ORIGINAL RESEARCH

Intraoperative PTH: Effect of sample timing and vitamin D status

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OBJECTIVE: To assess the effect of timing of intraoperative parathyromone (iPTH) samples and 25-hydroxyvitamin D (25-OHD) status on decision-making during parathyroidectomy.

METHODS: A total of 77 patients with primary hyperparathyroidism and iPTH levels (preincision, preremoval, 5 (T5) and 10 (T10) minutes postremoval) performed during parathyroidectomy were reviewed.

RESULTS: Forty-one percent of patients were 25-OHD insufficient. We noted a significant correlation between preoperative 25-OHD and preincision iPTH ($P = 0.002$) but not iPTH at postremoval levels (T5, $P = 0.89$; T10, $P = 0.42$). When compared with preincision iPTH, the use of either the higher preincision or preremoval iPTH baseline significantly improves the assay sensitivity from 83% to 93% at T5 ($P = 0.01$) and 87% to 97% at T10 ($P = 0.02$). Surgical cure was obtained in 98% of patients.

CONCLUSION: Obtaining preremoval iPTH allowed earlier decision with respect to operative completion in 38% of cases. 25-OHD status does not appear to significantly affect interpretation of iPTH levels.

SIGNIFICANCE: Obtaining both baseline levels significantly improves sensitivity in iPTH monitoring.

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Surgical intervention to treat hyperparathyroidism by an experienced parathyroid surgeon has a success rate of 95% to 98%. Preoperative localization studies with high resolution ultrasound and technetium-99m sestamibi scanning have been used in minimally invasive parathyroidectomy, which allows for a focused approach in patients with solitary adenoma, decreased operative time, and limited disruption of normal parathyroid glands. Intraoperative intact parathyroid hormone (iPTH) monitoring was introduced as a physiologic assay to determine adequate removal of hyperfunctioning parathyroid tissue due to its short half-life (less than 3 minutes). Previous studies have described variable accuracy rates when using iPTH that authors have attributed to the assay itself and questioned the use of iPTH assays to predict surgical cure. However, many of the differences in reported results arise simply from differences in timing of samples drawn that confound the interpretation of criteria used in predicting operative success.

Currently vitamin D deficiency is defined as the level below which secondary hyperparathyroidism risk is heightened. 25-Hydroxyvitamin D (25-OHD) has been found to be significantly lower in patients with primary hyperparathyroidism during all calendar months when controlling for age and sex. In addition, patients with 25-OHD insufficiency (less than 20 ng/mL or less than 50 nmol/L) and primary hyperparathyroidism have been found to have significantly higher PTH levels and higher PTH levels 6 months post-parathyroidectomy. The effect of 25-OHD insufficiency on iPTH levels measured with the intraoperative PTH assay, and thus impact on surgeon decision-making is not known. We hypothesize that 25-OHD insufficient patients with primary hyperparathyroidism have higher intraoperative PTH levels at intraoperative timepoints and may account for...
iPTH levels that remain above the normal reference range after adenoma excision.

During parathyroidectomy, manipulation of hyperfunctioning parathyroid tissue can result in increased parathormone release, and this has been shown to contribute to false-negative iPTH monitoring when only a preincision baseline level is drawn, presumably because the actual iPTH value at the time of adenoma removal was much higher than assumed. Conversely, surgical dissection of parathyroid adenomas has also been noted to compromise vascular supply, thus causing a decrease in parathormone levels before adenoma removal and further emphasizing the importance of a preincision baseline. Contrary to most surgeons who do not obtain both a preincision and a preremoval baseline, we believe that performing both preincisional and preremoval measurement of iPTH will aid in intraoperative decision-making, often allowing for an earlier decision with respect to surgical termination.

To critically evaluate these hypotheses, we analyzed our experience with iPTH monitoring to determine 1) the effect on 25-OHD level on intraoperative PTH, 2) the effect of timing of iPTH samples on sensitivity for correctly confirming surgical success after removal of a single adenoma, and 3) the use of the preremoval iPTH measurement to affect surgeon intraoperative decision-making.

