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Justified follow-up: A final ioPTH over 40 pg/mL is associated with an increased risk of persistence and recurrence in primary hyperparathyroidism

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Abstract

Introduction—After parathyroidectomy for sporadic primary hyperparathyroidism (PHPT), overall rates of persistence/recurrence are extremely low. A marker of increased risk for persistence/recurrence is needed. We hypothesized that final intraoperative parathyroid hormone (FioPTH) 40 pg/mL is indicative of increased risk for disease persistence/recurrence, and can be used to selectively determine degree of follow up.

Method—A retrospective review of PHPT patients undergoing parathyroidectomy with ioPTH monitoring was performed. An ioPTH decline of 50% was the only criteria for operation termination. Patients were grouped based on FioPTH of <40pg/mL, 40 to 59, and >60.

Results—Between 2001 and 2012, 1371 patients were included. Mean age was 61±0.4 years. 78% were female. Overall persistence rate was 1.4%, with 2.9% recurrence rate. 976 (71%) had FioPTH<40, 228 (16.6%) had FioPTH 40-59, and 167 (12.2%) had FioPTH ≥ 60. Mean follow-up was 21±0.6 months.

FioPTH<40 were younger, with lower preoperative serum calcium, PTH and creatinine (all p < 0.001). FioPTH<40 had the lowest persistence rate (0.2%) versus FioPTH 40-59 (3.5%) or FioPTH ≥ 60 (5.4%, p<0.001). Recurrence rate was also lowest in FioPTH<40 (1.3% vs. 5.9% vs. 8.2% respectively, p<0.001). Disease free status was greatest in FioPTH<40 at 2 years (98.5% vs. 96.8% vs. 90.5%) and 5 years (95.7% vs. 72.3% vs. 74.8%, p<0.01).

Conclusion—Patients with FioPTH<40 pg/mL had lower rates of persistence and recurrence, than FioPTH 40-59, or ≥ 60. Differences became more apparent after 2 years of follow-up. Patients with FioPTH ≥ 40 pg/mL warrant close and prolonged follow-up.

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Keywords

Intraoperative parathyroid hormone monitoring; minimally invasive parathyroidectomy; primary hyperparathyroidism; persistence; recurrence; final intraoperative parathyroid hormone level

Introduction

Primary hyperparathyroidism (PHPT) is a common endocrinopathy, and is only cured with surgical excision of the offending parathyroid gland(s)¹. With the advent of preoperative parathyroid localization studies, the use of intraoperative parathyroid hormone (ioPTH) monitoring, and radioguided parathyroidectomy (RPG), the surgical management of PHPT has largely moved to minimally invasive parathyroidectomy²⁻⁴. While preoperative imaging provides the surgeon with information regarding where to start the operation, RPG can provide immediate confirmation of parathyroid tissue resection, and ioPTH provides information regarding residual hyper-functioning parathyroid tissue⁵.

Protocols regarding timing of ioPTH draws and criteria to indicate termination of the operation vary slightly from institution to institution, however most focus on a decline of fifty percent or greater from baseline, after the excision of the diseased gland(s), and most require multiple post-excision values of ioPTH to be sent⁶⁻⁹. Additional stipulations required by some authors include falling into normal range for PTH within the assay specific criteria¹⁰⁻¹². Mild increases in ioPTH values (rebounding) even after initial decline criteria have been met may also be indicative of additional hyperfunctioning glands¹³. Nearly all of these nuances regarding interpretation of ioPTH values focus on directly altering what is done in the operating room to minimize the risk of persistent disease. But as the rate of disease persistence is generally <5% regardless of the specific protocol used, might some of these subtleties be better markers of which patients are more likely to persist or recur, and therefore require closer, and possibly, more frequent follow up.

