

A New Endpoint for Intraoperative PTH Measurement: Normal

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Background: We hypothesized that Io-PTH levels would decline to normal or near normal after successful parathyroidectomy.

Objectives: To evaluate efficacy and predictive factor of parathyroid hormone measurement during parathyroid resection.

Materials and Methods: Every Io-PTH level from 2001-10 at a single institution was evaluated. Charts were reviewed for preoperative diagnosis, final Io-PTH level, unilateral or bilateral exploration, calcium and parathyroid hormone levels.

Results: 225 patients underwent 594 Io-PTH measurements. 16 patients were excluded. Final Io-PTH levels were normal (< 65 pg/mL) in 189 patients and elevated in 20 patients. 12 of 20 patients with elevated final Io-PTH levels had > 80% decrease, so that 201 patients had Io-PTH levels that were normal or dropped by > 80%. 8 patients had Io-PTH levels that dropped by < 80%, 4 of whom had < 50% decline. Normal or near-normal Io-PTH level after resection of a parathyroid adenoma allowed unilateral exploration in 146 patients. Persistent elevation of Io-PTH levels led to bilateral exploration in 22 patients.

Conclusions: Io-PTH levels should become normal or to drop by at least 80% during successful parathyroidectomy. Persistent elevations of Io-PTH after resection of an abnormal gland dictates the need for bilateral exploration.

Keywords: Parathyroid Hormone; Parathyroid Neoplasms; Parathyroidectomy; Hypercalcemia

1. Background

While high cure rates after an initial surgical procedure for primary hyperparathyroidism (PHPT) were possible long before the measurement of intraoperative parathyroid hormone (Io-PTH) levels, the availability of these data intraoperatively (especially in combination with preoperative localization studies) has fostered the increased use of unilateral, directed, localized, or “minimally invasive” parathyroid explorations, without a significant decrease in the operative success rate. This less extensive approach has also been clearly demonstrated to reduce operating time, frozen sections (1), hospital length of stay, and has allowed surgery to be performed on an outpatient basis, through smaller incisions, with increased patient satisfaction, shortened return to normal activity, and reduced hospital costs (2). These advantages have led to the recommendation that Io-PTH be used routinely in operations for PHPT, especially for directed or limited surgical approaches (3).

Initial reports of rapid Io-PTH assays suggested that a 50% decline in baseline levels is associated with a successful surgical procedure. This value has been widely accepted as the goal for these procedures, and continues to be quoted as an endpoint (3). The half-life of intact, bio-intact, 84 amino-acid parathyroid hormone molecules is only approximately 2-5 minutes, which suggests that

true levels should fall even further, to normal or near-normal levels, more quickly during successful surgery. Early assays for Io-PTH use of an antibody to detect only a section, the nPTH portion, of the 84 amino-acid parathyroid hormone molecules, and might, therefore, also continue to detect a biologically inactive fragment of the molecule after it has been partially metabolized. Second and third generation assays to measure intact-PTH (iPTH) or bio-intact (1-84) PTH have become increasingly specific for larger portions of the entire hormone, or the entire hormone itself, and therefore may be expected to decline more quickly to normal or near-normal levels when measured intraoperatively. As the tests for Io-PTH become more specific for biologically active, iPTH, expected thresholds for post-resection Io-PTH that indicate a successful, curative procedure should decline, and given the very short half-life of the intact hormone, might be expected to decline into the normal range.

2. Objectives

We hypothesized that the use of a newer assay to measure iPTH during parathyroid surgery would result in a decline of Io-PTH levels to normal or near-normal levels, in patients who undergo successful removal of all diseased glands.

Implication for health policy/practice/research/medical education:

Intraoperative parathyroid hormone has been utilized by endocrine surgeons for a long time with great outcome. However, there was always a different translation of the outcome. We are presenting out data on a relatively high number of patients who underwent parathyroidectomy for primary hyperparathyroidism and analysis outcome. We also reveal follow up and outcome.