METHODS

Objective

We aimed to: 1) determine the effect on preoperative 25-OHD concentration on iPTH levels, 2) compare sensitivities of intraoperative iPTH based on timing of iPTH samples, and 3) determine the proportion of cases where obtaining a preremoval in addition to the standard preincisional baseline may allow for an earlier decision to terminate surgery.

Study Design and Subjects

We studied an historic cohort of adult patients from the University of Cincinnati otolaryngology practice with the diagnosis of primary hyperparathyroidism, who underwent parathyroidectomy over an 18-month period, and who were identified from a medical records database. A search was performed with Current Procedural Terminology (CPT) code to determine the type of surgery, and patient medical records were reviewed for indication for surgery. A retrospective medical record review was then undertaken to define patients who met the inclusion criteria. This study was approved by the Institutional Review Board at the University of Cincinnati College of Medicine.

Patients who had undergone minimally invasive parathyroidectomy for primary hyperparathyroidism with a complete set of intraoperative PTH results (preincision, preremoval, and 5 and 10 minutes after tumor removal) were included in this study. Patients with underlying renal failure, a history of multiple endocrine neoplasia (MEN) I or MEN IIa, or failure to intraoperatively identify a diseased parathyroid gland were excluded. Preoperative localization via Tc-99m sestamibi scanning, high resolution ultrasound, or both were used in all patients, and only patients with readily localized parathyroid glands underwent minimally invasive parathyroidectomy.

Laboratory Measurements

Intraoperative PTH was measured by a 2-site sandwich chemiluminescent immunoassay (ADVA Centaur Intact PTH Assay, Bayer Inc, Tarrytown, NY) with polyclonal antibodies targeting the N-terminal 1-34 and C-terminal 39-84 regions of the PTH molecule. Coefficient of variation for this assay in our laboratory is reported at 7.4%. Institutional iPTH protocols were followed such that samples were drawn from a peripherally placed IV catheter in an upper extremity, and iPTH samples were taken before incision (preincision iPTH), after identification and manipulation of the adenoma but before its removal (preremoval iPTH), 5 minutes after removal of the affected gland (T₁₀ iPTH), and 10 minutes postremoval of the affected parathyroid gland (T₁₀ iPTH). Preoperative 25-OHD concentrations were measured by radioimmunoassay (25-OH Vitamin D, Diasorin Inc, Stillwater, MN) or by chemiluminescent immunoassay (LIAISON analyzer, [Diasorin Inc]).

Outcomes and Analysis

The primary outcome measures were 1) sensitivities of iPTH monitoring with the various time points, 2) the frequency of the preremoval iPTH level significantly impacted surgical decision-making, and 3) the effect of preoperative serum 25-OHD concentrations on iPTH concentrations at each measured time point. The first outcome is defined as the sensitivity of the assay to predict surgical cure of hyperparathyroidism based on >50% from a baseline iPTH lab draw. The second outcome is defined as the proportion of cases in which the preremoval iPTH had risen above the preincisional iPTH level such that iPTH fell <50% from preincision but >50% from the preremoval baseline or in which the preremoval level was already >50% below preincision baseline. Appropriate descriptive statistics used to report these outcomes are sensitivity, positive predictive value, and the accuracy of the iPTH assay to predict postoperative normocalcemia, which were calculated with preincision, preremoval, or the higher of both as baseline iPTH. A true-positive is defined as at least >50% decrease from baseline in iPTH levels after gland removal (at T₅ or T₁₀ postremoval) and biochemical evidence of postoperative resolution of hypercalcemia and hyperparathyroidism. A false-positive is defined as >50% decrease from baseline in which a patient developed recurrent/persistent hypercalcemia and elevated iPTH levels after parathyroidectomy. A false-negative is defined as failure of iPTH to fall by >50% from baseline in a patient who remained eucalcemic with normalized PTH levels postparathyroidectomy. A true-negative is defined as failure of iPTH to drop by >50% from
baseline with multiglandular disease or persistent hyperparathyroidism after resection of a single gland. Sensitivity for correctly determining surgical resolution of disease is defined as the true-positives divided by the sum of true-positives and false-negatives. Positive predictive value is defined as the number of true-positives divided by the sum of true-positives and false-positives. Accuracy is defined as the sum of true-positives and true-negatives divided by the sum of true-positives, true-negatives, false-positives, and false-negatives. McNemar test of repeated measures was used to compare sensitivities of iPTH monitoring at the various timepoints. Matched pair \( t \) test was used to compare difference in means for preincision and preremoval iPTH levels. Univariate linear regression analysis was also performed and reported with \( P \) values and correlation coefficients. Statistical significance was defined as \( P < 0.05 \).