Heller et al initially evaluated final ioPTH (FioPTH) levels with regards to persistent elevation of parathyroid hormone after surgery and risk of disease persistence¹⁴. These conclusions were based off a small sample size with a median follow up of only 5 months, and stratified patients based on FioPTH values leading up to 40 pg/mL, with all patients with a FioPTH > 40 pg/mL grouped together. The conclusions from this study were not widely adapted as the FioPTH > 40 group included all patients who did not fall into a normal range of PTH values. We sought to further explore the concept of FioPTH value as a prognostic tool after parathyroid surgery, with stratification of patients with elevated FioPTH values which fell into normal range and those that did not. We hypothesized that a FioPTH of 40 to 59 pg/mL, as well as a FioPTH of > 60 pg/mL, were markers of increased risk of disease persistence and recurrence.

Methods

After approval by the IRB, a retrospective review of a prospective parathyroid surgery database at an academic endocrine surgery practice was performed. Patients with a diagnosis of PHPT undergoing initial operative management were included. Patients with positive

family history for PHPT, previous parathyroid surgery, concomitant thyroid surgery, or less than 6 month follow up were excluded.

Unilateral exploration was performed if preoperative imaging studies upon review by the surgeon suggested a single adenoma. Bilateral neck exploration was performed when patients did not localize on preoperative imaging, had discordant imaging results, or on cases with less than 50% ioPTH decline after 1st adenoma resection. Blood samples for ioPTH monitoring were drawn from a peripheral IV after induction but before incision to establish a baseline level and again at 5, 10 and 15 minutes following the excision of the enlarged gland. If the 5th minute post excisional sample value was above the baseline level, it would be considered as the baseline and 2 successive blood samples were drawn in 5 minutes intervals⁹. Additional samples were drawn at the discretion of the surgeon. Internal jugular vein sampling was reserved for patients with no reliable peripheral access. A decline of more than 50% from the baseline at any time points described above signified adequate resection and prompted termination of the operation⁹.

Patients were divided into 3 groups based on their FioPTH levels: <40pg/mL, 40 to 59 pg/mL, and 60 pg/mL or higher. Serum PTH and calcium levels were routinely checked at the time of post-operative visit 1 to 2 weeks after surgery, and again at 6 months following surgery.

Disease persistence was defined as hypercalcemia (>10.2 mg/dL) occurring within 6 months of surgery. Recurrence was hypercalcemia occurring beyond 6 months post op. Normocalcemia (≤ 10.2mg/dL) at 6 month follow up defined cured. A PTH of 60 pg/mL was considered as the upper limit of normal serum PTH range to account for the various reference ranges for different laboratory assays⁷.

Statistical analysis was performed by using IBM SPSS Statistics, version 21 (Armonk, NY, USA). ANOVA and Kruskal- Wallis were used to compare continuous variables. Categorical variables were compared using chi-square. The number of patients need to treat (NNT) in order to prevent one disease persistence or recurrence were calculated to determine if FioPTH should alter operative management on the day of surgery. Estimated disease free duration analysis was determined using Kaplan- Meier curves, and compared using Mantel-Cox Log Rank. P-value ≤ 0.05 was deemed significant. Results are expressed as mean ± SEM, unless otherwise stated.

Results

1371 patients met inclusion criteria between March 2001 and December 2012. 1068 (77.9%) patients were female. Mean age was 61± 0.4 years. During this time period a majority of patients (66.4%) were managed with a unilateral exploration. The most common finding at time of surgery was single adenoma (77.6%) followed by hyperplasia (12%) and double adenoma (10.4%). The overall cure rate was 98.6%. During a mean follow up of 21± 0.6 month, 39 patients (2.9%) experienced disease recurrence.

976 patients (71.2%) had FioPTH level <40, 228 (16.6%) between 40 and 59 and 167 (12.2%) had FioPTH ≥ 60 (Table 1). Gender distribution was similar among groups (p=

0.15). Patients with FioPTH 40 to 59 and 60 were older than patients with a FioPTH<40, and had higher preoperative serum calcium, PTH and creatinine levels (all $p < 0.001$). Pre-operative vitamin D level was similar among groups ($p = 0.36$).

Rates of bilateral exploration were similar regardless of FioPTH grouping ($p = 0.24$, Table 2). 18.8% of the study cohort had additional ioPTH samples sent after 15 minutes post excision. Patients with higher FioPTH had additional ioPTH samples sent during parathyroidectomy ($p < 0.001$). Serum calcium levels at time of post-operative visit were equivalent ($p = 0.14$); however serum post-operative PTH values were notably higher in patients with higher FioPTH ($p < 0.001$). This trend continued to through to the last measured PTH in follow up ($p < 0.001$).

