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Intra-operative parathyroid hormone monitoring through central laboratory is accurate in renal secondary hyperparathyroidism☆

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ABSTRACT

Objective: The usefulness, the methods and the criteria of intra-operative monitoring of the parathyroid hormone (ioPTH) during parathyroidectomy (PTX) for renal secondary hyperparathyroidism (rSHPT) in patients on chronic hemodialysis remain still matter of debate. The present study aimed to evaluate the ability of a low cost central-laboratory second generation PTH assay to predict an incomplete resection of parathyroid glands (PTG).

Methods: The ioPTH decay was determined In 42 consecutive patients undergoing PTX (15 subtotal and 27 total without auto-transplant of PTG) for rSHPT. The ioPTH monitoring included five samples: pre-intubation, post-manipulation of PTG and at 10, 20 and 30 min post-PTG excision. The patients with PTH exceeding the normal value (65 pg/ml) at the first postoperative week, 6 and 12 months were classified as persistent rSHPT.

Results: The concentrations of ioPTH declined significantly over time in patients who received total or subtotal PTX; however, no difference was found between the two types of PTX. Irrespective of the type of PTX and the number of PTG removed, combining the absolute and percentage of ioPTH decay at 30 min after PTG excision, we found high sensitivity (100%), specificity (92%), negative predictive value (100%) and accuracy (93%) in predicting the persistence of rSHPT.

Conclusions: The monitoring of the ioPTH decline by a low cost central-laboratory second generation assay is extremely accurate in predicting the persistence of disease in patients on maintenance hemodialysis undergoing surgery for rSHPT.

1. Introduction

The monitoring of intra-operative parathyroid hormone (ioPTH) has become a well recognized predictor of surgical success in primary hyperparathyroidism in which the diagnosis of uni- or multi-glandular disease is the crucial point for the choice of uni- or bilateral surgical access to the neck [1–3]. In this regard, the Miami criterion of a decrease of ioPTH to >50% of baseline within 10 min after excision has shown to be very accurate (93–98%) [4,5]. Conversely, in renal secondary hyperparathyroidism (rSHPT), in which the bilateral exploration of neck is always needed, the usefulness of ioPTH is less obvious.

The criteria to define the early and late success of surgery in primary hyperparathyroidism are clear: serum calcium and PTH in the normal range. In rSHPT the choice of the type of surgery as well as a standard definition of surgical success have not been standardized [6–11] because the normal range of PTH among the patients with normal kidney function is not applicable to patients on chronic hemodialysis in which values of PTH within the 150–250 pg/ml range may still be acceptable [12]. Indeed, the metabolism of the intact (1–84) PTH and its fragments is delayed in rSHPT because of the impaired renal function [13–18], the kinetics of the elimination of the PTH and its fragments in relation to surgical procedures and to PTH assay used [i.e. second generation or intact PTH (iPTH) and third generation or whole PTH (wPTH)]. These issues have not been adequately elucidated and especially it still remains to be defined which criterion of ioPTH decline performs best in predicting postoperative outcome of rSHPT [19–30]. Furthermore, the intraoperative estimation of the quantity of parathyroid tissue to be removed and the decision to perform subtotal or total parathyroidectomy (PTX) with or without immediate or delayed auto-transplantation is still arduous [27–31].

Abbreviations: rSHPT, renal secondary hyperparathyroidism; ioPTH, intra-operative parathyroid hormone; iPTH, intact PTH; wPTH, whole PTH; PTX, parathyroidectomy; PTG, parathyroid glands; TPTX, total PTX; SPTX, subtotal PTX.

☆ All authors designed and conducted the study and prepared and approved the manuscript.

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The present study aimed to evaluate the ability of a low cost central-laboratory second generation PTH assay to predict an acceptable surgical outcome or an incomplete resection of parathyroid glands (PTG) in patients who underwent total or subtotal PTX for rSHPT. The diagnostic accuracy of several values of the absolute concentrations and percentage of ioPTH decay was assessed in relation to: (a) the time after excision; (b) the type of PTX and (c) the number of PTG removed.

2. Patients and methods

2.1. Patients and surgical strategy

All patients who underwent parathyroidectomy for rSHPT with ioPTH monitoring at the Division of Transplantation and Hemodialysis of our University from 2007 to 2014 were included in this study. The study was approved by the local ethics committee, and written informed consent was obtained from all patients before the surgery.

The surgical indication was based on K/DOQI guidelines (patients with PTH level > 800 pg/ml with hypercalcemia and/or hyperphosphoremia, refractory to medical treatment prolonged at least for 6–12 months and including paricalcitol, phosphate binders, cinacalcet; patients with calciphylaxis) [12] and on the PTG size. The ultrasonography of the neck and 99mTc-sestamibi scanning were routinely performed prior to the surgery [32]. Subtotal parathyroidectomy (SPTX) was preferred in young patients or in candidates for kidney transplantation, whereas total parathyroidectomy (TPTX) without auto transplant was performed in older patients not candidate for transplantation.

A bilateral transcervical thymectomy was systematically performed in all patients.

Neck dissection, opening of the retro-pharyngeal and retro-esophageal space, and the carotid sheath, was not systematically performed in all patients. The surgery was deemed to be concluded if the percentage of ioPTH was <20% at 20 and /or 30 min. Instead, the search of the remaining PTG proceeded if fewer than 4 PTG were detected or if the percentage of ioPTH remained >20% of basal value at 20 and 30 min after PTG excision (i.e. a decline <80%). Anyhow, extension to mediastinal exploration was not undertaken in primary surgery, but early postoperative localization measures were preferably undertaken to guide a planned re-intervention.