RESULTS

Preoperative

A total of 77 patients were included in this study. Eleven patients were excluded because they failed to meet all inclusion criteria (two MEN2a, one failed exploration, and eight without all time points sampled). The average age was 63.5 years (range, 36.8 to 85.6 years) at the time of surgery. In this series, 63% of patients had associated morbidities related to their hyperparathyroidism: 34% had documented osteoporosis, 9% had experienced bone fractures, 12% had a history of renal calculi. In these patients, 8% were symptomatic with bone pain, and 23% reported fatigue. Preoperative 25-OHD averaged 24.7 ± 15.6; 41% of patients had preoperative 25-OHD insufficiency, defined as lower than 20 ng/mL (50 nmol/L). Patients with 25-OHD insufficiency had nonsignificantly different preoperative serum calcium (11.4 ± 1 vs 11.1 ± 0.6).

Intraoperative

In all cases, the excised parathyroid gland was histopathologically confirmed to be an adenoma, with average weight of 1435 ± 1850 mg (range, 100 to 10,000 mg). Regression analysis revealed a significant positive linear correlation between parathyroid adenoma weight and preincision iPTH (\( r = 0.35, P = 0.003 \), iPTH at \( T_{10} \) \( r = 0.4, P = 0.003 \), but not iPTH at \( T_{3} \) \( r = 0.1, P = 0.39 \)). In addition, there was no significant correlation between parathyroid adenoma weight and the percentage decrease from preincision iPTH to levels measured at \( T_{5} \) (\( r = 0.1, P = 0.20 \)) or iPTH at \( T_{10} \) (\( r = 0.0, P = 0.79 \)). Mean preincision iPTH (216 ± 192) was nonsignificantly higher than preremoval iPTH (186 ± 152, \( P = 0.19 \)), but the preremoval iPTH value was higher than the preincision value in 38% of cases. In these patients, the average increase was 179% ± 84% from the preincisional iPTH.

There was a significant negative linear correlation between preoperative 25-OHD levels and preincision iPTH (\( r = 0.4, P = 0.002 \)) such that lower 25-OHD levels correlate with higher preincision iPTH levels. This was not the case with either of the postremoval iPTH levels at \( T_{5} \) or \( T_{10} \) (\( r = 0.0, P = 0.89 \) and \( r = 0.1, P = 0.42 \), respectively). In addition, there was a significant linear correlation between preoperative 25-OHD levels and percentage decrease from preincision iPTH to \( T_{5} \) (\( r = 0.4, P = 0.002 \)) and \( T_{10} \) (\( r = 0.4, P = 0.003 \)) such that lower 25-OHD levels correlated with a larger percentage decrease in the iPTH levels.

We determined the proportion of cases wherein attaining the addition of a preremoval level may have impacted surgical decision-making. In 28% of cases, the preremoval baseline was >50% below preincision due to tissue dissection and compromised glandular vascular supply, which suggests surgical cure without awaiting postresection iPTH levels. At \( T_{5} \) postremoval, 10% patients had >50% drop from preremoval but not preincision iPTH. and at \( T_{10} \) 7% patients had >50% fall from preremoval but not preincision baseline. Taking into account the 28% patients in whom the preremoval value had already fallen >50% from preincision as well as these 10% patients who experienced >50% decrease at \( T_{5} \) but not preincision baseline, performing a preremoval iPTH could have influenced intraoperative decision-making and potentially allow the surgeon to terminate the procedure earlier in 38% of cases.