The highest cure rate following parathyroidectomy (99.8%) was inpatients with FioPTH<40 ($p < 0.001$, Table 3). After 21 ± 0.6 months of follow up, 1.3% of patients with FioPTH<40 ($n=13$) experienced disease recurrence which was the lowest recurrence rate ($p < 0.001$). Cure rate in FioPTH 40 to 59 was 96.5%. 22 ± 0.7 months of follow up revealed recurrent hyperparathyroidism in 5.9% ($n=13$) of FioPTH 40 to 59. About 95% of patients with FioPTH 60 were cured after parathyroidectomy. Recurrence rate was 8.2% ($n=13$) after 20 ± 1.7 months of follow up in FioPTH 60 cases.

For patients with FioPTH 40 to 59, more extensive parathyroidectomy would be performed on 30 patients to prevent one persistence, or 22 patients to prevent one recurrence. In those patients with a FioPTH 60 the NNT to prevent one persistence was 19 patients, and for recurrence was 15 patients.

Estimated disease free rate for the overall study population at 1 year after parathyroidectomy was 98.6%. The disease free rates at 2 and 5 years after parathyroidectomy were 97.2% and 89.6%. The difference in disease free status between FioPTH<40 and FioPTH 40 was minimal at 1 year follow up, but it became more marked after 2 and 5 years of follow up (Figure 1). The highest disease free rates were detected in patients with FioPTH<40 (99.5% at 1 year, 98.5% at 2 years, 95.7% at 5 years, $p < 0.001$, Table 4). Disease freerates were similar in patients with FioPTH 40 to 59, and FioPTH 60.

Discussion

Current practice in parathyroid surgery regarding the use of intraoperative parathyroid hormone (ioPTH) monitoring focuses the direct influence of ioPTH monitoring on intraoperative decision making^{5,7}. However, ioPTH values can also provide the surgeon and clinician with valuable information regarding patient prognosis and need for further follow-up. These data presented here demonstrate how FioPTH can be a marker for increased risk for disease persistence and recurrence in patients undergoing parathyroidectomy for PHPT. Patients with a FioPTH 40 experienced higher rates of disease persistence and recurrence after parathyroidectomy. This high rate of persistence and recurrence occurred even if the FioPTH fell within normal range but was still 40 or higher. Most patients (72%) experienced a drop in FioPTH to less than 40 pg/mL, but a disproportionately high number of patients with FioPTH 40 accounted for all cases of persistent (69%) and recurrent (89%) disease.

In the initial study by Heller et al, 194 patients were stratified by FioPTH in 10 pg/mL intervals up to 40 pg/mL, with all patients with a FioPTH $\geq$ 40 pg/mL made up the final comparison group.¹⁴ Patients with FioPTH $\geq$ 40 were more likely to have both persistent PTH elevation as well as persistent PHPT, similar to our findings. However due to the limited follow up, no conclusions could be made regarding disease recurrence and even disease persistence may be higher than reported as only 80% of patients had 3 month follow up. As this study was based on FioPTH levels drawn at 20 minutes post excision, they may represent slightly different PTH kinetics than those of this study, as our protocol generally stopped at the 15 minute value.

Although Heller et al first proposed the use of FioPTH, Wharry et al further explored the concept in a larger group of patients with a longer follow up.^{14,15} In efforts to determine the need for FioPTH to fall into a normal PTH range, patients were categorized as upper normal FioPTH (41 to 65 pg/mL) or elevated FioPTH (>65 pg/mL). They evaluated 1108 individuals with a mean follow up of 1.8 years, and found that patients with upper normal FioPTH have similar rates of persistence, but higher recurrence rates comparing to those with FioPTH $\leq$ 40 pg/mL¹⁵. However, Wharry et al found that only patients with elevated FioPTH (>65 pg/mL) experienced higher rates of disease persistence and recurrence. This is in contrast to the results presented here which demonstrated a stepwise increased in both disease persistence and recurrence in patients with FioPTH 40 to 59 and FioPTH $\geq$ 60, when compared to patients with FioPTH <40 . Our findings are based on a larger patient population, but with similar duration of follow up.

