

Parathyroid hormone between limits and possibilities in secondary hyperparathyroidism

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Abstract: Objective: The aim of our study was to evaluate the impact of intraoperative parathyroid hormone (PTH) measurement on surgical results in patients with renal hyperparathyroidism (HPT). Material and method: In our study have been included 31 patients, hospitalized in Department of General Surgery, Nephrology Carol Davila Hospital Bucharest. The patients have been included only after they have signed the informed consent for use of data and pictures. From June 2014 to December 2014, a series of 31 consecutive patients underwent total parathyroidectomy and intraoperative PTH measurement was made for renal HPT only for 8 of them (25%), for 6 patients (20%) were done frozen section, and for rest of them (55%) we made PTH postoperative measurement. Intraoperative PTH was measured at 30 minutes after parathyroidectomy with the Liaison analyzer assay for intact PTH. Results: The mean of PTH levels before surgery was 1576.41 with range 970-2300 pg/ml which declined to a mean of 133.87 with range 3-355 pg/ml at the end of the operation. Calcium levels before surgery was 10.8-11.5 mg/dl. Persistent renal HPT was seen in one patient, and recurrent HPT was diagnosed in two cases. In 8 patients (25%) the intraoperative PTH levels declined more than 50%. In first case: the intraoperative intact PTH dropped from 970 pg/ml to 18.5 pg/ml (PTH declined was 98.6%). In second case: from 1100 pg/ml to 3.18 pg/ml (99.7%). In third case: from 2300 pg/ml to 47 pg/ml (97.9%). In fourth case: from 1136 to 21 pg/ml (98.15%). In fifth case: from 2201 to 98.9 pg/ml (95.5%). In sixth case: from 1250 to 46.1 (96.31%). In seventh case: from 2130 to 38.3 pg/ml (98.20%). In eighth case: from 1813 to 92.90 (94.90%). Conclusions: Intraoperative PTH measurement with a decrease in intraoperative PTH of at least 50% is highly predictive of successful parathyroidectomy and normalization of postoperative calcium and PTH levels. Intraoperative PTH monitoring in patients with SHPT resulting from chronic renal failure may help surgeons confirm that the resection of hyper functioning parathyroid tissue was adequate and to emphasize the possibility of supernumerary parathyroid glands.

Key Words: secondary hyperparathyroidism (renal, SHPT), total parathyroidectomy, parathormon, supernumerary, persistent SHPT, recurrent SHPT.

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Introduction

Renal hyperparathyroidism is a major clinical problem resulting in elevated serum parathyroid hormone (PTH) levels. This condition is often called secondary hyperparathyroidism (SHPT), although the parathyroid cells changed their secretion of PTH from a secondary (reactive) pattern to a primary (autonomous) pattern. In the following sections, secondary hyperparathyroidism is used synonymously with renal hyperparathyroidism. Surgery for renal hyperparathyroidism reduces pruritus and bone pain in patients on chronic hemodialysis, improves renal osteopathy and quality of life, and may lead to a better cardiac function (Chow et al 2003). In 1991, Rothmund et al, described in a prospective randomized trial, significantly improved results for total parathyroidectomy and auto transplantation in patients with SHPT compared to subtotal parathyroidectomy. After total parathyroidectomy and auto transplantation the number of reoperations declined, serum calcium levels decreased more than after subtotal parathyroidectomy, and the radiologic and clinical signs of osteoporosis and pruritus improved to a higher extent. Intact parathyroid hormone consists of a polypeptide chain of 84 amino acids. PTH is secreted by the parathyroid glands to

regulate the calcium ion levels in the blood flow. PTH is eliminated mostly in the liver but also in the kidneys and bones. The N-terminal fragment of PTH contains the region that confers bioactivity but has a short half-life of 3 to 4 minutes. The C-terminal fragment of PTH has a half-life of several hours and is eliminated by glomerular filtration, thus depending on renal function (Kao 1992; Hruska et al 1981). The elimination kinetics of PTH has been well studied in patients with primary hyperparathyroidism with a normal renal function (Maier et al 1998). Since 1991, several quick PTH assays (Bergenfelz et al 1991; Irvin et al 1991) have been developed to enable unilateral instead of bilateral neck exploration for surgery of primary HPT (Bergenfelz et al 2002). In 1991, Proye et al described the reliability of a quick intraoperative PTH assay in patients with primary and secondary HPT, as well as for those with multiglandular disease. They noted that the PTH assay used was not hampered by renal insufficiency but concluded that the assay should not substitute for routine bilateral neck exploration. Since this publication, the half-life of PTH and the reliability of various routine and quick PTH assays have been discussed in many studies. The aim of our study was to evaluate the impact

of routinely performed intraoperative PTH measurement on the surgical results of 8 patients (25%) with renal HPT.

