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Extreme Elevation of Baseline Intraoperative Parathyroid Hormone Measurements: Should Usual Protocols Apply?

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ABSTRACT

Introduction: Intraoperative parathyroid hormone (IOPTH) monitoring is routinely used to facilitate minimally invasive parathyroidectomy. Many IOPTH protocols exist for predicting biochemical cure. Some patients are found to have extremely high baseline IOPTH levels (defined in this study as >500 pg/mL), which may affect the likelihood of satisfying certain final IOPTH criteria. We aimed to discover whether clinically significant differences exist in patients with extremely high baseline IOPTH and which IOPTH protocols are most appropriately applied to these patients.

Materials and methods: This is a retrospective review of 237 patients who underwent parathyroidectomy with IOPTH monitoring for primary hyperparathyroidism (pHPT) from 2016 to 2020. Baseline IOPTH levels, drawn prior to manipulation of parathyroid glands, were grouped into categories labeled "elevated" (>65-500 pg/mL) and "extremely elevated" (>500 pg/mL). Final IOPTH levels were analyzed to determine whether there was a >50% decrease from baseline and whether a normal IOPTH value was achieved. 6-wk postoperative calcium levels were also examined.

Results: Of the patients in this cohort, 76% were in the elevated group and 24% in the extremely elevated group. Male sex and higher preoperative PTH levels were correlated with higher baseline IOPTH levels. Patients with extremely elevated baseline IOPTH were less likely to have IOPTH fall into normal range at the conclusion of the case ($P = 0.019$), and final IOPTH levels were higher ($P < 0.001$), but the IOPTH was equally likely to decrease >50% from baseline. There was no difference in the mean postoperative calcium levels between the two groups at 6-wk or at longer term follow-up (mean 525 d).

Conclusions: Detection of baseline IOPTH levels >500 pg/mL during parathyroidectomy performed for pHPT is not uncommon. IOPTH in patients with extremely elevated baseline levels were less likely to fall into normal range, but follow-up calcium levels were equal,

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suggesting that applying more stringent IOPTH criteria for predicting biochemical cure may not be appropriate for this population.

Introduction

The use of intraoperative parathyroid hormone (IOPTH) monitoring is routinely used to predict biochemical cure for patients undergoing minimally invasive parathyroidectomy for primary hyperparathyroidism (pHPT).[1] Multiple different sets of criteria for interpreting IOPTH have been developed with the intent of more accurately predicting biochemical cure intraoperatively. Two commonly used protocols include Miami criteria, necessitating a decrease of more than 50% from the highest pre-excision IOPTH level, and dual criteria, necessitating a decrease of more than 50% from the highest pre-excision value and the final value lying within the normal range of the PTH assay.[2-4] Some authors have suggested that even more stringent criteria, such as a final IOPTH level less than or equal to 40 pg/mL, may be most accurate for prediction of biochemical cure.[5,6]

Few prior studies address the significance of extremely high elevations in baseline IOPTH levels. It is well known that IOPTH levels often increase during parathyroid adenoma mobilization, and the kinetics of these post-manipulation "spikes" have been well described in the literature.[7-11] This phenomenon has been demonstrated to increase patients' risk for postexcision IOPTH to remain elevated, leading to patients who have been cured to not appear so.[7] However, there is scant literature investigating whether very high pre-manipulation IOPTH levels should affect interpretation of postexcision IOPTH in a similar manner. One prior study, by Singh *et al.* described patients with high-baseline IOPTH levels >1000 pg/mL and concluded that IOPTH monitoring was still a reliable indicator for biochemical cure.[12] However, it has yet to be determined which IOPTH criteria are most appropriately applied to these patients.

In this retrospective study, we sought to determine whether there are any demographic factors that predispose patients to have extremely high-baseline IOPTH levels, which IOPTH criteria are most likely to be satisfied when baseline IOPTH levels are extremely high, and whether postoperative biochemical outcomes differ for these patients.

Materials and Methods

The study was reviewed by the Dartmouth Hitchcock Institutional Review Board and was determined to be institutional review board exempt. We performed a retrospective chart review of 237 patients who underwent minimally invasive parathyroidectomy with IOPTH monitoring for pHPT at our institution from May 2016 to March 2020. The inclusion criteria included patients aged 18 y or older who underwent parathyroidectomy for pHPT. The exclusion criteria included reoperative parathyroidectomy, secondary or tertiary hyperparathyroidism, patients with multiple endocrine neoplasia syndromes, missing baseline or final IOPTH data, or missing 6-wk follow-up labs.

