Intraoperative Parathyroid Hormone Measurement in Patients With Secondary Hyperparathyroidism

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Hypothesis: Secondary hyperparathyroidism decreases renal clearance of parathyroid hormone (PTH).

Objective: To determine whether rapid PTH assays can be used to predict the success of a total parathyroidectomy to treat symptomatic secondary hyperparathyroidism.

Design: Case series from August 1 to December 31, 2000.

Setting: Tertiary referral center.

Participants: Patients with symptomatic secondary hyperparathyroidism (n = 24) who underwent total parathyroidectomy and autotransplantation were included in the study.

Interventions: Blood samples for rapid PTH analyses were drawn from an indwelling catheter at the induction of anesthesia (baseline) and before (0 minutes), 10 minutes, and 30 minutes after the removal of the last parathyroid gland. Regular intact PTH (iPTH) assays were conducted later.

Main Outcome Measure: If a patient’s regular iPTH levels were below 65 pg/mL at 1 week or 3 months postoperatively, the operation was considered successful.

Results: All 24 patients had successful operations. Rapid PTH and regular iPTH correlated significantly at 0, 10, and 30 minutes. Rapid PTH levels decreased significantly at each time period and were 176 ± 40.9 pg/mL (mean ± SE) at 10 minutes. The percentage decrease in rapid PTH levels was 39.5% ± 12.7% at 0 minutes, 75.1% ± 6.2% at 10 minutes, and 91.0% ± 0.1% at 30 minutes (mean ± SE). A decrease of 60% or more from baseline PTH levels at 10 minutes and/or a decrease of 85% or more at 30 minutes predicted the successful removal of all parathyroid glands.

Conclusions: A drop in PTH levels is delayed until 30 minutes after total parathyroidectomy; however, a rapid PTH assay 10 minutes after the removal of the last parathyroid gland is as accurate as an assay performed at 30 minutes postoperatively. Intraoperative PTH monitoring demonstrates relevant decreases in rapid PTH levels after parathyroidectomy that are similar to those previously documented in patients with primary hyperparathyroidism.

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TOTAL parathyroidectomy and autotransplantation of tissue into the subcutaneous layer of the forearm or thigh is a well-accepted treatment of symptomatic hyperparathyroidism.1-3 The development of a rapid 2-site immunoradiometric assay (IRMA) and an intraoperative immunoluminometric assay to measure intact (amino acids, 1-84) parathyroid hormone (PTH) has provided a valuable tool for identifying any surgical failures during the operation.4-7

The purpose of this study is to describe the use of a rapid parathyroid hormone (PTH) assay in patients undergoing cervical exploration for secondary hyperparathyroidism. We evaluated the kinetics of PTH degradation during total parathyroidectomy and autotransplantation to determine the efficacy of this assay in predicting the success of this procedure.

RESULTS

During parathyroidectomy, we found 20 patients with 4 glands, 3 with 3 glands, and 1 with 5 glands. The operative time (skin to skin) ranged from 60 to 190 minutes (113 ± 6.6 minutes), and the removed parathyroids ranged in weight from 0.38 to 13.96 g (3.02 ± 0.58 g). No complications or operative deaths were noted. Two patients were readmitted because of symptomatic hypocalcemia. All patients had successful operations and experienced symptomatic improvement. The subjec-
PARTICIPANTS AND METHODS

From August 1 to December 31, 2000, a retrospective evaluation was conducted on 24 consecutive patients undergoing neck exploration for symptomatic secondary hyperparathyroidism. Informed consent was obtained from all patients included in this study. There were 15 women and 9 men with a mean ± SE age of 52 ± 2.4 years (age range, 22-68 years). The causes of renal failure were chronic glomerulonephritis (n = 11), hypertension (n = 5), diabetes mellitus (n = 1), and polycystic kidney disease (n = 1). In 9 patients, the origin of the renal failure was unknown. The symptoms and signs included bone pain in 16 patients (67%), general weakness in 12 patients (50%), pruritus in 11 patients (46%), soft tissue calcification in 3 patients (1%), and fracture in 2 patients (1%). The duration of dialysis was 91.9 ± 6.6 months (mean ± SE; range, 27-144 months) (Table 1). Preoperative serum levels of calcium, phosphate, alkaline phosphatase, and iPTH were measured. These levels were measured again 1 week and 3 months postoperatively. Bilateral cervical exploration with a careful search and removal of all parathyroid glands in the neck area and thymus was performed in all patients. The tissue was tested by frozen pathological examination. After total parathyroidectomy, autotransplantation of 60 to 90 mg of tissue to the 3 to 4 subcutaneous pockets of the arm or thigh was performed, no matter how many glands were found during surgery. Blood samples were drawn from an indwelling catheter for analyses at the induction of anesthesia (baseline) and just before (0 minutes), 10 minutes, and 30 minutes after the removal of the last parathyroid gland. Postoperatively, serum calcium levels were measured daily, and supplements of calcium carbonate (2-12 g) and calcitriol (0.5-1 µg) were given. Regular iPTH values were checked before patients were discharged from the hospital about 5 to 7 days after the operation. Follow-up was carried out 3 months later. A successful operation was defined by levels of iPTH within normal limits (less than 65 pg/mL) at 1 week and/or 3 months postoperatively with a regular iPTH assay.