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3. Materials and Methods

Consecutive measurements of Io-PTH performed at a single institution, from November 2001 through December 2010, were prospectively recorded in a single computer data-base in the hospital laboratory. The records of all patients who underwent these measurements were then reviewed retrospectively. Prior institutional review board (IRB) approval was obtained. Charts were reviewed for preoperative diagnosis, number of Io-PTH measurements and levels, unilateral versus bilateral neck exploration, pathologic findings, and if available, follow-up calcium and parathyroid hormone levels. Io-PTH levels of iPTH were measured using the ImmuliteR 1000 with Turbo intact PTH kit 2001 (Siemens Healthcare Diagnostic). Io-PTH levels above 65 pg/mL were considered abnormal, and at or below this level were considered normal. Serum calcium levels greater than 10.3 mg/dL were considered to be elevated.

Inclusion criteria for the study group included patients with a preoperative diagnosis of PHPT and performance of at least two measurements of Io-PTH, with at least one measurement taken before resection and one after resection. Patients were excluded if pre-resection Io-PTH levels were not elevated.

The preoperative diagnosis of PHPT was established with traditional serum and urine studies, including serum calcium, phosphate, and electrolytes, serum PTH level and 24 hours urine calcium excretion. All patients underwent preoperative localization studies, including nuclear medicine Tc-99 sestamibi scanning and/or ultrasound of the neck.

Operative notes were reviewed to determine if unilateral or bilateral exploration was performed, and the rationale for all bilateral explorations. Blood sample for Io-PTH measurement was drawn by the surgeon from the internal jugular or anterior jugular vein or by the anesthesia team from a peripheral blood vessel in the upper extremity. Io-PTH was measured again 10-20 minutes after removal of an enlarged gland. When multiple enlarged glands were removed and multiple additional Io-PTH levels were determined, the final Io-PTH level was used to calculate the percentage of decline from the initial or baseline level. The percent reduction of Io-PTH was calculated by dividing the initial pre-resection level by the final post-resection level. Calcium levels were obtained within 24 hours after surgery and 2-4 weeks later in follow-up.

4. Results

225 patients underwent measurement of Io-PTH during the study period. A total of 594 Io-PTH measurements were performed (mean: 2.64 per patient). Sixteen patients were excluded: 13 patients without a preoperative diagnosis of PHPT (10 were undergoing surgery for thyroid disease, one each for secondary hyperparathyroidism, tertiary hyperparathyroidism, and a neck mass), two patients who only had a single measurement

of Io-PTH, and one patient with a pre-resection Io-PTH level of less than 65 pg/mL. The remaining 209 patients comprised the study group.

Final Io-PTH levels declined by more than 50% from the initial intraoperative level in 205 (98%) of the 209 study patients, and by more than 80% from the initial level in 201 patients (96%). In 189 patients (90%), the final Io-PTH level was within the normal range (< less than 65 pg/mL). Unilateral exploration was only performed in 146 patients (70%) and bilateral exploration in 63 (30%). The rationale for bilateral exploration included a planned four-gland exploration (26 patients), concomitant thyroidectomy (15 patients) and persistent elevation of Io-PTH levels (22 patients). This latter group of 22 patients, 11% of the entire study group, underwent bilateral exploration prompted predominantly by persistent abnormal levels of Io-PTH that had not declined by 80% or more.

At least one abnormal parathyroid gland was found in all patients, with a parathyroid adenoma or single-gland disease found in 191 (91%), and multiple-gland disease was found in the remaining 18 patients (9%). With mean follow-up of 17 months, the serum calcium level was normal in 201 patients (96%), and elevated in four patients (2%). Four patients (2%) did not have a serum calcium level available.

5. Discussion

Parathyroid hormone (PTH) is a single-chain polypeptide made up of 84 amino acids. The ability to measure PTH levels has only been available since the 1960s, when an immunoassay was developed by Berson and Yalow, a discovery that led to the awarding of a Nobel Prize to these investigator (4). When PTH is metabolized by proteolysis in the liver, kidneys, bone and to a lesser extent in the parathyroid glands, it results in N-terminal, C-terminal and midregion fragments. The N-terminal region contains the portion that is bioactive, and disappears rapidly. The C-terminal fragment has a half-life of several hours. Immunoassays specific for various PTH fragments rely on antiserum specific for a portion of the polypeptide. More recently, assays for iPTH are widely commercially available and are now being used to measure Io-PTH (5).