Baseline IOPTH levels were defined as IOPTH levels obtained from a jugular vein after the induction of anesthesia but before manipulation of the parathyroid(s). The general practice at this institution is to draw the sample from the internal jugular vein ipsilateral to the suspected adenoma (if localized preoperatively) or on the first side explored (if non-localized preoperatively). For patients with a suspected single adenoma, a preexcision level is also routinely drawn. For patients with nonlocalized disease or suspected 4-gland disease, no postmanipulation level is drawn. In general, dual criteria were followed, and a bilateral exploration was done if 15-min levels were not in the normal range.

We grouped baseline IOPTH levels into two categories, termed "elevated" (ranging from >65 to 500 pg/mL) and "extremely elevated" (>500 pg/mL). The cutoff of >500 pg/mL was selected because previous literature had utilized >500 pg/mL as a cutoff for remarkably elevated baseline IOPTH levels[7], and this seemed appropriately applied to our cohort given the relatively low incidence of baseline IOPTH levels exceeding 500 pg/mL. Final IOPTH levels were analyzed retrospectively to determine whether the IOPTH decreased by >50% and whether IOPTH achieved normal range. Calcium levels at a 6-wk postoperative clinic visit were also examined. Achievement of normocalcemia at this time was termed as early biochemical response. Additional data which were collected during chart review and retrospectively analyzed included patient age and sex, preoperative PTH, preoperative calcium, preoperative vitamin D, previous diagnosis of osteoporosis or nephrolithiasis, number of parathyroid glands excised (single *versus* multiple), and the weight of the largest gland excised for each patient. When available, the 6-wk postoperative PTH and the most recent calcium level along with the duration since surgery were also collected. Data were collected using Excel 2016 (Microsoft Corp.) and analyzed with R (The R Foundation) and R Studio. Univariate statistical analysis was performed using the gtsummary package.[13-15] Continuous variables were evaluated with histograms for normality and comparisons were made with Wilcoxon rank-sum test, a nonparametric test. Categorical variables were evaluated with chi-squared or Fischer's exact tests. A P value of <0.05 was considered significant.

Results

The study cohort consisted of 237 patients; median age was 63 y (SD 12) and 82% were women (Table 1). 179 (76%) patients were found to be in the elevated group and 58 (24%) patients in the extremely elevated group. There was no statistically significant difference in median age between the two groups ($P = 0.8$). There was a larger percentage of men in the extremely elevated group with 31% compared with 15% in the

Table 1 — Demographics and preoperative testing.

Characteristic	Overall, N = 237*	Elevated baseline IOPTH, N = 179*	Extremely elevated baseline IOPTH, N = 58*	P-value†
Age (years)	64 (57, 71)	64 (57, 71)	64 (56, 72)	0.7
Sex				0.005
Female	193 (81%)	153 (85%)	40 (69%)	
Male	44 (19%)	26 (15%)	18 (31%)	
Preoperative serum calcium (mg/dL)	10.80 (10.50, 11.30)	10.80 (10.40, 11.30)	10.95 (10.60, 11.47)	0.019
Preoperative PTH (pg/mL)	116 (86, 153)	108 (84, 143)	148 (99, 194)	<0.001
Preoperative 25-OH vitamin D (ng/mL)	32 (24, 39)	31 (24, 39)	32 (23, 42)	>0.9
n Missing preoperative 25-OH vitamin D	40	32	8	
Osteoporosis diagnosis preoperatively	92 (39%)	70 (40%)	21 (38%)	0.8
n Missing osteoporosis data	5	3	2	
Nephrolithiasis preoperatively	76 (33%)	60 (34%)	16 (29%)	0.4
n Missing nephrolithiasis data	5	3	2	

IOPTH = intraoperative parathyroid hormone; PTH = parathyroid hormone.
* *n* (%); Median (IQR).
† Wilcoxon rank-sum test; Pearson's chi-squared test; Fisher's exact test.

elevated group ($P = 0.005$). Median preoperative calcium and PTH levels, drawn prior to a preoperative clinic visit were higher in the extremely elevated group: 10.95 mg/dL (interquartile [IQR] 10.60, 11.47) and 148 pg/mL (IQR 99, 194 pg/mL) compared to 10.80 mg/dL (10.40, 11.30) and 108 pg/mL (IQR 84, 143 pg/mL) in the elevated group ($P = 0.019$ for serum calcium levels and $P < 0.001$ for serum PTH levels). There was no difference in preoperative 25-OH vitamin D levels between the two groups. The incidence of osteoporosis and nephrolithiasis were also equal between the groups.

