Relation of Final Intraoperative Parathyroid Hormone Level and Outcome Following Parathyroidectomy

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Objective: To determine if final intraoperative parathyroid hormone (IOPTH) level predicts those at risk for recurrence after parathyroidectomy. Minimally invasive parathyroid exploration guided by preoperative imaging and IOPTH level is an accepted alternative to bilateral exploration for the treatment of primary hyperparathyroidism (HPT). However, additional enlarged, hypercellular parathyroid glands are present in some patients in whom IOPTH levels fall to normal after excision of a single adenoma. At least 15% of patients are normocalcemic with elevated PTH levels (PPTH) after parathyroidectomy. In these patients, a higher risk of recurrent HPT has been found.

Design: Retrospective review of medical records.

Setting: University teaching hospital.

Patients: The records of all 194 patients who underwent successful initial parathyroidectomy for nonfamilial HPT in 2007 and 2008 by 1 surgeon were reviewed.

Main Outcome Measures: Intraoperative PTH level was measured prior to incision (baseline); at excision of the abnormal gland; at 5, 10, 15, and 20 minutes after excision; and at various additional times as needed. Of the patients, 71% underwent minimally invasive parathyroid exploration. Calcium, PTH, and 25-hydroxyvitamin D levels were measured during the first month after surgery in all patients and after 3 months or more in 80%. Patients were divided into 5 groups depending on the following final IOPTH levels: lower than 10 pg/mL (group 1) (to convert PTH to nanograms per liter, multiply by 1.0); 10 to 19 pg/mL (group 2); 20 to 29 pg/mL (group 3); 30 to 39 pg/mL (group 4); and 40 pg/mL or higher (group 5).

Results: Of the patients, 82% had a single adenoma, 9% had double adenomas, and 9% had 3 or more abnormal glands. The final IOPTH/baseline IOPTH value in groups 1 to 5 was 7%, 11%, 16%, 23%, and 26%, respectively. There was no significant difference in the preoperative calcium among the groups. All 3 patients with persistent HPT and 5 patients with PPTH were in group 5. One of the 96 patients in groups 1 and 2 and 5 of the 72 patients in groups 3 and 4 had PPTH at the last evaluation.

Conclusion: Patients with a final IOPTH level of 40 pg/mL or higher are at higher risk of having persistent HPT and should be followed up closely and indefinitely following parathyroidectomy.


MINIMALLY INVASIVE parathyroidectomy (MIP) is gaining increasing acceptance as the preferred operation for nonfamilial primary hyperparathyroidism (HPT).1 Minimally invasive parathyroidectomy is based on the concept that most patients with HPT have a single adenoma, that the location of this adenoma can be determined by preoperative imaging studies, and that the failure of intraoperative parathyroid hormone (IOPTH) level to decrease sufficiently following removal of a single enlarged parathyroid gland identifies all patients with additional hyperfunctioning parathyroids not detected by these imaging studies. Cure rates following MIP are similar to those achieved by conventional bilateral exploration and exceed 95%.2-5 Preoperative imaging is usually performed using Tc 99m Sestamibi scans and/or ultrasonography.6 A decrease of IOPTH level by at least 50% from baseline is generally considered to indicate successful surgery.7 Several studies have questioned this approach because enlarged, hypercellular parathyroid glands were found in some patients whose IOPTH level decrease met the criteria for successful surgery.8-12 In addition, persistently elevated parathyroid hormone (PTH) levels have been detected.
postoperatively in patients whose calcium level has returned to normal (PPTH) following parathyroidectomy. In some of these patients, the presence of PPTH has predicted persistent or recurrent HPT.13-18

This study was undertaken to determine if the final value of IOPTH measured at the conclusion of surgery, rather than the percentage decrease in IOPTH level, could detect those patients at risk for persistent or recurrent HPT.

METHODS

The medical records of all patients who underwent surgery for primary HPT at NYU Langone Medical Center, New York, New York, by the senior author (K.S.H.) from January 1, 2007, through December 31, 2008, were reviewed. Two patients with multiple endocrine neoplasia type 1, 10 who had surgery for recurrent or persistent HPT, and 1 in whom no abnormal parathyroids were identified were excluded from further analysis, leaving 194 patients for study inclusion.

Of the 194 patients, 189 had preoperative Tc 99m Sestamibi scans performed at many different imaging centers using different imaging protocols and 183 had undergone preoperative ultrasonography of the neck. In 157 patients this was performed by the operating surgeon.

