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Five Minute Intraoperative Parathyroid Hormone Levels Can Identify Multigland Disease

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Abstract

Introduction—Intraoperative parathyroid hormone (IOPH) monitoring is crucial in the treatment of primary hyperparathyroidism (PHPT). Often, the 5 minute IOPH levels fall, but not by the requisite 50%. In such cases, the surgeon must decide whether to wait for additional levels or continue exploration. This study aimed to evaluate the 5 minute drop in IOPH for distinguishing single adenomas (SA) from multigland disease.

Methodology—A retrospective analysis of a prospectively collected database was performed on PHPT patients who underwent initial curative parathyroidectomy between 2001 and 2013. Those with familial disease, those taking lithium, or undergoing concomitant thyroidectomy were excluded. In double adenomas (DA) or hyperplasia (HA) cases, the IOPH values indicating additional glands were analyzed.

Results—1021 patients met inclusion criteria; 817 patients (82.2%) with SA, 99 (10.0%) with DA, and 78 (7.9%) with HA. SA patients exhibited $56.6 \pm 4.9\%$ decline in IOPH at 5 minutes compared to $21.3 \pm 4.5\%$ in DA and $22.5 \pm 4.3\%$ in the HA group ($p < 0.01$). Post hoc comparisons revealed that the 5 minute decrease in the SA group was significantly greater than either the DA or HA groups ($p < 0.01$). A 5 minute percentage decline of 35% best distinguished SA from multiglandular disease (85.3% vs. 24.9%).

Conclusion—These data suggest that when IOPH does not drop by at least 35% at 5 minutes post excision, the surgeon should consider further exploration rather than waiting for additional levels.

Keywords

Primary Hyperparathyroidism; Intraoperative Parathyroid Hormone; Multigland Disease

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Introduction

Parathyroidectomy is the only long-term curative therapy for primary hyperparathyroidism (PHPT) (1), with a success rate of at least 95%, if performed by an experienced surgeon (2). Since SA is the cause in up to 85% of cases of PHPT, surgeons can target a single gland for excision with a focused, or minimally invasive surgery (1, 2). Minimally invasive parathyroidectomy (MIP) relies on careful preoperative radiologic work-up to identify the location of the solitary parathyroid adenoma, and on intraoperative parathyroid hormone (IOPTH) monitoring (1–3).

A decrease in IOPTH level by at least 50% from baseline is generally considered to indicate successful surgery (4), although much debate surrounds the exact IOPTH algorithm used (5). This test often takes up to 30 minutes, which prolongs the operating time, especially in cases in which the level does not fall. Many experienced surgeons become impatient because they could perform a bilateral exploration during the time it took to get the PTH levels reported back, and it has been suggested that further operative exploration is more time efficient (6).

If the 5 minute IOPTH levels do not drop by 50%, the surgeon must either wait for more levels or continue exploration. In this study we hypothesize that the 5 minute IOPTH level alone can predict the presence of multiglandular disease. The aim of this study was to evaluate the early (5 minute) drop in IOPTH for distinguishing single adenomas (SA) from double adenomas (DA) and hyperplasia (HA).

Methods

A retrospective analysis of a prospectively collected database was performed on patients with PHPT who underwent initial parathyroidectomy at the University of Wisconsin Hospital between 2001 and 2013. Those with familial disease, secondary/tertiary disease, those taking lithium, patients who had previous parathyroidectomy surgery, or those undergoing concomitant thyroidectomy were excluded. Patients with at least 6 months of follow-up were included, and were divided into three groups according to the surgeon's final diagnosis: single adenoma (SA), double adenoma (DA), and hyperplasia (HA). In all cases of DA or HA, the initial IOPTH values indicating additional glands were analyzed.

An elevated post-operative serum calcium level > 10.2 mg/dL within 6 months of surgery was defined as a persistent disease while an elevated calcium after 6 months was defined as a recurrence. The baseline reading was defined as the pre-incision PTH level except for those patients who exhibited a five minute level above the pre-incision level due to manipulation of the gland.. In this case, the five minute PTH reading was considered as the baseline reading as we have previously reported (7). Thus, the higher of the preincision level or five minute level has been used as the baseline for all further calculations of slope or percentage decline in PTH.