The mean baseline IOPTH in the elevated group was 189 pg/mL (144, 272) and in the extremely elevated group was 999 pg/mL (638, 1805), $P < 0.01$ (Table 2). There was no statistically significant difference found between elevated and extremely elevated baseline IOPTH patients in terms of single *versus* multiple glands excised ($P = 0.8$). Patients in the extremely elevated group tended to have larger excised parathyroid glands, median 0.8 g (IQR 0.48 g, 1.54 g), when compared to patients in the elevated group, 0.61 g (IQR 0.29 g, 1.26 g) ($P = 0.10$), though this finding did not reach statistical significance. 158 patients (88%) in the elevated group and 55 patients (95%) in the extremely elevated group had IOPTH decrease >50% ($P = 0.2$). 149 patients (83%) in the elevated group and 40 patients (69%) in the extremely elevated group had IOPTH both decrease >50% and fall into normal range ($P = 0.019$). Final IOPTH levels were higher in the extremely elevated group, 48 pg/mL (36, 73), compared with the elevated group, 36 pg/mL (24, 51) ($P < 0.001$).

Table 2 — Intraoperative data and short-term postoperative outcomes.

Characteristic	Overall, N = 237*	Elevated baseline IOPTH, N = 179*	Extremely elevated baseline IOPTH, N = 58*	P-value†
Glands excised				0.8
Multiple	109 (46%)	83 (46%)	26 (45%)	
Single	128 (54%)	96 (54%)	32 (55%)	
Largest gland weight (g)	0.66 (0.32, 1.26)	0.60 (0.30, 1.23)	0.80 (0.49, 1.55)	0.085
Unknown	13	11	2	
Baseline IOPTH (pg/mL)	235 (157, 484)	189 (144, 272)	999 (638, 1805)	<0.01
Final IOPTH (pg/mL)	39 (26, 57)	36 (24, 51)	48 (36, 73)	<0.01
IOPTH decreased >50% and into normal range	189 (80%)	149 (83%)	40 (69%)	0.019
IOPTH decreased >50% only	213 (90%)	158 (88%)	55 (95%)	0.2
6-wk postoperative serum calcium (mg/dL)	9.50 (9.10, 9.80)	9.50 (9.15, 9.80)	9.40 (9.00, 9.70)	0.2
Calcium >10.5 mg/dL at 6-wk follow up	5 (2.1%)	1 (0.5%)	4 (6.9%)	0.012
6-wk postoperative PTH (pg/mL)	45 (31, 60)	45 (30, 59)	46 (31, 67)	0.6
Unknown	113 (47%)	89 (50%)	24 (41%)	

IOPTH = intraoperative parathyroid hormone; PTH = parathyroid hormone.
* *n* (%); Median (IQR).
† Wilcoxon rank-sum test; Pearson's chi-squared test; Fisher's exact test.

Serum calcium levels at routine 6-wk follow-up were available for 100% of the cohort. There was no difference in mean serum calcium levels in the two groups. Mean postoperative serum calcium in the group that had elevated baseline IOPTH was 9.50 mg/dL (9.15, 9.80) and in the extremely elevated baseline IOPTH group was 9.40 mg/dL (9.00, 9.70). In total, 5 patients, (2.1% of the entire cohort) remained hypercalcemic at their 6-wk postoperative clinic visit. Four of these patients were in the extremely elevated baseline IOPTH group (6.9% of extremely elevated patients) and 1 was in the elevated group (0.5% of elevated patients) ($P = 0.012$). However, on further review, 3 of the four patients in the extremely elevated IOPTH group with postoperative hypercalcemia had PTH levels that were below the normal range and were being over-replaced with supplemental oral calcium and calcitriol. The 4th patient in that group was later taken back to the operating room and found to have 3 additional hyperplastic parathyroids with subsequent biochemical cure after the removal of 2.5 more glands. The only patient in the elevated baseline IOPTH group that was found to be hypercalcemic at the 6-wk postoperative visit was later found to have a positive CaSR mutation, consistent with a diagnosis of familial hypercalcemic hypercalcuria.

Long-term follow-up data were available on 137 patients (58% of the original cohort). (Table 3). There was no difference in the mean long-term follow-up calcium: serum calcium was 9.40 mg/dL (9.20, 9.80) for the elevated baseline IOPTH group at a mean duration of follow-up of 561 d (249, 906). For the extremely elevated baseline IOPTH group, the mean long-term follow-up calcium level was 9.30 mg/dL (8.95, 9.65) at a mean duration of follow-up of 446 d (57, 929) ($P = 0.14$).