Intraoperative PTH levels were measured in all patients using the Immulite 1000 immunoassay system (Siemens Healthcare Diagnostics, Deerfield, Illinois). Blood samples were drawn from an indwelling peripheral intravenous or radial arterial catheter. Samples were taken at the following times: baseline (before skin incision or induction of anesthesia); at the time of excision of the abnormal parathyroid, at 5, 10, 15, and 20 minutes after gland excision; and at variable intervals thereafter when necessary. In patients with more than 1 enlarged parathyroid gland, samples were generally drawn at 10-minute intervals after each gland was excised. A decrease in IOPTH level by 50% from baseline and into the normal range (<65 pg/mL) (to convert to nanograms per liter, multiply by 1.0) was considered to indicate successful removal of all hyperfunctioning parathyroid glands. Patients were divided into 5 groups depending on the following final IOPTH levels: lower than 10 pg/mL (group 1); 10 to 19 pg/mL (group 2); 20 to 29 pg/mL (group 3); 30 to 39 pg/mL (group 4); and 40 pg/mL or higher (group 5).

Patients whose imaging study findings suggested the presence of a solitary adenoma underwent an MIP in which the single enlarged parathyroid gland was removed. No additional exploration was performed if the decrease in IOPTH level met the aforementioned criteria. Conventional bilateral exploration was performed in patients whose imaging result was negative or suggested more than 1 abnormal parathyroid, in patients with a history of lithium therapy, in patients whose IOPTH level did not decrease adequately after removal of a single parathyroid gland, and in patients requiring total thyroidectomy for unrelated, coexisting thyroid pathologic abnormalities. All patients received oral calcium supplements (1000 mg/d) postoperatively. Most received vitamin D supplements as well. Preoperative and postoperative laboratory values were measured at NYU Langone Medical Center or by various commercial laboratories as dictated by the patients' health insurance plans. Calcium, PTH, and 25-hydroxyvitamin D levels were measured at the time of the patients' first postoperative visit and at varying time intervals thereafter. Follow-up ranged from 1 to 24 months (median, 5 months). All patients were evaluated at least once after discharge from the hospital, and 155 patients (80%) were reevaluated at least 3 months after surgery. Statistical analysis was performed using GraphPad InStat version 3.0a for Macintosh (GraphPad Software, San Diego, California). Contingency tables were analyzed by the Fisher exact test and comparisons of means by the Mann-Whitney test.

RESULTS

There were 136 women and 58 men ranging in age from 16 to 93 years old (median 60 years). The median age increased as the final IOPTH level increased (Table 1). Preoperative serum calcium levels ranged from 9.9 to 14.8 mg/dL (median, 10.9 mg/dL) (to convert to millimoles per liter, multiply by 0.25). There was no difference in the preoperative calcium in the 5 groups of patients (Table 1). The preoperative PTH level increased as the final IOPTH level increased. This pattern was maintained even when 4 patients with preoperative PTH levels higher than 500 pg/mL were excluded (Table 1). In 27 patients (14%), the highest preoperative serum calcium was 10.3 mg/dL or lower. In 22 (11%), the highest preoperative PTH level was in the normal range (≤65 pg/mL).

At initial exploration, 160 patients (82%) had a solitary parathyroid adenoma, 17 (9%) had double adenomas, and 17 (9%) had at least 3 hypercellular parathyroid glands. Of the 194 patients, 138 (71%) underwent MIP; 10 (5%), a unilateral exploration; and 30 (15%), a bilateral exploration. In an additional 15 patients (8%), the procedure was started as an MIP and converted to a bilateral exploration when the IOPTH level did not decrease adequately following the removal of a single enlarged parathyroid gland. In 1 patient, preoperative imaging identified the adenoma just below the submandibular gland. That adenoma was removed through an incision high in the neck.

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>No. of Patients</th>
<th>Median Age, y</th>
<th>Mean Preoperative Calcium, mg/dL</th>
<th>Mean Preoperative PTH, pg/mL</th>
<th>Mean Preoperative PTH, pg/mL a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>56</td>
<td>10.8</td>
<td>93</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>71</td>
<td>58</td>
<td>11</td>
<td>104</td>
<td>104</td>
</tr>
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<td>65</td>
<td>10.8</td>
<td>294</td>
<td>174</td>
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<tr>
<td>P value</td>
<td>.02</td>
<td>.36</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: PTH, parathyroid hormone.

SI conversion factors: To convert calcium to millimoles per liter, multiply by 0.25; PTH to nanograms per liter, multiply by 1.0.

a Four patients with preoperative PTH levels greater than 500 pg/mL were excluded.

Table 1. Characteristics of 194 Patients Who Underwent Successful Initial Parathyroidectomy for Nonfamilial Hyperparathyroidism.
In 131 of the 138 patients who underwent MIP (95%), the IOPTH level fell more than 50% and into the normal range within 10 minutes after excision of the adenoma. In the remaining 7 patients, the IOPTH level at excision was substantially higher than the baseline intraoperative PTH level. In all of these patients, IOPTH level decreased more than 50% from baseline by the end of the surgical procedure. The status of these patients at the last follow-up examination is summarized in Table 2. Three patients had elevated serum calcium and PTH levels and were considered to have persistent HPT. One was cured by a successful reoperation in which a second adenoma was identified and removed. The remaining 2 patients continue under observation. Twelve patients had PPTH with calcium levels of 9.6 mg/dL or higher and were considered to be at risk for developing overt HPT.