Two comparisons have been included; the first one was between cured SA, DA, and HA; the second one was between the cured SA and the SA patients with persistence and/or recurrence. Patient data, preoperative calcium and PTH levels, the mean and the percentage of the IOPTH decline were compared between those groups. Comparisons between groups

were evaluated using ANOVA, Chi-squared test, Fisher's exact test, student t-test, and Wilcoxon Rank Sum tests where appropriate. Selected post-estimation comparisons were performed using the Bonferroni adjustment. Finally, sensitivity analysis was carried out to determine a threshold decline in IOPTH that identified multigland disease. All statistical calculations were completed using statistical software SAS version 9.2. (SAS Institute Inc, Cary, NC). A p-value of 0.05 was considered to represent statistical significance for all comparisons.

Results

In total, 1021 patients met inclusion criteria, and the success rate of parathyroidectomy was 97.3%. The median age was 61 and range between 18 to 91 years, and 79% were female. The median preoperative calcium level was 10.9 and ranged between 8.06 to 16.2 mg/dl, and the median of the preoperative PTH level was 98 and ranged between 35 to 2000 pg/ml. The overall number of failures (persistence and recurrence) PHPT together was 2.7%. The median follow up time was 14 months and ranged between 6–127 months.

817 patients (82%) had an SA, 99 patients (10%) with DA, and HA was found in 78 patients (8%). There were no differences between the groups in terms of age, gender, or creatinine. However, SA has a higher preoperative calcium and PTH levels 11.0 ± 0.88 mg/dl and 123.3 ± 10.0 pg/ml, respectively, compared with 10.7 ± 0.91 mg/dl and 105.5 ± 8.0 pg/ml for the DA group, and 10.7 ± 0.84 mg/dl and 99.1 ± 7.5 pg/ml for the HA group ($p < 0.01$, Table 1).

The rates of decline in IOPTH at five minutes post excision were 22.17 ± 1.09 vs. 5.08 ± 1.32 vs. 5.85 ± 1.33 pg/ml/min, for patients with SA, DA, or HA, respectively ($p < 0.01$). Patients with SA exhibited $56.6 \pm 4.9\%$ decline in IOPTH at five minutes compared to $21.3 \pm 4.5\%$ in DA and $22.5 \pm 4.3\%$ in the HA group ($p < 0.01$). Post hoc comparisons revealed that the five minute decrease in the SA group was significantly greater than either the DA or HA groups ($p < 0.01$), but there was no difference between the DA and HA groups ($p = 0.90$, Table 1, Figure 1). Sensitivity analysis revealed that a five minute percentage decline of 35% best distinguished SA from DA and HA with a sensitivity of 84%, a specificity of 79%, a positive predictive value of 95%, and a negative predictive value of 52%. 85.3% of SA achieved a 35% decline in IOPTH at five minutes while only 24.9% of those multigland disease met this threshold ($p < 0.01$, Figure 2). In our cohort, there were 120 patients (12%) who would have gone onto bilateral exploration using the 35% at 5 minute rule that ultimately only had a single adenoma.

SA Subset Analysis

In the SA group, recurrence or persistence was identified in 27 patients (2.7%). Within the SA group, we compared those cured to those with recurrence or persistence, and we found that there were no differences in terms of age, gender, and preoperative calcium. However, SA (cured) has a higher preoperative PTH level, 123.3 ± 10.0 pg/ml vs. 115 ± 11.0 pg/ml for the SA (recurrence or persistence) ($p < 0.01$). Moreover, by comparing the percentage decrease in IOPTH at five minutes, the cured group dropped by 56.6%, whereas those with recurrence or persistence dropped by 43% ($p = 0.01$, Table 2).

Discussion

Our data suggest that the percentage of decline in IOPTH at 5 minutes post excision was higher among the cured SA group compared to those with multigland disease, but there was no difference between the DA and HA groups. Moreover, the percentage decline in IOPTH at 5 minutes post excision was higher among the cured SA group compared with recurrence/persistence SA group. Finally, a 5 minute percentage decline of 35% best distinguished SA from multigland disease.