Material and methods

In our study have been included 31 patients, hospitalized in Department of General Surgery, Nephrology Carol Davila Hospital Bucharest. The patients have been included only after they have signed the informed consent for use of data and pictures. From June 2014 to December 2014, a series of 31 consecutive patients (14 females, 17 males) underwent 34 operations for secondary hyperparathyroidism. The age of the patients was (52.4±11.1 years). Of the 31 patients, 3 (12.5%) were referred to our hospital because of persistent or recurrent renal HPT. In 3 of patients requiring reoperation for HPT, the initial procedure was performed at our department. In all the patients with renal HPT, serum calcium levels were elevated preoperatively (10.8-11.5 mg/dl). In 7 patients a standardized total parathyroidectomy with auto transplantation was performed. A portion of the smallest parathyroid gland was fragmented and transplanted in cervical region. In patients with recurrent HPT, three parathyroid glands were resected (subtotal parathyroidectomy).

All resected glands were confirmed as parathyroid tissue by frozen sections at 6 patients (20%). In 4 patients (12.5%), additional subtotal resection or lobectomy of the thyroid gland was performed for multinodular goiter. Intraoperative PTH was measured in 4 ml of ethylenediaminetetraacetic acid (EDTA) peripheral blood, after general anesthesia and 30 minutes after resection of the last (in most cases the fourth) parathyroid gland with the Liaison analyzer assay for intact PTH. The assay requires binding of two enzyme-labeled antibodies specific for the C-terminal (amino acids 44–84) and N-terminal (amino acids 1–34) regions of the intact PTH molecule. In patients with chronic renal failure, C-terminal fragment clearance by glomerular filtration is impaired. Consequently, assays that detect only the C-terminal end of the PTH molecule are unreliable. Assays analyzing intact PTH, however, can be used for intraoperative PTH measurement in patients with chronic renal failure and secondary HPT. For the intact PTH, the *in vivo* half-life is 2 to 5 minutes (Kao *et al* 1992). The normal range of the intact PTH level is 10-70 pg/ml. The PTH level 30 minutes after removing the last parathyroid gland was analyzed for predicting a successful parathyroidectomy in patients with SHPT.

Statistical analysis was performed using MedCalc Statistical Software version 15.2.1 (MedCalc Software bvba, Ostend, Belgium). Data was analyzed for normality of distribution using the Kolmogorov-Smirnov test. Continuous variables were characterized by mean and standard deviation or median and 25-75 percentiles. The comparison of data before and after the surgery was performed using the paired t-test or Wilcoxon test, when appropriate. A $p < 0.05$ was considered as statistically significant.

Results

After a median follow-up period of one month, 28 of 31 patients presented with normal serum calcium and PTH levels. The mean of PTH levels before surgery was 1576.41 with range 970-2300 pg/ml which declined to a mean of 133.87 with range 3-355 pg/ml at the end of the operation. At 30 minutes after total parathyroidectomy, the PTH levels declined to a median of 18

(6.6; 36.5) pg/ml. The decrease was highly statistically significant ($p < 0.001$). In the present study, we evaluated the results of intraoperative intact parathyroid hormone measurement in 8 patients (25%) undergoing with renal HPT. Total parathyroidectomy and auto transplantation was performed in 7 of these patients (23%), because renal transplantation is not accessible for everyone and addressability is very low. Preoperative serum calcium levels fell from a mean of 11.12±0.24 mg/dl to 8.97±0.23 mg/dl on the first postoperative day. The decrease was highly statistically significant ($p < 0.001$).

In first case: the intraoperative intact PTH dropped from 970 pg/ml to 18.5 pg/ml (PTH declined was 98.6%). In second case: from 1100 pg/ml to 3.18pg/ml (99.7%). In third case: from 2300 pg/ml to 47 pg/ml (97.9%). In fourth case: from 1136 to 21 pg/ml (98.15%). In fifth case: from 2201 to 98.9 pg/ml (95.5%). In sixth case: from 1250 to 46.1 (96.31%). In seventh case: from 2130 to 38.3 pg/ml (98.20%). In eighth case: from 1813 to 92.90 (94.90%).

Altogether 27 patients presented with normal PTH postoperatively. At follow-up, recurrent SHPT was found in two patients and persistent SHPT in another. A 57-year-old woman developed recurrent hyperplasia of a parathyroid gland located in the neck after the resection of four parathyroid glands in June 2014. During the first operation, the intraoperative intact PTH level dropped adequately from 970 pg/ml to 18.5 pg/ml. At four months postoperatively, the calcium and PTH levels rise again and a secondary operation with a resection of a hyperplastic parathyroid gland had to be performed. At one month after the second operation, the calcium and PTH levels are within the normal range (parathyromatosis - recurrent SHPT). Persistent SHPT was diagnosed in one patient. In a 27-year-old woman, four parathyroid glands were removed, but the PTH (355 pg/ml) remained elevated. The transplanted parathyroid graft in the cervical region was removed two months after the first operation, but the PTH (178 pg/ml) remained elevated. Ultrasound and CT scans found a suspicious nodule (ectopic gland - recurrent SHPT) in the left side of the neck, for which a cervical reoperation is planned.