MEASUREMENT OF PTH

Blood samples were collected in glass tubes containing EDTA and were immediately spun in a refrigerated centrifuge to separate serum from cells. For the measurement of rapid PTH, 200 µL of plasma and 100 µL of tracer were incubated with anti-iPTH IRMA antibody (IBL GmbH; Immunobiological Laboratories, Hamburg, Germany) at 37°C for 25 minutes. Each sample was washed with 2 mL diluted wash buffer and then counted in a gamma counter for 1 minute. Rapid PTH results were available within 30 minutes. For concomitant measurements of regular iPTH, the serum stored at −79°C was used. Serum regular iPTH concentrations were measured with a 2-site IRMA (Nichols Institute Diagnostics, San Juan Capistrano, Calif). The incubation period was 24 hours.

PARATHYROID AUTOTRANSPLANTATION

The smallest parathyroid gland without nodular hyperplasia was placed in isotonic sodium chloride solution at 4°C, and 60 to 90 mg of the chopped tissue was positioned in 3 to 4 pockets of the subcutaneous tissue of the forearm or thigh.

STATISTICAL ANALYSIS

A repeated-measures analysis of variance was applied in association with a paired-sample t test. The Pearson product moment correlation was also performed. Statistical tests were performed using an SPSS program (Statistical Product and Service Solutions Inc, Chicago, Ill). Data were significant if P < .05. All data are expressed as mean ± SE unless otherwise indicated.

| Table 1. Demographic Characteristics of 24 Consecutive Patients With Secondary Hyperparathyroidism |
|-----------------|-------------|-----------|
| Characteristic   | Patients    |           |
| Age, mean ± SE, y| 52 ± 2.4    |           |
| Duration of dialysis dependence, mean ± SE, mo | 91.9 ± 6.6 |
| Causes of renal failure, No. of patients |           |
| Chronic glomerulonephritis | 8         |
| Hypertension | 5           |
| Polycystic kidney disease | 1         |
| Diabetes mellitus | 1         |
| Unknown origin | 9           |
| Symptoms, No. of patients |           |
| Bone pain | 16          |
| General weakness | 12         |
| Pruritus | 11          |
| Soft tissue calcification | 3         |
| Bone fracture | 2           |

Tive feeling of pruritus improved soon after surgery in all patients (n = 11), and 4 (25%) of 16 patients still had bone pain 3 months later. Serum levels of calcium, phosphate, and iPTH decreased significantly (P < .001 for all) 1 week postoperatively, but alkaline phosphatase increased significantly (P = .007) (Table 2). Three months postoperatively, serum levels of calcium gradually increased to within the reference range (P = .004). Serum levels of phosphate and iPTH remained stationary, and alkaline phosphatase gradually returned to reference levels (P = .008) (Table 2).

Regular iPTH levels were 1480 ± 112.7 pg/mL at baseline, 837 ± 107.4 pg/mL at 0 minutes, 474 ± 59.9 pg/mL at 10 minutes, 319 ± 43 pg/mL at 30 minutes, and 22 ± 4.8 pg/mL at 1 week. Significant decreases were found between each time period (P < .001 for all) (Table 3). Rapid PTH levels were 988 ± 107.3 pg/mL at baseline, 478 ± 91.9 pg/mL at 0 minutes, 176 ± 40.9 pg/mL at 10 minutes, and 96 ± 23.2 pg/mL at 30 minutes. Significant decreases were also found between each time period (P < .001, P < .001, and P = .001, respectively) (Table 3). A strong correlation was found between standard iPTH and rapid PTH at baseline (r = 0.92; P < .001), 0 minutes (r = 0.90; P = .001), 10 minutes (r = 0.95; P < .001), and 30 minutes (r = 0.94; P < .001). There was also a strong correlation between rapid PTH levels at 10 minutes and those at 30 minutes (r = 0.94; P < .001).
Of the 3 patients who had 3 glands removed in this study, one had a primary operation and the other 2 had secondary operations because they had undergone thyroid surgery more than 10 years earlier. These 3 patients’ rapid PTH levels were 59 pg/mL (a 91.4% decrease), 29 pg/mL (an 88.3% decrease), and 0 pg/mL (a 100% decrease), respectively, 10 minutes after total parathyroidectomy and 16 pg/mL (a 97.7% decrease), 10 pg/mL (a 96.2% decrease), and 0 pg/mL (a 100% decrease), respectively, at 30 minutes. Their operative procedures were terminated with confidence. Their regular iPTH levels at 1 week and 3 months postoperatively were all below 65 pg/mL.