Older assays for rapid-PTH used an antibody developed to bind to the nPTH fragment of the hormone. While these assays were initially thought to bind to the first 34 amino acids or (1-34) PTH, it has since been discovered that the anti-nPTH antibody used in these assays binds only to amino acids 13-34, or (13-34) PTH (6). This limiting factor in detecting iPTH, or (1-84) PTH might explain why Io-PTH levels reported in earlier studies saw only modest (50%) decrease in Io-PTH levels, even after successful surgical resection of all diseased glands. A 50% drop of Io-PTH from baseline within 5-10 minutes after excision of an abnormal gland had been reported in earlier studies to be predictive of a cure in 95% of patients. This threshold of a 50% decline in Io-PTH levels may no longer then

be appropriate if second and third-generation tests that measure iPTH or bio-intact (1-84) PTH are used. Older assays may not be measuring biologically active hormone alone, instead, measuring longer lasting fragments of the metabolized hormone, and therefore may not decline as much or be as biologically accurate.

In addition to assays for the metabolized fragments of PTH, assays for iPTH attempt to more completely identify the intact 84 amino acid hormone. In this study, we used a commercially available, automated, multipurpose analyzer (Immulite 1000 with Turbo intact PTH kit) with highly specific antibodies for iPTH. The assay requires binding by both a solid-phase antibody specific for the C-terminal region [(44-84) PTH] and by an enzyme-labeled antibody that only recognizes the N-terminal region [(1-34) PTH], and therefore is able to only recognize iPTH and very large PTH fragments that are nearly as long as the iPTH molecule itself. One such large fragment, 7-84 PTH, can cross react, but the clinical significance of this potential cross reaction is unknown. In 2002, Kao et al. reported that 45 of 47 patients undergoing parathyroidectomy for PHPT using this same assay had iPTH levels decrease to < 25% of baseline levels (5).

We report a large, consecutive, experience measuring Io-PTH during procedures for PHPT. The results confirm the hypothesis that Io-PTH levels decline to normal, or near-normal, within 10-20 minutes, when all abnormal parathyroid glands are removed at surgery. We observed that Io-PTH levels decline to the normal reference range in 90% of patients, or by more than 80% of the initial level in 96% of patients at the conclusion of surgery for PHPT. Levels that declined by 50%, but were still significantly elevated, would be interpreted by the authors to indicate the need for further, bilateral, four-gland, exploration of the neck in an attempt to find additional enlarged, hyperfunctioning glands. Given the known short half-life of bioactive (1-84) PTH of only 2-5 minutes, persistently elevated levels of iPTH 10-20 minutes after resection of an abnormal gland strongly suggest additional diseased gland(s).

The ability to measure intraoperative parathyroid hormone (Io-PTH) has supported the increasing use of unilateral exploration in selected patients with primary hyperparathyroidism (PHPT), and is felt to be especially important for these directed or limited surgical approaches. Combined with preoperative localization

studies, especially 99Tc-labeled sestamibi imaging, 70% of patients in the current study were able to undergo only unilateral neck exploration, yet serum calcium returned to normal in 96% of study patients. Conversely, a persistent elevation of Io-PTH levels after resection of an abnormal gland led to otherwise unplanned bilateral exploration in 22 patients (11%), emphasizing the value of measuring Io-PTH if less than a full, bilateral, four-gland exploration is planned (2).

Given the short half-life of bio-intact (1-84) PTH, Io-PTH levels of iPTH should become normal, or to drop by at least 80%, during successful parathyroidectomy for PHPT. Normal or near-normal post-resection Io-PTH levels can support unilateral exploration in PHPT. Persistent elevations of Io-PTH after resection of an abnormal gland dictate the need for bilateral exploration. As assays become more specific for iPTH, and thus more accurately reflect biologically active PTH hormone in the blood, the previous standard of a 50% decline of Io-PTH levels is no longer appropriate.

Authors' Contribution

The entire work including patient's history and physical examination taken, follow up, chart review and summary was performed by Roya Azadarmaki and Ashwin Kurian. Literature review and summary, manuscript design and concept, administrative, technical and material support, writing and editing was performed junior author, Masoud Rezvani, and senior author, Christopher Pezzi.

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