Discussion

Detection of extremely elevated baseline IOPTH levels >500 pg/mL during parathyroidectomy performed for pHPT is not uncommon. In fact, 24% patients in this cohort were found to have an extremely elevated baseline IOPTH level. These patients pose a unique challenge for parathyroid surgeons because the kinetics of IOPTH may preclude them from meeting more stringent final IOPTH criteria to predict biochemical cure. It has yet to be determined which IOPTH protocols are most appropriately applied to these patients.

Our data indicate that patients with extremely elevated baseline IOPTH were less likely to achieve both a >50% reduction in IOPTH and a normal IOPTH at the conclusion of the parathyroidectomy. However, their postoperative serum calcium (both at 6 wk and longer term) and serum PTH levels were comparable. While patients with extremely high baseline IOPTH were more likely to be hypercalcemic at their 6-wk visits, this difference was attributable to calcium and calcitriol over-replacement in patients with postoperative hypoparathyroidism. Therefore, a 50% decrease in the IOPTH for these patients appears to be sufficient to predict cure.

Singh *et al.*[12] also concluded that the single criterion of a >50% decrease in IOPTH showed the highest negative predictive value and maximum accuracy for predicting biochemical cure for patients with extremely high baseline IOPTH levels. Our data were consistent with these findings. In our cohort, while only 69% achieved a normal IOPTH at the conclusion of the parathyroidectomy, 95% had a >50% decrease from baseline. This suggests that using IOPTH criteria that necessitate achieving an IOPTH level within normal limits could lead to an increased incidence of false negative results in patients with baseline IOPTH levels >500 pg/mL. Other authors have shown that the majority of patients who do not achieve a normal IOPTH level continue to be eucalcemic after parathyroidectomy.[16] Our data also supports this, since there was no difference in postoperative calcium levels between the two groups.

More recent literature has suggested that the criteria for final IOPTH levels predicting biochemical cure may need to be more strict.[5,6] However, the kinetics of IOPTH in patients with extremely high baseline PTH levels may make it impossible to achieve levels <40 pg/mL, for example, in this population. Our work suggests that a 50% decrease in IOPTH in this population appears to be adequate, as there were no differences seen in serum calcium level in both short and long terms. More research should be done to determine which intraoperative criteria should be applied to patients with extremely elevated IOPTH levels in order to most accurately predict durable cure.

There are limitations to this study, including those inherent to its retrospective nature. It is impossible to determine retrospectively how knowledge of an extremely elevated baseline IOPTH level might have affected real-time interpretation of subsequent IOPTH levels and related intraoperative decision-making, such as extent of exploration and total number of glands excised. There may be unmeasured factors unique to patients with extremely elevated baseline IOPTH levels affecting PTH kinetics. While it has been suggested by Libutti *et al.*[17] that false negative IOPTH findings can result from patient-specific variability in PTH half-life, Leiker *et al.*[18] argued that PTH half-life between patients does not typically vary to any clinically significant degree. Therefore, we can assume that the high number of patients in the extremely elevated group who did not achieve a normal IOPTH level are indeed due to higher PTH levels and likely not due to a difference in patient-specific PTH kinetics. Another important limitation of this study is the fact that long-term follow-up data on patients' serum calcium levels is missing for approximately half the cohort. Future studies investigating

Table 3 – Calcium at long-term follow-up.

	Overall, N = 137*	Elevated, N = 105*	Extremely elevated, N = 32*	P-value†
Calcium (mg/dL)	9.40 (9.10, 9.80)	9.40 (9.20, 9.80)	9.30 (8.95, 9.65)	0.14
Duration of follow-up (d)	525 (238, 921)	561 (249, 906)	446 (57, 929)	0.3

*Median (IQR).
†Wilcoxon rank-sum test.

this question would benefit from consistent collection of serum Ca levels at the 6-month postoperative period, to assess for true biochemical cure *versus* failure.

Conclusions

Patients with extremely elevated baseline IOPTH levels (>500 pg/mL) were less likely to achieve a normal final IOPTH value compared to patients with baseline IOPTH levels <500 pg/mL. However, their follow-up calcium levels were equal, suggesting that applying more stringent IOPTH criteria for predicting biochemical cure may not be appropriate for this population. Further investigation is needed to determine the optimal intraoperative criteria that will predict durable biochemical cure for patients with extremely elevated baseline IOPTH.

Author Contributions

DB, CB, PG, ME, and MS made substantial contributions to conception and design of the study. DB, GN, and PG were responsible for data acquisition. Data analysis was done by DB and CB. The manuscript was drafted by DB, CB, and MS. All authors have read and approved the final manuscript and agreed to be accountable for all aspects of the work.

Disclosure

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