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Significance of rebounding parathyroid hormone levels during parathyroidectomy

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Abstract

BACKGROUND—Using minimally invasive parathyroidectomy (MIP), most surgeons require a 50% decline in intraoperative parathyroid hormone (IoPTH) to determine cure, but the significance of IoPTH kinetics occurring after this drop remains unknown. The aim of this study was to determine the impact of IoPTH levels that first meet criteria for cure, but then increase again, or rebound, between 10 and 15 minutes post-excision.

METHODS—We conducted a retrospective review of patients undergoing initial parathyroidectomy for primary hyperparathyroidism at our institution from 2001 – 2011. Rebound IoPTH was defined as an increase in PTH ≥ 5 pg/mL after achieving the 50% drop required for cure. Comparisons were evaluated with the student's t-test, Chi-squared test, or Fisher's exact test where appropriate.

RESULTS—Of the 1,386 patients who met selection criteria, 86 (6.2%) patients exhibited rebound IoPTH. The mean magnitude of rebound was 13.8 ± 3.6 pg/mL. Compared to those not displaying rebound, more patients with rebound IoPTH were treated with open parathyroidectomy rather than MIP (10.8% vs. 4.5%, $p < 0.01$). The recurrence rate among those with rebound IoPTH was more than double that of patients without rebound IoPTH (5.8% vs. 2.2%, $p = 0.03$). Magnitude of rebound, however, did not correlate with recurrence. The rate of persistent disease was not different between those with and without rebound IoPTH. Rebound was a much better indicator of recurrence than patients whose final IoPTH levels were not within the normal range.

CONCLUSIONS—Rebound IoPTH is more common in patients who develop recurrent hyperparathyroidism. Therefore, surgeons should closely monitor patients with rebound IoPTH for disease recurrence.

Keywords

primary hyperparathyroidism; intraoperative parathyroid hormone monitoring; recurrence; minimally invasive parathyroidectomy

Introduction

Primary hyperparathyroidism (PHPT) is a common endocrine disorder with over 100,000 new cases diagnosed annually in the United States (1). The disease manifests with hypercalcemia and a range of associated symptoms such as bone and joint pain, kidney stones, fatigue, abdominal pain, and depression. Surgery remains the only curative treatment with long-term success rates exceeding 95% (2, 3). Traditionally, parathyroidectomy was

accomplished with a bilateral neck exploration where all four glands were identified and grossly abnormal glands resected. The development of intraoperative parathyroid hormone (IoPTH) monitoring enabled surgeons to offer patients a minimally invasive parathyroidectomy (MIP) (4). Since the etiology of PHPT is a single adenoma in roughly 80% of patients with PHPT, MIP involves resecting a preoperatively localized adenoma through a small incision, and then using IoPTH to confirm a cure while the patient is still in the operating room. Recurrence rates with MIP have been shown to be equivalent to the traditional, open approach (5, 6).

Although numerous IoPTH protocols exist in the literature, most parathyroid surgeons require a 50% decline in PTH from the pre-excision level in order to terminate the operation (5, 7). One criticism of MIP is that IoPTH may miss multigland disease (MGD) leading to persistence or recurrence (8, 9). This has led many to re-evaluate a 50% decline in IoPTH as criterion for a cure (10, 11). Alternatively, Heller et al. investigated the final (20 minute) IoPTH level, and found that a final level of 40 pg/mL or greater put patients at higher risk of persistent disease (12). Others have suggested that the final, curative IoPTH level needs to be within the normal range, although this has been disputed (13–16).

In this context, the kinetics of IoPTH *after* the criteria for cure are met remains understudied. The purpose of this study was to determine the impact of IoPTH levels that first meet criteria for cure, but then increase again, or rebound, between 10 and 15 minutes post-excision.

Methods

We conducted a retrospective review of a prospectively collected parathyroid database. Initial neck operations for PHPT between 2001 and 2011 were selected for further analysis. Familial disease, secondary, tertiary, or re-operative cases were excluded. We also excluded patients who underwent concomitant thyroid operation or who underwent a thoracic procedure to remove a parathyroid adenoma. At the University of Wisconsin, almost all patients with biochemical evidence of PHPT were evaluated with sestamibi scan and some patients also undergo neck ultrasound. Radioguidance and IoPTH were employed for localization and to guide the extent of exploration as previously described (17). At our institution, we require a 50% drop in PTH from the peak PTH level measured at 5, 10, or 15 minutes post-excision. All three levels are sent after excision of the diseased gland(s). Results are reported back to the operating room 25–30 minutes from the time the first level is sent, and all levels are reported even if a 50% decline from the peak level does occur. The laboratory error for the PTH assay used at our institution is 2 pg/mL. Rebound IoPTH was defined as an increase in PTH ≥ 5 pg/mL after achieving the 50% drop required for cure. That is, rebound IoPTH occurred after meeting criteria for cure and the procedure was terminated. A threshold of 5 pg/mL was chosen since it is more than twice the assay's inherent error. In cases where either the IoPTH levels failed to decline by 50% or the five minute value increased above the baseline, additional IoPTH levels were sent (18). However, only the last, or curative, set of IoPTH values were analyzed for rebound.

