors declare that they have no conflict of interest.

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