CME

ORIGINAL ARTICLE

Rapid Intraoperative Parathyroid Hormone Assay in the Surgical Management of Hyperparathyroidism

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Abstract

Context: Historically, successful surgical management of primary hyperparathyroidism has required bilateral exploration of the neck. By confirming complete removal of hypersecreting tissue, an intraoperative parathyroid hormone (IO-PTH) assay allows use of a more limited procedure.

Objective: Our objective was to evaluate the utility of IO-PTH assay used in 32 parathyroid explorations versus conventional bilateral exploration used before the advent of IO-PTH assays.

Methods: Minimally invasive parathyroidectomy (MIP) was used. Plasma samples were obtained at several intervals and were analyzed for IO-PTH by use of a rapid immunochemiluminescent assay (ICMA). Outcomes were assessed by univariate inferential testing, yielding one-tailed *t*-test results.

Results: The study group had a mean plasma IO-PTH level decrease of 87% at ten minutes after excision. All 32 patients who underwent MIP using IO-PTH monitoring had successful surgery. At last postoperative follow-up examination, all 32 patients were normocalcemic. There were statistically significant decreases in duration of surgery, length of hospital stay, and surgery cost.

Conclusions: IO-PTH levels predicted the postoperative outcome for all patients studied, can provide valuable information to surgeons, and can decrease the duration of surgery and hospital stay.

Introduction

Primary hyperparathyroidism (PHPT) has become a common disease, affecting an estimated 28 per 100,000 people each year in the United States.[1] Increased recognition of PHPT—resulting from advances in screening tests—has produced a clinical profile of hyperparathyroidism characterized by mild hypercalcemia with absent or subtle symptoms. The number of parathyroidectomies performed for PHPT has also increased dramatically since 1996. In the surgical management of PHPT, intraoperative PTH (IO-PTH) assays have been shown to improve the success of parathyroid gland surgery.[2–4] Minimally invasive parathyroidectomy (MIP) has replaced the traditional four-gland bilateral exploration as the procedure preferred by many institutions.[1,5]

Surgical treatment of PHPT is challenging and carries uncertainty concerning presence or absence of disease in a single gland, two glands, or several hyperplastic glands.[6] Sestamibi scans[2–4] can provide some information about locating adenomas, but they may not be sensitive enough to detect second adenomas or multigland hyperplasia. Historically, endocrine surgeons have performed bilateral exploration to ensure detection of the reported 5% to 30% incidence of second hyperplastic glands. The success of surgical treatment depends on successfully localizing abnormal glands. Difficulties associated with parathyroidectomy relate to variability in the number of parathyroid glands, different locations of normal and abnormal glands, and problems distinguishing normal from subtly diseased glands.[7] Although 80% to 85% of parathyroid adenomas are found adjacent to the thyroid gland in its normal location, 15% to 20% are ectopic.[8,9] The number of glands present may further complicate locating the adenoma. About 85% of individuals have four glands, 5% have five, and 10% have three glands identified.[8,9] In some cases, patients have four normal glands in the neck as well as an abnormal fifth gland in the mediastinum.[7–9] Approximately 9% of all patients with PHPT have parathyroid hyperplasia in which all four parathyroid glands are enlarged.[10]

IO-PTH assays have been used by many surgeons to detect decreases in plasma PTH levels after all hypersecreting tissue has been excised.[11,12] We here describe our experience with a rapid intraoperative PTH

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immunochemiluminescent assay (ICMA) in patients undergoing exploration for parathyroid adenoma or multigland hyperplasia. The status of the IO-PTH assay has shifted from investigative to routine clinical tool;[13] the test allows a more limited procedure by confirming complete removal of hypersecreting tissue.[1] It also reduces the need for repeat surgeries[5] and reduces the extent of neck exploration in patients with single-gland disease.

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Methods

The Kaiser Permanente Southern California Institutional Review Board approved this study. MIP using IO-PTH assays was performed for 32 patients at the Kaiser Permanente (KP) Fontana Medical Center, Fontana, California, between August 2003 and June 2006. Rapid IO-PTH assays were used primarily to determine whether all hyperfunctioning tissue had been removed.[6] In one patient, the MIP was a repeat surgical exploration necessitated by a failed parathyroid surgery done at a non-KP medical center; one patient showed multigland hyperplasia and one exhibited secondary hyperparathyroidism.