Therefore, the use of early IOPTH levels can identify multigland disease. Here, we attempt to provide guidance when the initial five minute level drops from the baseline, but does not meet the 50% threshold. Should the surgeon wait for the next level, or simply undertake further exploration? When IOPTH does not drop by at least 35% at 5 minutes post excision, the surgeon should consider further exploration rather than waiting for additional levels. This information enables the surgeon to utilize operative time in the most efficient manner.

The literature clearly demonstrates the important role of at least 50% drop of the baseline PTH level within 10–20 minutes after excision of an abnormal gland in predicting a curative result (8, 9, 10, 11). If IOPTH fails to drop by at least 50%, the surgeon must consider multiglandular disease and undertake additional exploration (12). However, some controversy exists surrounding IOPTH's role in multiglandular disease, specifically double adenoma cases (13, 14). From one view, Stratmann et al. demonstrated the reliability and the accuracy of the IOPTH assay in multiglandular parathyroid disease (15, 16). Similarly, data from our group showed that IOPTH assay is sensitive for multigland disease detection, and allowed surgeons to recognize and resect additional hyperfunctioning parathyroids intraoperatively which improved cure rates in patients undergoing MIP (10, 17). Here we have refined this even further to show that the five minute IOPTH data can identify multigland disease.

Alternatively, Gauger et al showed that IOPTH assay was unsuccessful in detection of multiglandular disease, specifically double adenomas (18). Moreover, Hacıyanlı et al found that the IOPTH assay was incorrect in 57% of the patients with double adenoma; but the accuracy of double adenoma detection increased up to 80% if IOPTH has been used together with preoperative US, and sestamibi scan (19). Similarly, Gill et al found that the accuracy of multiglandular disease increased when the sestamibi combined with the IOPTH (20). Moreover, Weber et al and Miller et al found that the “50% rule” have missed a multiglandular disease in 20%, and 25% of their patients respectively (21, 22). The data presented here only evaluated the usefulness of the 5 minutes IOPT drop to predict the likelihood of additional hyperfunctioning parathyroid glands during parathyroidectomy. However, this is not intended to replace the overall accuracy of the IOPTH assay in determining operative cure. Rather, percentage decline at five minutes is useful in determining whether to wait for additional levels or continue exploration.

Karakousis et al studied the interpretation of the IOPTH levels in patients with PHPT due to multiglandular disease. They found that 29% of the patients in which their 10–15 min PTH levels decreased by more than 50% after single gland excision, but the PTH levels failed to

normalize, had multiglandular disease. Those patients had greater serum creatinine concentrations and a lower IOPTH compared with patients with single adenomas. Thus, they concluded that >50% decrease in IOPTH levels for patients who undergo MIP may lead to an appreciable number of missed parathyroid adenomas or hyperplastic disease (23). In this study, we examined the utility of the five minute slope, not to definitively determine a cure, but rather, to help with intraoperative decision making. We found that 85.3% of SA achieved a 35% decline in IOPTH at 5 minutes compared 24.9% of those multigland disease. In addition, in our study there was no difference between the SA group, DA, and HA groups in form of preoperative creatinine, but we did not calculate the glomerular filtration rate (GFR).

While we found that a 5 minute percentage decline of 35% best distinguished SA from multiglandular disease, Kandil et al, specifically studied the utility of IOPTH monitoring for PHPT patients due DA. They found that the mean percentage of decrease in the 10 minutes IOPTH levels was 43.6% after removing the first gland. However, the mean percentage of decrease in the 10 minutes IOPTH levels was 79.7% after removing the second gland. They report a cure rate of 98%. Therefore, they conclude that IOPTH monitoring can accurately predict the success of parathyroidectomy in 98% of patients with DA (24).

