



Intraoperative parathyroid hormone levels ≤ 40 pg/mL are associated with the lowest persistence rates after parathyroidectomy for primary hyperparathyroidism

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ABSTRACT

Background: Intraoperative parathyroid hormone (IOPTH) monitoring is used to predict biochemical cure during parathyroidectomy for primary hyperparathyroidism; however, there is variability in the intraoperative parathyroid hormone criteria used by surgeons to predict normocalcemia after parathyroidectomy. This study sought to determine the intraoperative parathyroid hormone criteria correlated with the lowest rates of persistent hyperparathyroidism after parathyroidectomy for primary hyperparathyroidism.

Materials and Methods: This is a retrospective cohort study of 2,654 patients with primary hyperparathyroidism who underwent parathyroidectomy with intraoperative parathyroid hormone monitoring at a single institution from 1999 to 2014. Multivariate logistic regression analysis was used to measure the association between the lowest intraoperative parathyroid hormone level and the persistence of primary hyperparathyroidism after parathyroidectomy.

Results: A total of 66 patients (2.5%) had persistent hyperparathyroidism after parathyroidectomy. Using the traditional intraoperative parathyroid hormone criteria of a $\geq 50\%$ decrease from the baseline level, the rate of persistent primary hyperparathyroidism was greater when intraoperative parathyroid hormone did not decrease to $\geq 50\%$ from the baseline level (17 of 180 patients [9.4%] vs 49 of 2,474 [2.0%], [OR 5.9, 95% CI 3.2–10.5, $P < .001$]). Regardless of whether intraoperative parathyroid hormone decreased $\geq 50\%$, patients with a lowest intraoperative parathyroid hormone above the normal range (10–65 pg/mL) had greater persistence rates compared with patients with an intraoperative parathyroid hormone < 65 pg/mL (30 of 350 [8.6%] vs 36 of 2,304 [1.6%], [OR 6.6, 95% CI 3.4–12.7, $P < .001$]). Furthermore, patients with a lowest intraoperative parathyroid hormone 40 to 65 pg/mL had increased rates of adjusted persistence compared with patients with lowest intraoperative parathyroid hormone ≤ 40 pg/mL (13 of 385 [3.4%] vs 23 of 1,919 [1.2%], [OR 4.2, 95% CI 2.0–8.7, $P < .001$]). Patients with lowest intraoperative parathyroid hormone < 5 to 20 pg/mL did not have decreased rates of persistence compared with patients with lowest intraoperative parathyroid hormone 20 to 40 pg/mL (9 of 996 [0.9%] vs 14 of 923 [1.5%], [OR 0.5, 95% CI 0.2–1.2, $P = .14$]).

Conclusion: Patients with a lowest intraoperative parathyroid hormone ≤ 40 pg/mL compared with the traditional criteria of a $\geq 50\%$ decrease from baseline and a final parathyroid hormone in the normal range (< 65 pg/mL) had the lowest rates of persistent primary hyperparathyroidism after parathyroidectomy for primary hyperparathyroidism. The single criteria of a lowest intraoperative parathyroid hormone level ≤ 40 pg/mL may best predict the lowest persistent disease rates after parathyroidectomy for primary hyperparathyroidism.

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Introduction

Primary hyperparathyroidism (PHPT) affects 1% to 2% of the adult population in the United States, and parathyroidectomy (PTX) is recommended if patients meet the criteria for treatment recommended by national treatment guidelines.¹ During PTX, intraoperative decision-making is in part guided by intraoperative parathyroid hormone (IOPTH) monitoring.² The short half-life of parathyroid hormone (PTH) allows for the rapid assessment of the function of the remaining parathyroid glands after the resection of abnormal parathyroid glands, and the degradation kinetics of PTH after curative PTX have been well described.^{3,4} There is variation in the level to which IOPTH should decrease after parathyroid excision to indicate successful PTX based on criteria derived from the current literature. The least strict of these criteria suggest that IOPTH must decrease to at least half of the baseline level,^{2,5,6} and other research suggests that an additional criterion of a value in the normal range (<65 pg/mL) should be included to better correlate with biochemical cure.^{7–11} Multiple studies have demonstrated persistent rates of hyperparathyroidism of 2% to 3%, using these criteria for IOPTH monitoring during focused PTX.^{7–12}