Four parathyroid glands were found intraoperative in a 69-year-old woman. The PTH level in this patient fell postoperative from 993 pg/ml to 322 pg/ml.

Post operatory, the serum calcium and PTH levels increased again, and diagnostic procedures to localize the remaining parathyroid gland are ongoing (supernumerary gland – persistent SHPT). Postoperative complications never were seen in our patients (like lesions of great vessels, lesions of laryngeal recurrent nerve).

Discussion

In an autopsy study of 503 cases, Akerstrom *et al* in 1984 found four parathyroid glands in 84% of the neck explorations and three parathyroid glands in 3%. Supernumerary glands were detected in 13% of the cases, mostly localized in the thymus. Because the localization and number of parathyroid glands are not determined, it can be difficult, even for experienced surgeons, to identify all of the parathyroid glands in patients with SHPT and chronic renal failure.

In our patients with primary operations for SHPT, four parathyroid glands were identified in 90% of cases (28 patients), five

parathyroid glands in 3.5% (one patient), and three glands in 6.5 % (two patients) of the patients.

The extent of parathyroid surgery in patients with renal HPT is still considered to be a subject for discussion. Whereas subtotal versus total parathyroidectomy and auto transplantation attracted the most interest in randomized trials during the last few years (Rothmund 1991; Malmaeus et al 1982), parathyroidectomy without auto transplantation for patients with chronic hemodialysis is now the focus (Nicholson 1996; Hampl et al 1999; Ockert et al 2002). The advantage of total parathyroidectomy and auto transplantation compared to subtotal parathyroidectomy is the significantly higher normalization rate of calcium and alkaline phosphatase levels (Rothmund 1991). Total parathyroidectomy without auto transplantation might only be considered in patients with renal HPT who are not eligible for renal transplantation. The intraoperative use of frozen section during parathyroid surgery, which was done at 6 patients (20%) in our institution, is controversial in the literature (Irvin et al 1999; Lokey et al 2000). The time of confirmation of resected parathyroid tissue by frozen section at our hospital is comparable to intraoperative PTH measurement, and both examinations take about 60 minutes. Intraoperative PTH measurement during operations for SHPT might help the surgeon finish the procedure after PTH levels decline to a certain level without identifying the number of anatomically existing parathyroid glands in the individual patient.

Careful exploration, bilateral central neck dissection and surgery experience is recommended for surgery of renal hyperparathyroidism (fig. 1).

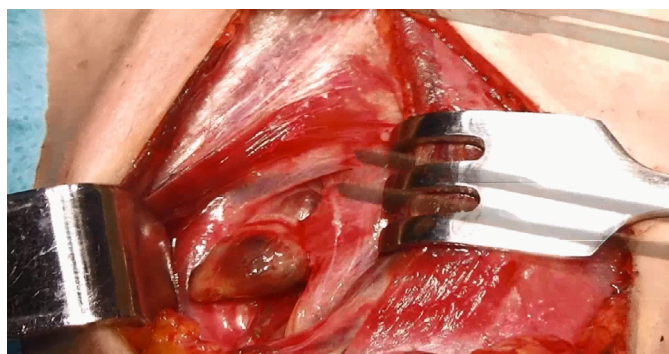


Fig. 1 Parathyroid gland – intra operatory picture

Probably the most important question about intraoperative measurement of intact PTH is the reliability on the various assays in patients with SHPT and chronic renal failure. Interference with the PTH half-life by renal function is still a matter of discussion. Lokey et al (2000) and Brossard et al (1996) found a prolonged half-life of PTH in patients undergoing chronic hemodialysis, but other authors (Clary et al 1997; Seehofer et al 2001) could not support these data.

Mean intraoperative PTH decrease in patients with secondary hyperparathyroidism (34 operations) and postoperative normalization of calcium and PTH levels.

In the present study we used the Liaison analyzer PTH assay and found a mean decrease in PTH levels of 100% at 30 minutes after parathyroidectomy with duration of the test of 30 minutes. By using the Liaison analyzer PTH assay, 8 patients with an intraoperative PTH decline of more than 50% and all

of patients with a drop in PTH levels into a normal range were considered to have a postoperative cure.

Conclusions

Intraoperative PTH monitoring in patients with SHPT resulting from chronic renal failure may help surgeons confirm that the resection of hyper functioning parathyroid tissue was adequate and to prevent of any remaining, a supernumerary parathyroid. Because each of the PTH assays exhibits a different decay curve, which suggests successful parathyroidectomy, care must be taken to ensure that the timing and results are appropriate for the assay used.

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