We used the Immulite analyzer (Diagnostic Products Corporation, Los Angeles, CA), which employs a solid-phase goat polyclonal anti-PTH and an alkaline phosphatase-labeled mobile-phase goat polyclonal anti-nPTH antibody. The standard PTH assay in the Immulite analyzer has a 60-minute incubation time, requires a serum sample, and has an analytic range of 5 to 5000 pg/mL.[14] The testing method used in this study was a second-generation Immulite PTH assay: the Turbo Intact PTH assay, which shortens incubation time to 14 minutes and produces an analytic range of 10 to 2500 pg/mL. Our laboratory uses a rolling turbo cart with a StatSpin Express 2 primary tube centrifuge (StatSpin, Inc, Norwood, MA) and an uninterrupted power supply for point-of-surgery testing during MIP.[14]

To determine the assay's clinical utility, we performed univariate inferential testing for duration of surgery, duration of hospital stay, and surgery cost. We wanted to have at least a 95% likelihood of true decreases in these parameters. Our hypotheses were tested with a one-sample, one-tailed *t*-test.

Results

Figure 1 shows the percentage decrease in PTH levels for each of the 32 patients ten minutes after excision. Figure 2 shows the patients' *t*-test data.

At our institution, historical mean duration of surgery needed to complete bilateral parathyroid explorations was 210 minutes. This mean reflected length of surgery per bilateral exploration done during the year before advent of MIP with IO-PTH assay.

Our mean time for MIP with IO-PTH assay was 119 minutes, a 43% decrease, with $t = 2.111$ (critical value for $t_{.025,31}$ was 2.039). Thus, we estimate a 97.5% likelihood ($p = .025$) that the mean duration of surgery was decreased by 38% using MIP with IO-PTH assay, compared with the mean duration of surgery for bilateral exploration (Figure 2).

Mean length of hospital stay was also reduced by MIP, compared with the mean duration of hospital stay observed before advent of MIP with IO-PTH assay.[3,15,16] Historically, the mean historical duration of hospital stay was 1.3 days.[16,17] For patients undergoing MIP with IO-PTH assay at our institution, the mean duration was 0.65 days, a 54% decrease ($t = 2.073$ vs the critical t table value of

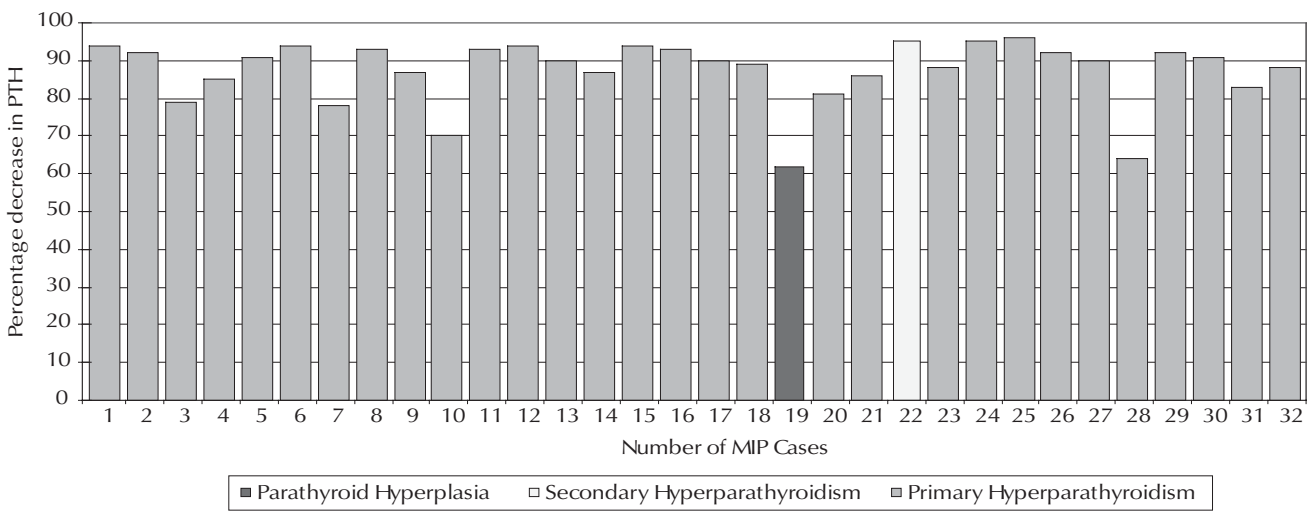

Figure 1. Percentage decrease in parathyroid hormone (PTH) levels for 32 patients who underwent minimally invasive parathyroidectomy (MIP).

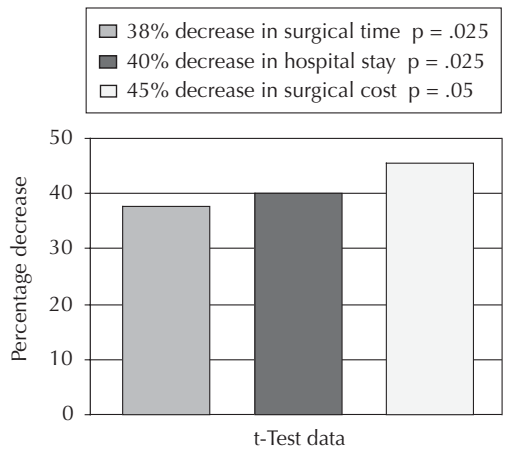

Figure 2. Data from *t*-test for 32 patients who underwent minimally invasive parathyroidectomy.