Although current IOPTH criteria have been associated with low rates of recurrence, it remains unclear whether these current criteria are strict enough to produce the lowest possible rates of persistent hyperparathyroidism after PTX. It is plausible that values even lower in the normal range may correlate with lower persistent rates of hypercalcemia after PTX than the traditional criteria of a $\geq 50\%$ decrease from the baseline and a level in the normal range. Two studies have suggested that postexcision IOPTH levels <40 pg/mL may be associated with lower rates of persistent or recurrent disease after PTX.^{13,14}

In this study, we examined the relationship between the lowest IOPTH and persistence of hyperparathyroidism after PTX in an attempt to provide greater insight and granularity to understanding the impact of stricter IOPTH guidelines on the rates of persistent hyperparathyroidism. The hypothesis of this study is that stricter IOPTH criteria with lower final postexcision PTH levels will be associated with lower rates of persistent primary hyperparathyroidism after PTX compared with the commonly used criteria of a $\geq 50\%$ decrease from the baseline and an IOPTH level within the normal range.

Materials and Methods

Study population

This was a retrospective analysis of an institutional review board–approved database of patients who underwent PTX at the University of Michigan Health System, Ann Arbor, between the years 1999 and 2014. We excluded patients with the following: secondary or tertiary hyperparathyroidism, reoperative PTX, multiple endocrine neoplasia type 1, history of lithium use, and incomplete lab values (complete lab values included preoperative and postoperative serum calcium and PTH values, and complete IOPTH levels, including a baseline level before gland excision and each of the 5-, 10- and 15-minute levels after parathyroid gland excision).

Data collection

Preoperative laboratory measurements included peak serum calcium and peak serum PTH levels obtained within 1 year before PTX. The operative approach to PTX included the following: a focused (image-directed) PTX, a planned bilateral parathyroid

exploration, or a focused approach that was later converted to a bilateral parathyroid exploration because of concern for multigland disease, inaccurate preoperative localization, or failure of IOPTH to decrease appropriately. Patients with a single parathyroid abnormality localized on preoperative imaging initially underwent a focused operative approach that was converted to a bilateral exploration if required. Patients without preoperative imaging localization or those suspected of having multigland disease preoperatively underwent a planned bilateral exploration.

The IOPTH criteria used during the study period was a $\geq 50\%$ decrease from the baseline PTH and a final level within or less than the normal range (10–65 pg/mL). IOPTH samples were either drawn peripherally via intravenous catheter in the greater saphenous vein or directly from the internal jugular vein, as dictated by surgeon preference. The site of IOPTH sampling has been shown to have little effect on outcomes.⁴ A baseline IOPTH level was obtained shortly after the induction of anesthesia and before operative manipulation of parathyroid tissue. A preexcision PTH level was obtained after identification, dissection, and isolation of the suspected abnormal parathyroid onto its vascular pedicle. In cases of the preexcision IOPTH level being greater than the baseline IOPTH level (suggesting some level of PTH release caused by manipulation of the abnormal parathyroid gland), this greater level was used to calculate the $\geq 50\%$ decrease as a “true” baseline. After completion of parathyroid excision, IOPTH levels were obtained at 5-, 10-, and 15-minutes postexcision, and the kinetics and absolute values were used to determine biochemical indication of cure based on the IOPTH criteria used throughout the study period. The lowest IOPTH was defined as the lowest IOPTH value obtained after completion of parathyroid gland excision and could be either the 5-, 10-, or 15-minute level. A failure to meet IOPTH criteria indicative of biochemical cure prompted conversion to a bilateral parathyroid exploration in the case of a focused approach. In cases of IOPTH levels that decreased initially but then increased substantially on subsequent levels, either further parathyroid gland exploration was performed or additional postexcision IOPTH levels were drawn at a time after the 15-minute postexcision level. If these additional IOPTH levels decreased in accordance with PTH degradation kinetics and met criteria for biochemical cure, the exploration was terminated. If not, further gland exploration and excision was performed to satisfy IOPTH criteria used at the time of the procedure.