The relation of surgical outcome to final IOPTH level is summarized in Table 3. Of 22 patients in group 5 (final IOPTH ≥40 pg/mL), 8 (35%) had either PPTH with a calcium level of 9.6 mg/dL or higher or persistent HPT. In the remaining 168 patients with final IOPTH levels lower than 40 pg/mL, there were no patients with recurrent HPT and only 6 (4%) had PPTH with a calcium level of 9.6 mg/dL or higher. This difference was significant (P < .001). Although the mean final IOPTH/baseline IOPTH value increases as the final IOPTH level increases, in all 5 groups the fall in IOPTH level from baseline was well within the usual criteria predicting successful surgery. There was no difference in postoperative 25-hydroxyvitamin D levels among the 5 groups.

Using the standard criteria for successful MIP, we were not able to predict these surgical failures or potential failures. The mean (SD) IOPTH/baseline IOPTH value at 10 minutes was 0.35 (0.32) in patients with PPTH with a calcium level of 9.6 mg/dL or higher or persistent HPT compared with 0.30 (0.27) in the patients with normal calcium and PTH levels postoperatively. This difference was not significant (P = .20). If one does the same comparison using final IOPTH level rather than the 10-minute IOPTH level, the comparable fraction is 0.21 (0.12) compared with 0.14 (0.08). While this difference is statistically significant (P = .02), again, in both groups the percentage decrease from baseline satisfies the criteria for successful surgery.

### Table 2. Status of Patients at the Last Follow-up Examination

<table>
<thead>
<tr>
<th>Serum Calcium, mg/dL</th>
<th>No. of Patients</th>
<th>Patients With PTH &gt;65 pg/mL, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;9.6</td>
<td>73</td>
<td>11 (6)</td>
</tr>
<tr>
<td>9.6-10.3</td>
<td>108</td>
<td>12 (6)</td>
</tr>
<tr>
<td>≥10.3</td>
<td>13</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Total</td>
<td>194</td>
<td>26 (13)</td>
</tr>
</tbody>
</table>

Abbreviation: PTH, parathyroid hormone.

SI conversion factors: To convert calcium to millimoles per liter, multiply by 0.25; PTH to nanograms per liter, multiply by 1.0.

The use of accurate preoperative imaging and IOPTH measurement results in the excellent cure rates reported for MIP. However, there are reports in the literature that question the sensitivity of this approach for detecting all hyperfunctioning parathyroid glands. In a series of 112 patients with HPT, Weber and Ritchie measured IOPTH levels but did not use it to limit the extent of surgical exploration. All patients underwent bilateral exploration. Twenty-one patients were identified as having more than 1 enlarged, hypercellular parathyroid gland. In 12 of these patients, IOPTH levels had fallen more than 50% before the additional abnormal glands were identified and removed. In a similar study, Gordon et al reported that in 17 patients found to have multigland disease, 4 patients had IOPTH levels that fell more than 50% after the first abnormal gland was removed.

Gauger et al and Haciyanli et al reported on the use of IOPTH monitoring in patients with double parathyroid adenomas. In both series of patients, the second adenoma would sometimes have been missed if the extent of exploration had been limited because the IOPTH level had fallen more than 50%.

Siperstein et al reported on the largest series of patients studied in this manner. A total of 350 patients underwent bilateral exploration after preoperative Tc 99m Sestamibi scans and ultrasonography were performed. Intraoperative PTH levels were measured in all patients. If a unilateral exploration based on imaging studies had been performed, IOPTH level would have failed to predict the presence of multigland disease in 9% of patients. Multigland disease would have been missed in 15% of patients if an MIP had been performed.

It is difficult to reconcile these results with the observation of cure rates greater than 95% in patients undergoing MIP. Either these additional enlarged, hypercellular parathyroid glands are of no clinical significance or some patients whose calcium level returns to normal after parathyroidectomy have persistent disease of which we are unaware. The presence of PPTH has been reported in 8% to 40% of patients following parathyroidectomy. In most patients, PTH levels eventually return to normal. In some, PPTH is associated with a low serum calcium level, frequently due to low serum vitamin D level. Vitamin D experience with this technique in 1994 and showed that a decrease in IOPTH level of more than 50% from baseline values was predictive of cure. Recent reports by this group confirm the validity of this approach.