2.039). This yields an estimated 97.5% likelihood (p = .025) that, compared with hospital stay required after bilateral exploration, mean duration of hospital stay was decreased by 40% by using MIP (Figure 2).

Historically, the reported mean surgical cost of bilateral exploration in the US during our study period (August 2003 through June 2006) averaged $6865.[16–18] This figure includes a surgical cost of $4135, as well as a 1.3-day hospital stay, costing $2730. The mean estimated cost for our 32 patients was $3194, 53.4% lower than the reported US average. The estimated *t*-test value for this comparison was 1.828 (vs 1.695 cited as the critical value in the *t* table, indicating a 95% likelihood [p = .05] that MIP reduced mean cost per surgery by 45%).

Collectively, the 32 patients had an 87% mean decrease in PTH level measured at ten minutes after excision. Calcium levels of all 32 patients remained normal at last postoperative follow-up examination, and none of the patients showed persistent or recurrent hyperparathyroidism at follow-up examination.

Discussion

Criteria for Predicting Cure

Chemical assays used for intraoperative determination of adequate resection rely on the specific, unique products produced by the parathyroid glands. Whereas standard PTH assays, with routine incubation times and temperatures, can require more than an hour, the rapid PTH assay generally has a higher incubation temperature, uses an agitation cycle, and has a shorter incubation time.[19,20] First-generation PTH assays were radioimmunoassays, a methodology seldom used today because of lengthy turnaround time and poor diagnostic utility.[12,21–23] Test methodology has greatly improved in the second- and third-generation assays, which include immunoradiometric assay (IRMA) and the more current ICMA method.

IRMAs and ICMAs use an excess of capture antibody specific for one end of the PTH molecule. The capture antibody is bound to a solid phase, commonly a bead. After blood specimen collection, serum or plasma is separated and an aliquot is added to the solid phase along with the capture antibody. The PTH in the specimen binds to the capture antibody during incubation. Next, the signal antibody is added because it recognizes an immunologic site (on the PTH molecule) distinct from the site recognized by the capture antibody. After unbound material is removed, the bound signal is measured. The signal output is directly proportional to the level of PTH present in the specimen.[4,13]

The IRMAs—considered-second generation assays—have disadvantages that are substantially overcome by ICMAs, the third-generation assays. The latter have a long shelf life (six months or longer), are technically easy to use, do not require radioactive safety precautions, and have high analytic accuracy. Portable ICMA automated formats are available so that monitoring can be done directly in the operating room. Carter and Howanitz[14] calculated the cost of reagents for the Immulite turbo assay to be $100.00 per surgery. Our actual cost per surgery averaged $80.00.[2]

The IO-PTH concentration used to indicate a surgical cure relied on the half-life of the PTH molecule and on the postresection interval after which the specimen was drawn.

As our main criterion, we used a >50% drop in PTH measured at ten minutes after resection. When a patient's PTH level has decreased and been maintained at a level 50% below the baseline value (determined at commencement of surgery), the surgeon can be confident that production of PTH has ceased as a result of complete excision of all hypersecreting tissue.[24] We routinely drew four samples for PTH assay: the preincision baseline sample, the postincision–preexcision (second) baseline sample, the sample drawn five minutes after excision, and the sample drawn ten minutes after excision. The second baseline sample was drawn to determine stability of the original baseline. The higher of the two baseline values was used as our working PTH baseline, from which we calculated the required ≥50% decrease in PTH level.[24]

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Comparison with the Literature

Many studies have now demonstrated the clinical utility of IO-PTH testing,[6] which has proven highly effective for predicting the success of MIP done for primary hyperparathyroidism. All of our 32 patients had successful

surgery, and there were statistically significant decreases in duration of surgery, duration of hospital stay, and surgery cost. Of course, continued follow-up is needed.[25]

Udelsman's review of 656 cases[15] showed that among patients having conventional bilateral explorations without IO-PTH assays, nearly 18% required repeat surgery. Thus, by extrapolation we might have expected a need to reoperate in about six of our 32 patients. Experienced surgeons can appreciate the promise this technique offers for eliminating the risk of missing hypersecreting tissue.

Future investigations for IO-PTH assays might include evaluating their role in guiding surgeons performing parathyroid surgery in patients with secondary hyperparathyroidism, surgeons performing bilateral exploration in patients with ectopic second adenomas, and surgeons performing parathyroid tissue autotransplant when surgical hypoparathyroidism might be a risk. ❖

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