Table 1
Patient demographics and characteristics (n = 2,654)

Variable	Value
Age (years), mean \pm SD	58.9 \pm 13.2
Female, (%)	76.9%
Preoperative PTH (pg/mL), median (range)	122 (30–3,025)
Preoperative calcium (mg/dL), mean \pm SD	10.9 \pm 0.7
Operative approach	
Focused approach, patients (%)	1,636 (61.6%)
Bilateral exploration, patients (%)	1,018 (39.4%)
Number of parathyroid glands removed	
One, patients (%)	2,122 (80.0%)
More than one, patients (%)	532 (20.0%)
Baseline IOPTH (pg/mL), median (range)	207 (34–3,111)
IOPTH (pg/mL)	
5 min postexcision, median (range)	49 (5–2,500)
10 min postexcision, median (range)	34 (5–2,500)
15 min postexcision, median (range)	28 (5–667)
Lowest IOPTH, median (range)	26 (5–667)
Follow-up calcium (mg/dL), mean \pm SD	9.3 \pm 0.7
Follow-up PTH (pg/mL), median (range; n = 212)	32 (3–284)
Persistent primary hyperparathyroidism, patients (%)	66 (2.5%)

Table II
Number of patients meeting >50% decrease from highest baseline intraoperative PTH value and lowest intraoperative PTH value in the normal range

Criteria met	Entire cohort n = 2,654	Persistent hyperparathyroidism (%) n = 66
> 50% decrease and normal range	2,278 (85.8%)	36 (21%)
> 50% decrease only	196 (7.4%)	13 (76%)
Normal range but not >50% decrease	26 (1.0%)	0
Neither criteria	154 (5.8%)	17 (11%)

Outcomes

The primary outcome investigated in this study was persistence of primary hyperparathyroidism at a follow-up visit between 2 weeks and 6 months post-PTX. Persistent disease was defined as a serum calcium level > 10.2 mg/dL in the absence of calcium supplementation within 6 months post-PTX. Recurrence of primary hyperparathyroidism more than 6 months after PTX was not included in this analysis because of the lack of complete biochemical follow-up data and short mean follow-up time available in the database. Postoperative PTH labs were not ordered routinely throughout the study period, thus PTH levels were considered in this definition when available but were not available for every patient. When available, PTH levels that were >65 pg/mL were used to confirm HPT in cases of concurrent increased serum calcium levels.

Statistical analysis

Patients were grouped initially into 4 cohorts based on the lowest IOPTH level within 15 minutes after completion of parathyroid gland excision: <5–20 pg/mL, 20–40 pg/mL, 40–65 pg/mL, and >65 pg/mL. The Student's *t* test was used for comparison of continuous variables, and the χ^2 test was used for comparison of categorical variables. Multivariable logistic regression models were created to compare rates of disease persistence between the groups, where lowest IOPTH was formatted as an ordinal variable based on the groups outlined. These models were adjusted for age, sex, biochemical severity of disease (preoperative PTH and preoperative calcium), and whether PTH was halved from the baseline level. Odds ratios (ORs) and 95% confidence intervals (CIs) were reported. *P* values < .05 were considered statistically significant for all analyses. All statistical analyses were performed using STATA statistical software v 14 (StataCorp, College Station, TX). Continuous data are expressed as mean \pm standard deviation or median values and range whenever appropriate.