Preoperative patient characteristics and perioperative lab values were recorded. Operative findings were classified as either a single adenoma when one enlarged gland was identified or multigland disease when more than one gland was identified (double adenomas or hyperplasia).

The parathyroid database is maintained with each patient's most recent calcium and PTH values. Postoperative PTH and calcium are drawn one to two weeks after surgery and then again at 6 months. Follow-up labs beyond 6 months are also captured. Outcomes were

categorized as persistence or recurrence. Persistence was an elevated calcium and PTH within six months of surgery. Recurrence was defined as an elevated calcium and PTH beyond six months postoperatively, with calcium greater than our laboratory's upper limit of normal (>10.2 mg/dL) representing recurrence. PTH levels above normal or inappropriately normal for the calcium level were also considered in determining persistence or recurrence.

Comparisons were made with the student's t-test, Chi-squared test, or the Fisher's exact test where appropriate. Statistical analysis was performed with STATA v. 12.1 software (StataCorp, College Station, TX). $P < 0.05$ was considered significant.

Results

Of the 1,386 patients undergoing an initial neck operation for PHPT, the mean age was 61 years old, and 1,067 (77.7%) were female. When comparing the rebound group to the non-rebound patients, there were no differences in age or gender. 86 patients (6.2%) exhibited rebound IoPTH, and the mean magnitude of rebound was 13.8 ± 3.6 pg/mL.

Patients with rebound IoPTH had slightly lower preoperative calcium levels compared to patients without rebound IoPTH (10.9 ± 0.1 mg/dL vs. 11.1 ± 0.0 mg/dL, $p = 0.04$, Table 1), but there was no difference in preoperative PTH or creatinine (Table 1). Of note, patients with rebound were less likely to have positive sestamibi scan localization compared to patients who did not exhibit rebound (63.0% vs. 78.4%, $p < 0.01$, Table 1). Multigland disease was also more common in the rebound group compared to the non-rebound group (34.9% vs. 18.5%, $p < 0.01$, Table 1). Accordingly, only 52.3% of patients in the rebound group were treated with MIP while 73.9% of patients in the non-rebound group were treated with MIP ($p < 0.01$, Table 1).

Requiring IoPTH levels to fall within the normal range is another commonly applied criterion for achieving intraoperative cure (13–15). Although we do not require IoPTH levels to fall within the normal range (16), we further analyzed the subset of patients whose IoPTH level that met our criteria for cure (50% drop from the peak level) was *not* within the normal range (> 72 pg/mL). There were 186 such patients (13.4%). Of these, two patients (0.1%) had persistent disease and one patient (0.07%) recurred. Looking at all patients who had either persistent disease or recurrence (40 patients total), 12 (30%) had rebound IoPTH (Figure 1). Three patients (6%) met criteria for cure (50% decline in IoPTH from the peak level) with an IoPTH level that was not within the normal limits. Two of the three had persistent disease, and only one had recurrence (Figure 1).

Importantly, the recurrence rate among patients who exhibited rebound IoPTH was more than double that of patients who did not display rebound IoPTH (5.8% vs. 2.2%, $p = 0.04$, Table 1). Median follow-up time was 9.2 months (inter-quartile range 13.96); 71.1% of patients had follow-up time of at least 6 months. There was no difference in the rates of persistent disease between these two groups. Magnitude of rebound did not correlate with recurrence. Furthermore, the postoperative (1–2 weeks after surgery) calcium and PTH levels did not differ between those with and without rebound IoPTH.

Discussion

This study characterizes patients with primary hyperparathyroidism whose IoPTH first meets criteria for cure, but then rebounds between 10 and 15 minutes post-excision. Patients who exhibit rebound IoPTH have lower calcium levels and are less likely to localize on sestamibi scans. This likely relates to a greater frequency of multigland disease in this cohort compared to patients who do not exhibit rebound IoPTH. Most importantly, patients with

rebound had a significantly higher recurrence rate (5.8%) compared to patients without rebound (2.2%).

Although this study examines the kinetics of IoPTH after criteria for a cure are met, other investigators have studied the absolute value of the final IoPTH level or the PTH shortly after surgery. For example, Heller et al. reported that a final (20 minute) IoPTH level of 40 or greater was associated with the greatest risk of persistent disease (12). Similarly, the study reported here found a relationship between the kinetics of final IoPTH levels and outcome. Rather than an absolute value in IoPTH or short-term outcomes, the present study suggests that a rebounding pattern of IoPTH portends a higher risk of recurrent disease, and not persistent disease. That is, rebound IoPTH was associated with recurrence, an outcome measured beyond 6 months postoperatively.