The calculated sensitivity, positive predictive value, and accuracy for iPTH based on >50% decrease from respective baseline values are presented and defined in Table 1. As expected, there was a small improvement in sensitivity at \( T_{10} \) from \( T_{5} \) apart from the baseline used, but this was not significant. In both the \( T_{5} \) and \( T_{10} \) postremoval time points, the preincision baseline alone yielded higher sensitivity than preremoval alone. However, when the higher of either baseline level is used, sensitivity is significantly improved at \( T_{5} \) (93% vs 83% for preincision, \( P = 0.01 \)) and at \( T_{10} \) (97% vs 87% for preincision, \( P = 0.02 \)). There was a significant linear correlation between preincision iPTH and levels measured at \( T_{5} \) (\( r = 0.4, P = 0.002 \)) and at \( T_{10} \) (\( r = 0.4, P < 0.001 \)) such that higher preincision iPTH concentrations correlated with higher iPTH levels measured at \( T_{5} \) and \( T_{10} \). There is a significant linear correlation between preremoval iPTH and iPTH at \( T_{5} \) (\( r = 0.5, P < 0.0001 \)) and \( T_{10} \) (\( r = 0.7, P < 0.0001 \)).

When more stringent criteria are used, a decrease in iPTH of >50% and an iPTH falling into the normal reference range, the sensitivity of the assay decreases from 97% to 70% at \( T_{10} \) and further from 93% to 57% at \( T_{5} \). Thus, in 17% of patients, the \( T_{10} \) postremoval iPTH remained above the normal reference range. In nine of these patients, the decrease from baseline to \( T_{10} \) postremoval iPTH was at least 50%, and each of these patients was eucalcemic postoperatively. One patient with an elevated \( T_{10} \) postremoval iPTH failed to have >50% decrease from baseline until another iPTH was measured at 30 minutes after removal of the adenoma. This patient represents one of the two false-negatives in iPTH monitoring of our series and had a de-
ni ne ty -eight percent of patients had surgical cure with resolution of hypercalcemia. The average preoperative serum calcium level was 11.3 ± 1.0, and the average postoperative calcium level was 9.3 ± 0.6. Patients with 25-OHD insufficiency had no difference in postoperative serum calcium when compared with patients with 25-OHD in the reference range (9.3 ± 0.5 vs 9.2 ± 0.6).

One patient represents a false-positive in iPTH monitoring. Intraoperatively, this patient’s iPTH fell to 56% of preincision and preremoval baseline at T10. Postoperatively, this patient developed asymptomatic hypercalcemia and elevated intact PTH at approximately 6 months after surgery.

Of note, the aforementioned false-negative patient had undergone a thyroidectomy several years previously and underwent bilateral neck exploration during parathyroidectomy due to failure of iPTH to fall >50%. As mentioned, exploration yielded three normal parathyroid glands. Postoperatively, this patient experienced transient postoperative vocal cord paresis on the contralateral side from the adenoma.

**DISCUSSION**

Though the majority of endocrine surgeons agree that iPTH is useful to guide the completion of parathyroidectomy and to predict postoperative calcium levels, the reported accuracy of this approach varies based on the criteria used to interpret iPTH levels. Our study suggests the addition of a preremoval baseline iPTH increases the sensitivity and potentially results in an earlier operative decision in 38% of cases. By obtaining both preincisional and preremoval baseline, we increase sensitivity and reduce false-negatives. In addition, patients may avoid prolonged anesthesia while awaiting subsequent levels and possible unnecessary further neck exploration and its potential morbidity.

We noted a significant positive linear correlation between parathyroid adenoma weight and preincision iPTH (r = 0.35, P = 0.003) and iPTH at T10 (r = 0.4, P = 0.003). There was no significant linear correlation between parathyroid adenoma weight and iPTH measured at T5 (r = 0.1, P = 0.39), presumptively due to the 38% of patients with a preremoval iPTH higher than the respective preincision level. In addition, there was no significant correlation between parathyroid adenoma weight and the percentage decrease from preincision iPTH to levels measured at T5 (r = 0.1, P = 0.20) or iPTH at T10 (r = 0.0, P = 0.79). This can likely be attributed to the preremoval level either acutely increasing or decreasing from surgical adenoma manipulation. Higher preincision iPTH, preremoval iPTH, and parathyroid adenoma mass correlated with higher T10 postremoval levels. Among these, preremoval iPTH was the strongest correlate.