Results

A total of 2,831 patients underwent PTX for primary hyperparathyroidism at the University of Michigan Health System from

the years 1999 to 2014. Of those, 177 (6.3%) were excluded for multiple endocrine neoplasia type 1, a history of lithium use, or incomplete laboratory data, leaving a final cohort of 2,654 patients (Table I). The study cohort had a mean age of 58.9 years (\pm 13.2), was 76.9% female, and had a median preoperative serum PTH of 122 pg/mL (range 30–3,025). The rate of persistent primary hyperparathyroidism after PTX was 2.5% (*N* = 66). Regarding intraoperative PTH findings, 2,474 patients (93%) had a lowest IOPTH level that decreased \geq 50% from the baseline or pre-excision IOPTH value, and in 180 patients (7%), the IOPTH did not decrease >50% (Table II). Patients with a final IOPTH level that did not decrease to half the baseline level had greater adjusted rates of persistence compared with patients in whom the IOPTH decreased by more than half of the baseline level (17 of 180 patients [9.4%] vs 49 of 2,474 [2.0%], [OR 5.9, 95% CI 3.2–10.5, *P* < .001]; Table III).

When the lowest IOPTH value was evaluated, 350 patients (13.1%) had a lowest IOPTH > 65 pg/mL, 385 patients (14.5%) had a lowest IOPTH <65 but \geq 40 pg/mL, 923 patients (34.8%) had a lowest IOPTH < 40 but \geq 20 pg/mL, and 996 patients (37.5%) had a lowest IOPTH < 20 pg/mL (Table IV). Patients with a lowest IOPTH > 65 pg/mL had a greater adjusted rate of persistent postoperative hypercalcemia than patients with a lowest IOPTH < 65 pg/mL (30 of 350 [8.6%] vs 36 of 2,304 [1.6%], [OR 6.6, 95% CI 3.4–12.7, *P* < .001]).

Patients with a lowest IOPTH > 40 pg/mL had increased rates of adjusted persistence compared with patients with lowest IOPTH \leq 40 pg/mL (43 of 735 [5.9%] vs 23 of 1,919 [1.2%], [OR 5.3, 95% CI 2.9–9.6, *P* < .001]). When patients with a lowest IOPTH > 65 were excluded, patients with a lowest IOPTH from 40 to 65 pg/mL still had increased rates of adjusted persistence compared with patients with lowest IOPTH \leq 40 pg/mL (13 of 385 [3.4%] vs 23 of 1,919 [1.2%], [OR 4.2, 95% CI 2.0–8.7, *P* < .001]). Patients with lowest IOPTH < 5 to 20 pg/mL did not have statistically significantly decreased rates of persistence compared with patients with lowest IOPTH 20 to 40 pg/mL (9 of 996 [0.9%] vs 14 of 923 [1.5%], [OR 0.5, 95% CI 0.2–1.2, *P* = 0.14]; Figure).

A subgroup analysis was performed for the 231 patients with baseline IOPTH levels \leq 100 pg/mL to better understand this demographic because a decrease of at least half in the PTH of these patients should have resulted in IOPTH values < 50 pg/mL. In this subset of patients, 7 patients (3.0%) had persistent disease at follow-up, and 13.4% had a lowest IOPTH of > 40 pg/mL. Patients with lowest IOPTH > 40 pg/mL had greater rates of persistence compared with patients with lowest IOPTH 0 to 40 pg/mL (3 of 31 [9.7%] vs 4 of 200 [2.0%], [OR 5.3, 95% CI 2.9–9.6, *P* < .001]). Finally, this analysis was repeated for 41 patients with normo-hormonal hyperparathyroidism (baseline IOPTH levels \leq 65 pg/mL). In this subset of patients, 2 patients (4.8%) had persistent disease at follow-up, and patients with lowest IOPTH > 40 pg/mL had greater rates of persistence compared with patients with lowest IOPTH <5 to 40 pg/mL (1 of 6 [16.7%] vs 1 of 35 [2.9%], [OR 5.3, 95% CI 2.9–9.6, *P* < .001]).