### Comment

The success rate following parathyroidectomy for HPT by an experienced surgeon exceeds 95%. In patients in whom preoperative imaging findings show a solitary adenoma, MIP results in cure rates similar to conventional bilateral exploration. Solitary adenomas occur in approximately 85% of patients with HPT. Preoperative imaging, usually using Tc 99m Sestamibi scanning and/or ultrasonography, can detect the location of most solitary adenomas. These same imaging studies are much less accurate in their ability to identify those patients with more than 1 hyperfunctioning parathyroid gland.

The first successful use of IOPTH level to determine the adequacy of parathyroidectomy was reported by Nussbaum et al in 1988. Irvin et al reported their initial
supplementation can reduce the incidence of PPTH. Some authors have suggested that PPTH is of little clinical significance.

In some patients, however, PPTH is associated with a serum calcium level in the high-normal range. Several reports have suggested that this subgroup of patients may have mild, persistent HPT. Wang et al reported an incidence of PPTH of 15%. In 38 patients with PPTH and calcium levels of 9.6 mg/dL or higher, 3 progressed to obvious recurrent HPT after 1 year. None of the patients with PPTH and lower calcium levels developed recurrent HPT. In a similar study, Ning et al observed an incidence of PPTH of 18%. Recurrent HPT occurred in 5.4% of patients with PPTH, but in only 1.2% of patients with normal calcium and PTH levels postoperatively. In patients with PPTH and calcium levels of 9.7 mg/dL or higher, the recurrence rate was 16%, compared with no recurrences when the calcium level was lower than 9.7 mg/dL.

These observations should not be surprising. With increasing frequency patients with normocalcemic HPT are being referred for surgery. Mazzaglia et al report that at the Cleveland Clinic, Cleveland, Ohio, the percentage of patients undergoing parathyroidectomy with calcium levels lower than 10.5 mg/dL increased from 1% in 1985 to 6% in 1995 and to 13% in 2003. Lowe et al from the Metabolic Bone Unit in the Department of Medicine at Columbia University, conclude that patients seen in a referral center with normocalcemic hyperparathyroidism have more substantial skeletal involvement than is typical in PHPT [primary hyperparathyroidism] and develop more features and complications over time. These patients may represent the earliest form of symptomatic, rather than asymptomatic, PHPT.

Is it reasonable, then, in evaluating our results following MIP to ignore those patients with PPTH?

The results described in this article are consistent with the aforementioned reports. As observed at the Cleveland Clinic, 14% of our patients underwent surgery for normocalcemic HPT. We observed a recurrence rate of 1.5% and an incidence of PPTH of 13%, similar to other reports in the literature and to our own previous report. Of the 23 patients with PPTH, 11 (48%) had a calcium level of 9.6 mg/dL or higher. These 11 patients must be considered to be at risk for recurrence and may have persistent normocalcemic HPT. If this is true, according to the traditional criteria for adequate surgery of a 50% decrease in IOPTH level from baseline, the failure rate may be as high as 8%.

In the present report we correlate the final IOPTH level with the outcome of surgery. All 3 of the patients who already had a recurrence and 5 of the patients at highest risk for further recurrence had final IOPTH levels of 40 pg/mL or higher. This group of patients had a preoperative PTH level that was higher than those with a lower final IOPTH level. Others have observed the correlation of higher preoperative PTH level with postoperative PTH. The lack of any difference in postoperative 25-hydroxyvitamin D among the 5 groups suggests that the high incidence of PPTH in group 5 is not due to vitamin D deficiency. The importance of the association of increasing age with increasing final IOPTH level is not obvious, although Ning et al describe an association between increasing age and incidence of PPTH. Our study suggests that the final IOPTH level rather than the percentage decrease in IOPTH level is the most accurate predictor of outcome following parathyroidectomy.

Final IOPTH level was measured no earlier than 20 minutes following excision of the abnormal parathyroid glands. It may not be reasonable to keep patients in the operating room until these results are obtained. It may be possible to calculate the predicted final IOPTH level based on earlier IOPTH measurements. At the very least, patients with final IOPTH levels of 40 pg/mL or higher should be followed up closely after surgery in the same fashion as one would follow up patients with asymptomatic HPT, in whom observation rather than surgery was chosen.

Submitted for Publication: April 30, 2009; final revision received May 21, 2009; accepted June 3, 2009.

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Author Contributions: Dr Heller had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Heller and Blumberg. Acquisition of data: Heller. Analysis and interpretation of data:
Heller. Drafting of the manuscript: Heller and Blumberg. Critical revision of the manuscript for important intellectual content: Heller. Statistical analysis: Heller. Administrative, technical, and material support: Heller. Study supervision: Heller.

Financial Disclosure: None reported.

Previous Presentation: This study was presented at the American Head and Neck Society 2009 Annual Meeting; May 31, 2009; Phoenix, Arizona.

REFERENCES