In 94% cases in our series, the T10 iPTH value continued declining from the T5 iPTH, and in the remaining cases in which the T10 value increased, the rise was inconsequential to the operative decision-making. In most instances, the procedure was terminated after the T5 iPTH value was used to calculate the decrease without awaiting the T10 value. Irvin et al demonstrated that >50% decrease in iPTH values from the highest baseline iPTH T10 postremoval is predictive of postoperative normocalcemia. In our series, we found the T10 level more sensitive than T5, but obtaining a level at T5 and T10 allows for earlier termination of procedure in 93% of cases based on the T3 level alone. If the T5 level fails to fall >50% from highest baseline, then awaiting the T10 result is strongly recommended before pursuing further dissection. (Table 1).

With the use of criteria that require the iPTH level to fall to >50% of baseline and to fall into the reference range of the rapid iPTH assay, some authors13,14,18,22
actually decrease the sensitivity of the assay. In our study, requiring the iPTH to fall into the normal range would result in sensitivity of 81% and 89% at T5 and T10, respectively. Further, 10% of patients (n = 7) would have required further unnecessary surgical exploration or prolonged anesthesia while awaiting subsequent levels. We note a significant linear correlation between preincision iPTH to iPTH at T5 (r = 0.4, P = 0.002) and iPTH at T10 (r = 0.4, P < 0.001) such that higher preincision iPTH concentrations correlated with higher iPTH levels measured at T5 and T10. In this respect, requiring iPTH to fall into the reference range has potential to increase false-negatives in patients with higher preincision iPTH as their postremoval iPTH concentrations will be higher than patients with lower preincision iPTH values.

Several mechanisms could explain the failure of the iPTH to fall within the reference range including coexisting medically reversible secondary hyperparathyroidism from 25-OHD insufficiency. When controlling for age and sex, 25-OHD was found to be significantly lower in patients with primary hyperparathyroidism during all calendar months. In addition, patients with 25-OHD insufficiency and primary hyperparathyroidism have been found to have significantly higher PTH levels and higher PTH levels 6 months postparathyroidectomy. Though concomitant 25-OHD insufficiency was present in 41% of our patients, this had no effect on interpretation of iPTH levels for intraoperative decision-making. In our study population, we found that 25-OHD insufficiency to be associated with higher preincisional iPTH concentrations, but 25-OHD does not correlate with iPTH at T5 or T10. We attribute this to the confounding effects of the changes noted in preincisional iPTH from preincisional levels and the variance in parathyroid adenoma mass. Hence, knowledge of 25-OHD level likely does not significantly impact intraoperative interpretation of iPTH levels after gland removal and, as such, 25-OHD was not a useful parameter in predicting operative cure of hypercalcemia in our series.

Ultimately each surgeon must balance the benefits of focused minimally invasive parathyroidectomy with the potential for missed multiglandular disease, potentially requiring re-exploration. Given the limited discretion in focused minimally invasive parathyroidectomy, the risk to patients associated with re-exploration (recurrent laryngeal nerve injury, hypocalcemia due to ischemia to normal parathyroid glands) is likely lower than in cases in which traditional bilateral exploration has been performed.

CONCLUSION

Sensitivity of iPTH monitoring in parathyroidectomy is primarily dependent on the timing of samples and criteria used for interpretation of iPTH levels. Though in most cases the preremoval iPTH value frequently differs substantially from the preincision baseline. Including the preremoval iPTH allows for an earlier decision to terminate the procedure in 38% of cases. We advocate standardization of iPTH protocols to include obtaining a preincision baseline iPTH value as well as a preremoval baseline iPTH. Including both values to arrive at a baseline iPTH results in fewer false-negatives and improves the sensitivity of the iPTH assay regardless of other criteria used. Use of the higher baseline may then allow for earlier termination of parathyroidectomy, greater surgeon confidence of operative cure, and may prevent unnecessary further surgical exploration with its associated morbidities. Preoperative 25-OHD contributes to higher preincision iPTH concentrations but does not correlate to postremoval iPTH values, and as such, does not influence intraoperative interpretation of iPTH levels and prediction of surgical cure.

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REFERENCES