Previous authors suggested that an ioPTH decline $\geq$ 50% and falling into normal limit is the optimal method of ioPTH monitoring^{10-12,16}. Although this describes a more restricted criterion for ioPTH monitoring, studies have not assessed number of patients who would undergo unnecessary additional surgery by practicing this criterion. In the presented study, the number of patients who would undergo more extensive parathyroid resection if FioPTH dictated intraoperative decision making is addressed (Table 3). More extensive parathyroid resection in patients with PHPT has been previously demonstrated to result in increased rates of post-operative transient hypocalcemia and permanent hypoparathyroidism¹⁷. This must be balanced with the risks of disease persistence and recurrence. Additional data suggests normalization of PTH in the post-operative period results in a more rapid improvement in symptomology¹⁸. Exposing a considerable number of patients to bilateral exploration to minimize disease persistence and/or recurrence may not be a proper strategy to manage PHPT. Rather, a more effective strategy involves identifying those patients as individuals in need of close follow up to ensure timely diagnosis and intervention of disease persistence and/or recurrence¹⁹.

Rates of disease persistence and recurrence were comparable between FioPTH 40 to 59 and FioPTH $\geq$ 60. In contrast to previous published studies which recommend ioPTH decline to normal range to minimize disease persistence and recurrence, these data presented above suggest that FioPTH decline into normal range may not reduce risk of persistence and/or recurrence unless it drops to <40 pg/mL¹⁰⁻¹². In addition, the noted differences between disease free intervals did not become evident until roughly 2 years of follow-up, with continued divergence out at 5 years. This supports ongoing, active surveillance in these

patients who are at increased risk, well beyond the 6 month mark often used by many surgeons.

Patients with FioPTH<40 were younger and had lower pre-operative serum calcium, PTH and creatinine levels and post-operative PTH level. Conversely, patients with higher FioPTHs were notably older, and with higher serum creatinine levels. Previous studies discussed the controversial aspects of age, and glomerular filtration rate (GFR), and their respective influences on ioPTH decline in patients with PHPT^{20,21}. Although FioPTH decline to <40 pg/mL may be multi-factorial, younger age and more efficient renal function may play a role. The kinetics of ioPTH, as well as PTH level measured at the post-operative visit, are also influenced by pre-operative vitamin D levels^{22,23}. Patients with vitamin D deficiency have less of a decline in ioPTH at 5 minutes post-excision, and higher post-operative PTH level. Vitamin D deficiency may result in persistent PTH elevation with normocalcemia after parathyroidectomy, which may be prevented or resolved by vitamin D supplementation^{24,25}. Within our study population, vitamin D levels were not differing based on the FioPTH group suggesting vitamin D deficiency is not the sole contributor to FioPTH elevation.

This study was a retrospective review of a prospective database, and thus has inherent limitations. While a majority of patients had FioPTH levels representing 15 minute post-excision values, nearly 20% had FioPTH drawn beyond that, or after additional glands were excised. As the initial description by Heller was using a 20 minute sample, addition decline may occur if 20 minute values are measured almost 20% of patients had their FioPTH taken after 15 minutes following gland excision. Comparison of their FioPTH level with the FioPTH of the rest of the study population may not be accurate. About 37% of the study population didn't have pre-operative vitamin D evaluation which may affect this comparison across FioPTH levels. Disease free survival was estimated at the end of 2nd and 5th follow-up years which may have some discrepancies with the actual disease free rates if all patients had follow-up through those time points.

After parathyroidectomy for PHPT, patients with FioPTH 40 pg/ml have a greater risk of disease persistence and/or recurrence than patients with FioPTH<40pg/mL. Patients with a FioPTH 40pg/mL experienced lower disease free status after 2 and 5 years of follow up. These findings do not necessarily support more extensive parathyroidectomy due to the high number of patients need to treat in order to prevent a single episode of persistence and/or recurrence. Instead, we propose FioPTH as a marker of patients at increased risk of disease persistence and/or recurrence, which justifies closer, and more frequent, follow up.