All but 2 patients had rapid PTH levels 60% below the baseline levels 10 minutes after the removal of the last parathyroid gland and 85% below at 30 minutes. These 2 patients had rapid PTH levels of 496 pg/mL and 486 pg/mL, respectively, 30 minutes after the removal of 4 glands. A more careful neck exploration, including the thyroid and thymus glands, was performed for these 2 patients during the operation, but no parathyroid tissue was found. One week later, both had regular iPTH levels below 65 pg/mL (11 pg/mL and 8 pg/mL, respectively). Three months later, their standard iPTH levels were still in the normal range.

All patients except one had regular iPTH levels below 65 pg/mL at 1 week. The one exception had a regular iPTH level of 110 pg/mL. 1 week postoperatively, but 3 months later, the level was within the normal range (45 pg/mL). The percentage decrease in rapid PTH levels compared with the baseline was 39.5%±12.7% at 0 minutes, 75.1%±6.2% at 10 minutes, and 91%±0.1% at 30 minutes (**Figure**). Except for 2 patients with high rapid PTH levels after total parathyroidectomy, this assay seemed to change the operative procedure very little.

Use of a rapid intraoperative PTH assay in the surgical management of parathyroid tissue has been reported primarily in primary hyperparathyroidism, either adenoma or hyperplasia. A direct unilateral cervical exploration based on preoperative localization results combined with intraoperative rapid PTH determinations appears to be effective in reducing the possibility of overlooking multiple gland disease, while also minimizing operative time, cost, and potential morbidity.5-7,11 However debates continue about the use of routine bilateral neck exploration in multiple endocrine neoplasm or secondary hyperparathyroidism.12-14 We conducted this study of rapid PTH degradation during and after parathyroidectomy to treat secondary hyperparathyroidism to determine the usefulness of this assay during the procedure.

Because an immunochemiluminescent assay machine was not available in the Department of Surgery, Chang Gung Memorial Hospital, Kaohsiung Hsien, Taiwan, we sent blood samples to the Department of Nuclear Medicine for an immunoradiometric assay. The results were available within 30 minutes, and a 30-minute delay in surgery was noted when compared with our previous cases. Because total or subtotal parathyroidectomy is required for successful treatment, one would expect that the 50% decrease in PTH levels used in estimating an appropriate therapy response in primary hyperparathyroidism may be inadequate.3,15 Using rapid PTH assays, the average declines in this study were 75.1%±6.2% at 10 minutes and 91%±0.1% at 30 minutes. Patients, especially those with pruritus, had low PTH levels and symptomatic improvements in the follow-up period. When the last parathyroid gland remained, the average decline in PTH levels was 40%±12.7% pg/mL, and the rapid PTH levels were
478±91.9 pg/mL. Ten minutes after the removal of the last gland, the average decline was 75.1%±6.2%, and the rapid PTH levels were 176±40.9 pg/mL. Two patients had percentage decreases less than 60% 10 minutes after 4 glands were removed and less than 85% at 30 minutes. We do not know why rapid PTH levels decreased less than 85% at 30 minutes in these 2 patients, yet the final results (at 1 week and 3 months postoperatively) were below normal. The observation that intraoperative PTH levels were variably affected by surgical manipulation is consistent with previously published results. Both increases and decreases of 50% to 60% were seen. However, we have shown, as a previous report has also shown, that intraoperative PTH levels do decrease significantly (about 84.6%) after total parathyroidectomy.12 Regular iPTH and rapid PTH levels were removed and less than 85% at 30 minutes. We do not know why rapid PTH levels decreased less than 85% at 30 minutes. We do not know why rapid PTH levels decreased less than 85% at 30 minutes. We do not know why rapid PTH levels decreased less than 85% at 30 minutes. We do not know why rapid PTH levels decreased less than 85% at 30

Complete surgical removal can be ensured if rapid PTH levels are less than 60% of baseline levels at 10 minutes; then, no more exploration is necessary. This is especially helpful in repeated neck exploration because of previous surgery or when 3 glands are found in the field. If the PTH levels after parathyroidectomy do not decrease by more than 60% at 10 minutes or more than 85% at 30 minutes, a careful exploration should again be carried out. If the remaining glands are still not identified, postoperative localization studies should be conducted.12

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