Table III
Patient characteristics, grouped by whether lowest IOPTH value was less than half baseline value

Variable	Lowest IOPTH > half baseline (n = 180)	Lowest IOPTH \leq half baseline (n = 2,474)	<i>P</i> value
Age (years), mean \pm SD	60.0 \pm 13.6	59.0 \pm 13.2	.24
Female, %	77.2%	76.9%	.92
Preoperative calcium, mean \pm SD	10.7 \pm 0.7	11.0 \pm 0.7	<.01
Preoperative PTH (pg/mL), median (range)	115 (32–586)	122 (30–3,025)	.04
Baseline PTH (pg/mL), median (range)	143 (35–965)	409 (34–3,111)	<.01
Persistent hyperparathyroidism, number (%)	17 (9.4%)	49 (2.0%)	<.01

Table IV
Characteristics of patients grouped by lowest intraoperative PTH

Variable	Lowest IOPTH (pg/mL)				P value
	> 65	65–41	40–21	20–<5	
N (%)	350 (13.2%)	385 (14.5%)	923 (34.8%)	996 (37.5%)	
Age (years), mean ± SD	60.4 ± 13	62.1 ± 13	59.6 ± 12	56.4 ± 14	.08
Female, %	74%	77%	76%	79%	.25
Preoperative calcium (mg/dL), mean ± SD	11.0 ± 0.9	11.0 ± 0.8	11.0 ± 0.8	10.9 ± 0.6	.17
Preoperative PTH (pg/mL), median (range)	138 (32–1,810)	136 (30–2,000)	128 (36–3,025)	110 (33–1,753)	< .01
Baseline PTH (pg/mL), median (range)	290 (64–3,111)	254 (40–2,500)	219 (35–2,500)	172 (34–2,500)	< .01
Persistent hyperparathyroidism, number (%)	30 (8.6%)	13 (3.4%)	14 (1.5%)	9 (0.9%)	
OR compared with > 65 cohort [95% CI]	N/A	0.36 [0.17–0.77]	0.14 [0.07–0.31]	0.07 [0.03–0.18]	

Discussion

In this retrospective study of patients undergoing PTX for primary hyperparathyroidism, we investigated optimal IOPTH criteria to predict operative success after PTX. First, this study confirms that IOPTH levels should decrease to less than half of the baseline level to predict operative success rates.^{5,13,15} In our study, patients whose lowest IOPTH level was less than half its baseline level had significantly lesser rates of persistent hyperparathyroidism, as has been demonstrated in multiple studies. Additional studies have concluded that in addition to the ≥50% decrease in IOPTH levels, a final IOPTH into the normal range (10–65 pg/mL) is a better predictor of cure.^{13,14} The findings of this study demonstrate that the lowest persistence rates after PTX are associated with IOPTH level of ≤ 40 pg/mL at 1.2% compared with the traditional criteria of a 50% decrease from the baseline and a level in the normal range that have a persistence rate of 3.4%. This association holds true for patients with a preoperative PTH < 100 pg/mL and for patients with normo-hormonal primary hyperparathyroidism, populations that can be problematic when using the traditional IOPTH criteria.³

Recent literature has evaluated whether more stringent criteria for IOPTH levels beyond the ≥50% decrease from the baseline and a level in the normal range criteria could improve prediction of cure after PTX.^{7,13} One study showed no difference in persistent disease rates between patients with a final decrease in IOPTH levels to 41 to 65 pg/mL vs ≤ 40 pg/mL, but long-term recurrence of hyperparathyroidism was more likely in patients with a final IOPTH level of 41 to 65 pg/mL compared with ≤ 40 pg/mL.¹³ A second study investigated similar criteria and found that patients whose final IOPTH level was < 40 pg/mL had significantly lesser rates of persistent hyperparathyroidism and lesser rates of long-term recurrence compared with patients whose final IOPTH was