Unlike this study, Heller's IoPTH protocol requires that the PTH fall by 50% of baseline *and* into the normal range. At the University of Wisconsin, we do not wait for IoPTH levels to fall into the normal range. Reihner et al. found that requiring IoPTH to fall within the normal range (<60 pg/ml) would fail to reduce rates of persistence or recurrence (16). In contrast, Heller's study suggests that a more strict IoPTH protocol, requiring levels to fall into the normal range resulted in a subset of patients (11.34%) at higher risk of persistent disease (12). In this series, a large number of patients (186) had IoPTH levels that met criteria for cure but did not fall within the normal range. Of these, only two patients (0.1%) had persistent disease and one (0.07%) experienced a recurrence. Far more patients with recurrence exhibited rebound compared to curative IoPTH levels that did not fall within normal limits (Figure 1). The present study showed no difference in persistence but a higher risk of recurrent disease without requiring IoPTH levels to fall into the normal range (Table 1). Therefore, rebound is a more reliable indicator for recurrence than IoPTH levels that do not fall within the normal range.

These data suggest that the pattern of IoPTH may indicate subsequent risk of recurrence regardless of the absolute final values. Such information becomes available to the surgeon only *after* the operation has been terminated. Since the operation has ended, and the patient is awake (or in the process of waking up), further neck exploration is not possible. Furthermore, our data indicate that rebound predicts recurrence and not persistent disease, so further exploration at that time may not affect long-term outcomes in the case of a metachronous presentation of multigland disease. The surgeon should pay close attention to the remaining IoPTH results even after the operation is terminated as it may indicate a subset of patients at risk for recurrence.

The dilemma becomes how to manage these patients in the postoperative period. Since rebound IoPTH identifies a subset of patients at higher risk for recurrence, the surgeon should use this data to tailor follow-up schedules. At our institution, patients with rebound IoPTH are seen at three and six months postoperatively. If both calcium and PTH are normal at 6 months, labs are rechecked at 12 months.

Similar to the final IoPTH levels, several authors have reported on normocalcemic elevations in PTH after successful parathyroidectomy. The incidence of this phenomenon ranges from 12 to 43% of cases (19), and these patients tend to be older, deficient in Vitamin D, and have biochemical markers of more severe hyperparathyroidism (20–24). Similar to this study, our group has previously shown that recurrence is higher in the subset of patients who display elevations in PTH postoperatively (24). Interestingly, the group with rebound IoPTH did not have higher postoperative (1–2 week) PTH compared to the group without rebound. This suggests two different patterns for disease recurrence, and reinforces the need

to pay careful attention to these intraoperative and postoperative lab values in determining a patient's risk for recurrence.

This study is limited by its retrospective nature. Although there were nearly 1400 patients in this cohort, relatively few patients exhibit rebound IoPTH. Despite very good follow-up (> 70% of patients followed for at least 6 months), a longer follow-up time may capture more events of recurrent disease, and may bias the results reported here. As we have previously reported, recurrence is often quite delayed, occurring five or more years postoperatively (25), and perhaps more of the patients with rebound will recur with longer follow-up.

Despite these limitations, patients with rebound IoPTH suffered more than double the recurrences compared to patients without rebound IoPTH. Therefore, patients found to exhibit rebound IoPTH at the completion of a parathyroidectomy operation should be monitored more closely for recurrent disease.

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Figure 1. Operative Failures by IoPTH Pattern

Data are represented as the percentage of patients with either recurrence or persistence displaying each type of IoPTH pattern. *NOT WNL* = IoPTH fell by 50% from the peak level but *not* within the normal range. *BOTH* = patients experiencing recurrence/persistence, rebound IoPTH, *and* a curative IoPTH level not within the normal limits.

TABLE 1

Comparison of Patients with and without Rebound IoPTH

Variable	Rebound IoPTH	Non-Rebound IoPTH	P value
PRE-OPERATIVE STUDIES			
Calcium (mg/dL)	10.9 ± 0.1	11.1 ± 0.0	0.04
PTH (pg/mL)	126.1 ± 10.2	123.6 ± 2.6	0.81
Creatinine (mg/dL)	1.0 ± 0.0	1.0 ± 0.0	0.52
Sestamibi localization	51 (63.0)	974 (78.4)	<0.01
OPERATIVE FINDINGS			
MIP	45 (52.3)	961 (73.9)	<0.01
Multigland disease	30 (34.9)	240 (18.5)	<0.01
Gland weight (mg)	981.5 ± 175.5	651.7 ± 28.1	0.66
OUTCOMES			
Persistent Disease	1 (1.2)	6 (0.5)	0.36
Recurrence	5 (5.8)	28 (2.2)	0.04

Data are represented as the number with the percentage in parenthesis for categorical variables and the mean ± the standard error of the mean for continuous variables.

IoPTH = intraoperative parathyroid hormone, mg = milligram, dL = deciliter, pg = picogram, mL = milliliter, PTH = parathyroid hormone, MIP = minimally invasive parathyroidectomy