While outpatient parathyroidectomy have significantly reduced the cost of parathyroidectomy, the cost reduction is mainly due to lowering the turnover times which reduces OR staffing, and increase OR utilization for hospitals (25–27). In fact, it has been estimated that the cost of a single OR to a patient or health insurance provider is approximately \$20 per minute (28). If the 5 minute PTH level did not drop the surgeon should wait for the 10 minutes level and if it is also still high will indicate a bilateral exploration which will take another 30–60 minutes. Waiting for IOPTH may increase the operative (OR) time. Therefore, using the 5 minute IOPTH data can potentially reduce operative times and save healthcare dollars may save the surgeon a waiting time of 5–10 minutes which is the time the surgeon need to wait to get the extra IOPTH level.

However, despite our findings, our data should be interpreted cautiously as there were limitations. This study is a retrospective study, and the data originates from a single, high volume university hospital could limit its generalizability. Importantly, the differences in GFR that might account for PTH clearance was not considered in this study. Moreover, PTH half-life has been reported to be vary substantially (30). In addition, if the surgeon uses the 35% cutoff then 25% of multigland disease will be missed, so the surgeon's judgement still plays an important role. The five minute decline becomes another adjunct the surgeon can utilize in the complex decision of whether to pursue a bilateral exploration. Therefore, future studies of specific patient subsets can further elucidate the utility of the five minute levels.

Conclusion

These data suggest that the use of early IOPTH levels can predict the likelihood of additional hyperfunctioning parathyroid glands during parathyroidectomy. When IOPTH does not drop by at 35% at 5 minutes post excision, the surgeon should consider further exploration rather than waiting for additional levels. This simple intraoperative tool may be used to guide the decision of whether to wait for IOPTH results or to proceed with further neck exploration.

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Synopsis

When Intraoperative parathyroid hormone (IOPH) does not drop by at least 35% at 5 minutes post excision, the surgeon should consider further exploration rather than waiting for additional levels.

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Figure 1.
Percentage of Five Minutes Drop in IOPTH SA (Cured) vs DA and HA.

Figure 2.
Percentage of SA and Multigland Disease Cases Meeting the 35% Threshold at Five Minutes

Table 1

Demographic Data

	SA (Cured)	DA	HA	p value
n (%)	817 (82%)	99 (10.0%)	78 (8%)	-
Age (year)	61 ± 13	62 ± 12	63 ± 13	0.37
Female	651 (79.7%)	76 (76.8%)	66 (84.6%)	0.58
Preoperative Calcium (mg/dl)	11.0 ± 0.88	10.7 ± 0.91	10.7 ± 0.84	<0.01
Preoperative PTH (pg/ml)	123.3 ± 10.0	105.5 ± 8.0	99.1 ± 7.5	<0.01
Preoperative creatinine (mg/dl)	1.00 ± 0.7	0.98 ± 0.3	1.00 ± 0.6	0.862
Five minute slope (pg/ml/5min)	-22.17 ± 1.09	-5.08 ± 1.32	-5.85 ± 1.33	<0.01
• SA vs. DA	-22.17 ± 1.09	-5.08 ± 1.32		<0.01
• SA vs. HA	-22.17 ± 1.09		-5.85 ± 1.33	<0.01
• DA vs. HA		-5.08 ± 1.32	-5.85 ± 1.33	0.72
Five minute % drop (pg/ml/5min)	56.6 ± 4.9%	21.3 ± 4.5%	22.5 ± 4.3%	<0.01
• SA vs. DA	56.6 ± 4.9%	21.3 ± 4.5%		<0.01
• SA vs. HA	56.6 ± 4.9%		22.5 ± 4.3%	<0.01
• DA vs. HA		21.3 ± 4.5%	22.5 ± 4.3%	0.90

Table 2

Single Adenomas

	SA (Cured)	SA (Recurrence/Persistence)	p value
n (%)	817 (96.8%)	27 (3.2%)	-
Age	61 ± 13	62 ± 14	0.76
Female	651 (79.7%)	22 (81.5%)	1.00
Preoperative Calcium (mg/dl)	11.0 ± 0.88	11.0 ± 0.71	1.00
Preoperative PTH (pg/ml)	123.3 ± 10.0	115 ± 11.0	<0.01
Five minute % drop	56.6 ± 4.9%	43.0 ± 4.9%	<0.01