Finally, a bilateral neck exploration was performed in all cases of recurrent rSHPT and the PTG detected by 99Tc-sestamibi scintigraphy and computed tomography were removed.

2.2. Blood sampling, i.o. PTH monitoring and surgical outcome

The blood samples, drawn from the saphenous vein at the level of malleolus, were collected: before tracheal intubation (t_0), after all PTG have been identified (post-manipulation), but before any tissue has been excised (t_1). Further samples were collected after the removal of the last PTG every 10 min over a maximal period of 30 min. The ioPTH monitoring was expressed as absolute concentrations (t_{10-30}) and as remaining percentage ($\%t_{10-30}$) of pre-excision values using the highest of the two pre-excision values (t_0 or t_1).

For intra-operative measurements, the samples were promptly analyzed in the central laboratory located in the same floor of the operating room. The serum PTH concentrations were determined using a second generation intact-PTH electrochemiluminescence immunoassay (Roche Intact PTH) assay running on a Roche Modular E 170 analyzer. The uses a biotinylated monoclonal antibody, which reacts with amino acids 26–32, and a capture ruthenium-complexed monoclonal antibody, which reacts with amino acids 55–64. Normal PTH values range from 15 to 65 pg/ml and the intra-assay CV was 2.9% and the inter-assay CV was 5.8% at concentrations of 35.0 and 180.0 ng/l, respectively.

These systems are routinely used in our institution and the turn-around time (TAT) was 25 min including 18 for the assay.

The early surgical outcome and the definitive cure of patients were respectively assessed on the basis of PTH concentrations within the first postoperative week (t_{1stw}), after 6 months and at the end of 1 year follow-up. The surgical outcome was classified as follows: when the PTH value exceeds 65 pg/ml on first postoperative week and at 6 and 12 months, we considered that the patient had persistent SHPT; when PTH decreased to a value under 65 pg/ml on first postoperative week and then increased after sixth months, recurrent rSHPT was present [8,9,33,34].

2.3. Statistical analysis

Data were analyzed by MedCalc Software (Belgium Version 12.5 for Microsoft Windows). Continuous variables were first tested for normality and equality of variances using the Kolmogorov–Smirnov test. Continuous variables were expressed as mean ± standard deviation (SD) and categorical and interval variables as frequencies or median and interquartile range (IQR). The appropriate parametric or non-parametric tests were used when comparing groups [*t* test, analysis of variance (ANOVA), Friedman's test, Mann–Whitney and chi-square test).

Receiver operating characteristic (ROC) analysis and Area Under Curve (AUC) with 95% confidential interval [95%CI] were used in order to determine the ioPTH cut-off value corresponding to 100% sensitivity with the higher specificity. Once identified the values of absolute and relative ioPTH cut-off by ROC curve analysis, the sensitivity, specificity, positive (PPV) and negative predictive value (NPV) and accuracy of test were calculated using the following definitions: TN (True Negative) = true decline: a sufficient decline of ioPTH and a t_{1stw} lower or within the normal range; FN (False Negative) = false decline: a sufficient decline of ioPTH and a high t_{1stw}; TP (True Positive) = true failure to decline: an insufficient decline of ioPTH and a high t_{1stw}; FP (False Positive) = false failure to decline: an insufficient decline of ioPTH and a normal t_{1stw}.

Moreover, we also evaluated the accuracy of the simultaneous achievement of the absolute and percentage decline of ioPTH: the test was defined TP (true positive for persistence of rSHPT) if both criteria were inadequate (i.e. true failure to decline: both the concentration and the percentage of remaining ioPTH more than the cut-off identified by ROC curve analysis). $P < 0.05$ was considered statistically significant.

3. Results

3.1. Surgical procedures, PTG removed and persistence of rSHPT

We studied 42 patients (12 females, 30 males) who underwent surgery for rSHPT (37) or its recurrence (5). The mean age (mean ± SD) of patients was 53.9 ± 14.8 years and the mean dialysis duration was 4.7 ± 2.5 years. In all patients the diuresis was null.

In the 37 patients who underwent for the first time PTX, 15 subtotal and 22 total PTX without auto-transplant of PTG were performed. In patients with recurrent rSHPT, we removed a hyperplastic remnant of an orthotopic PTG in 1 patient, an ectopic retroesophageal PTG in 2 patients and 3 or 6 multifocal nests of hyperplastic parathyroid tissue infiltrating the sternocleidomastoid muscle in the remaining two. These surgical procedures were considered as total PTX.

Mortality was null. A temporary recurrent nerve palsy, was observed in one patient.

In the 37 patients who underwent parathyroidectomy for the first time, we detected 3 PTG in 7 patients (19%), 4 PTG in 26 (70%) and more than 4 PTG in 4 (11%) [6 PTG in 2, 5 PTG in 2]. Fifteen (9%) out of 159 PTG removed were ectopic (7 intra-thymic, 3 retro-jugular, 3 retro-esophageal, 1 intra-thyroidal and 1 in the carotid sheath).

Table 1 shows the pre- and post-operative metabolic parameters in patients who underwent total and subtotal PTX.