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Synopsis

IoPTH monitoring during parathyroidectomy focuses on rates of decline in addition to absolute values, however the final or last ioPTH levels is often overlooked if criteria for termination of surgery have been met. We found a final ioPTH (FioPTH) level of 40 pg/mL or higher was indicative of higher rates of both disease persistence and recurrence. Due to high numbers needed to treat if operative intervention was to be modified, we instead purpose using FioPTH as a marker for patients in need of closer and more frequent follow-up.

Figure 1. Disease free status based on FioPTH levels

Table 1

Patients demographics and lab values

	FioPTH < 40 pg/mL	FioPTH= 40-59 pg/mL	FioPTH 60 pg/mL	P- value
Number	976 (71.2%)	228 (16.6%)	167 (12.2%)	
Age (years)	60± 0.5	64± 1	64± 1.1	<0.001
Female Gender	772 (79.1%)	175 (76.8%)	121 (72.5%)	0.15
Pre-operative	Calcium (mg/dL)	10.9 ± 0.02	11.3 ± 0.1	0.001
	PTH (pg/mL)	102 ± 2	219 ± 15	< 0.001
	Creatinine (mg/dL)	0.98 ± 0.02	1.21 ± 0.08	< 0.001
	Vitamin D (ng/mL)	31± 0.6	29± 1.4	0.34

FioPTH, final intraoperative parathyroid hormone; PTH, parathyroid hormone; Data expressed as mean ± SEM.

Table 2
Intra-operative findings and immediate post-operative lab results

	FioPTH < 40 pg/mL	FioPTH = 40-59 pg/mL	FioPTH ≥ 60 pg/mL	P- value
Number				
Bilateral Exploration N (%)	976 (71.2%)	228 (16.6%)	167 (12.2%)	
	329 (34%)	84 (37%)	48 (30%)	0.24
Etiology N (%)	Adenoma	169 (74%)	139 (83%)	0.2
	Double Adenoma	31 (14%)	13 (8%)	
	Hyperplasia	28 (12%)	15 (9%)	
Patients with Additional Samples after 15 minutes N (%)	141 (14%)	58 (25%)	59 (35%)	<0.001
Post-operative Labs	Calcium (mg/dL)	9.4 ± 0.04	9.4 ± 0.05	0.14
	PTH (pg/mL)	41 ± 1	71 ± 4	<0.001

FioPTH, final intraoperative parathyroid hormone; PTH, parathyroid hormone; Data expressed as mean ± SEM.

Table 3

Operation outcome

		FioPTH < 40 pg/mL	FioPTH= 40-59 pg/mL	FioPTH 60 pg/mL	P- value
6 month Outcome	Number	976 (71.2%)	228 (16.6%)	167 (12.2%)	
	Cure	974 (99.8%)	220 (96.5%)	158 (94.6%)	
	Persistence	2 (0.2%)	8 (3.5%)	9 (5.4%)	<0.001
	NNT-Per		30	19	
Recurrence		13 (1.3%)	13 (5.9%)	13 (8.2%)	
	NNT-Rec.		22	15	<0.001
Follow up (months)		22± 0.7	20± 1.4	20± 1.7	0.55
Most recent follow up	Calcium (mg/dL)	9.3 ± 0.02	9.5 ± 0.04	9.4 ± 0.1	0.02
	PTH (pg/mL)	42 ± 1	66 ± 9	77 ± 7	<0.001

FioPTH, final intraoperative parathyroid hormone; NNT-Per, number needed to treat to prevent one persistence; NNT-Rec, number needed to treat to prevent one recurrence; Data expressed as mean ± SEM.

Table 4**Estimated disease free status**

Disease Free Status		FioPTH < 40 pg/mL	FioPTH= 40-59 pg/mL	FioPTH 60 pg/mL	P- value
	1 year	99.5%	96.8%	96.3%	<0.001
	2 years	98.5%	96.8%	90.5%	
	5 years	95.7%	72.3%	74.8%	

FioPTH- final intraoperative parathyroid hormone