40 to 59 pg/mL.¹⁴ Another study (194 patients) found great persistence rates in patients whose final IOPTH was > 40 pg/mL and found no difference in persistence rates when they attempted to further stratify patients whose final IOPTH was < 40 pg/mL.⁷ The advent of recent literature suggesting the added benefit of a decrease in IOPTH levels to ≤ 40 pg/mL prompted the question of potential added utility of even further reductions. Our study adds to other studies by evaluating the largest patient population to date addressing this question, which allows for more detailed categorization of IOPTH levels. We compared persistence rates in patients whose lowest IOPTH levels decreased to between 40 and 21 pg/mL and those with levels ≤20 pg/mL and found no significant difference in persistence rates, indicating that there is no added benefit to achieving IOPTH levels < 20 pg/mL with regard to decreasing persistence rates after PTX. This finding is important because attempts to push IOPTH lower and lower to achieve the ultimate prediction of cure introduces a potential risk of rendering patients hypoparathyroid attributable to overzealous, unnecessary resection of other parathyroid glands in the majority of these patients.

This study has several limitations. The study analysis was performed retrospectively from data collected at a single tertiary center and is therefore, subject to potential referral bias. Because of a lack of long-term follow-up and low incidence rates, this study is not adequately powered to comment on rates of postoperative permanent hypoparathyroidism. In addition, not all patients have postoperative PTH data, which would define more accurately whether postoperative hypercalcemia or hypocalcemia is directly related to persistent hyperparathyroidism or hypoparathyroidism, respectively. Prospective postimplementation studies are also needed to determine whether implementing stricter criteria of a final IOPTH level ≤ 40 pg/mL would lead to increased operative time and unnecessary exploratory or multigland procedures without any meaningful decrease in persistence of hyperparathyroidism or increasing rates of hypoparathyroidism. Finally, no criteria should supplant a skilled surgeon’s judgment. IOPTH level should always be considered within the context of the baseline or pre-excision PTH level and with the morphologic appearance of the parathyroid glands noted during the PTX. These criteria are meant to guide operative decision-making and improve surgeons’ ability to predict postoperative persistent disease, using a singular criterion of <40 pg/mL in conjunction with traditional IOPTH criteria.

This study shows that a postexcision IOPTH <40 pg/mL is associated with the least rate of persistent hypercalcemia after PTX for primary hyperparathyroidism. This finding holds true regardless of whether a 50% decrease in IOPTH from the baseline level is achieved and is applicable to the challenging subset of patients with low baseline IOPTH levels < 100 pg/mL or normo-hormonal primary hyperparathyroidism. Our criteria are meant to streamline operative decision-making, and our analysis indicates that,

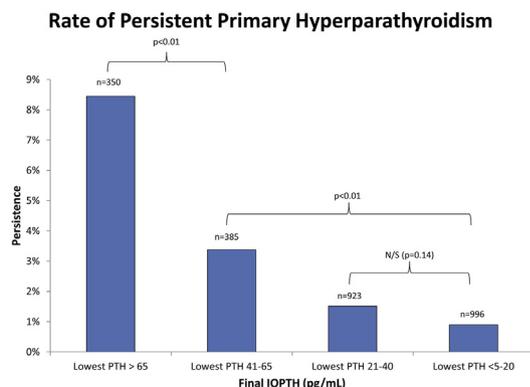


Figure. Rates of persistent primary hyperparathyroidism grouped by lowest IOPTH.

regardless of the time of IOPTH draw after parathyroid excision, an IOPTH below 40 pg/mL is associated with lesser rates of persistent disease than traditional criteria and can be used to terminate parathyroid exploration with the lowest risk of persistent hyperparathyroidism.

Conflict of interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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