A Spike in Parathyroid Hormone During Neck Exploration May Cause a False-Negative Intraoperative Assay Result

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Hypothesis: We hypothesize that false-negative results using the rapid intraoperative parathyroid hormone (IOPTH) assay can be caused by spikes in the level of parathyroid hormone that occur during mobilization of the adenoma.

Design: Retrospective analysis of a case series.

Setting: University tertiary care center.

Patients: Ten consecutive patients with primary hyperparathyroidism.

Interventions: All patients underwent neck exploration with IOPTH monitoring. Using a sampling protocol described in the literature, IOPTH values were checked at the time of incision, during mobilization of the adenoma, and 10 minutes after resection of the adenoma.

Main Outcome Measures: Patients were evaluated for adequate parathyroid tissue excision as determined by IOPTH levels and examination of ipsilateral glands. All patients had normal serum calcium values documented postoperatively. Parathyroid hormone half-life was calculated assuming first-order kinetic decay.

Results: Nine patients had an appropriate decline in IOPTH with a mean ± SD parathyroid hormone half-life of 3.9 ± 1.08 minutes. Mobilization of the adenoma resulted in a spike in the IOPTH value, with 1 patient's value increasing from a baseline of 95.5 pg/mL (10.1 pmol/L) to 751 pg/mL (79.1 pmol/L). Another patient who was confirmed to have a solitary adenoma had a false-negative postexcision value. A spike in IOPTH that occurred during neck dissection was not detected by the sampling protocol and explains the false-negative value.

A literature review revealed that most protocols check baseline values early in the operation and are at risk for false-negative results due to a spike from mobilization of the adenoma.

Conclusions: These data demonstrate that false-negative IOPTH assay findings can result from a spike in parathyroid hormone level during exploration, which may go unrecognized if baseline values are measured during the early stages of mobilization of the adenoma. We have altered our assay protocol and have begun measuring IOPTH at the time of neck incision, at the time the adenoma is completely removed (time zero \( t_0 \)), and 10 minutes after excision.

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Surgery for hyperparathyroidism by an experienced parathyroid surgeon has a success rate of 95% to 98%.\(^1\,^2\) Localization studies with high-resolution ultrasound and technetium-99m sestamibi have been used in an attempt to shorten the operative time and limit exploration of normal parathyroid glands.\(^3\,^4\) Preoperative localization allows a unilateral approach in most patients with a solitary adenoma.\(^5\,^7\) However, 5% to 20% of patients with primary hyperparathyroidism have multigland disease and require bilateral neck exploration.\(^6\,^8\) In patients with multigland disease, imaging studies can be misleading. In addition, parathyroid gland enlarge-ment in the setting of multigland disease is commonly asymmetric and may not be obvious after unilateral exploration. Intraoperative parathyroid hormone (IOPTH) monitoring has been introduced as a physiologic assay to determine if adequate parathyroid tissue has been removed.\(^9\,^10\) A 50% reduction in the parathyroid hormone (PTH) value from baseline is often used as an indication that the exploration has been successful.\(^10,^31\)

We have analyzed the data from our initial 10 patients operated on with IOPTH monitoring. Previous studies indicated an accuracy of approximately 97%.\(^12\) However, the assay may have significantly reduced accuracy in the setting of multigland disease.\(^11,^13,^14\) In this study we have identified the occurrence of PTH spikes that result from mobilization of the para-
PATIENTS AND METHODS

Intraoperative parathyroid hormone values were determined in all patients using the Quick Intraoperative Intact PTH kit (Nichols Institute Diagnostics, San Juan Capistrano, Calif). Two preexcision baseline values were obtained. The first baseline value (BL1) was obtained at the start of the operation and coincided with the time of the neck incision. A second baseline value (BL2) was obtained during the initial stages of the neck dissection and mobilization of the parathyroid adenoma but before ligation of vessels to the adenoma. The BL2 was used in the calculation of PTH half-life (see following equations). A postexcision value (PE1) was obtained 10 minutes after excision of the adenoma. Additional postexcision levels were determined in 3 patients.

Our criteria for successful parathyroidectomy required a fall of at least 50% from the greater of the 2 baseline values and a postexcision value of less than the upper limit of normal, 65 pg/mL (6.8 pmol/L). In addition, a bilateral neck dissection was undertaken if morphologic evidence of hyperplasia was noted at the time of exploration. A kinetic analysis of these data assumed an exponential decay based on the equation:

\[ PE1 = (BL2) e^{-kt}, \]

where \( k \) is the rate constant and \( t \) is time (minutes).

The rate constant (\( k \)) is reported in units of min\(^{-1}\) and was calculated by the equation:

\[ k = (-1/10) \ln (PE1/BL2). \]

The PTH half-life (\( t_{1/2} \)) was calculated by the equation:

\[ t_{1/2} = (1/k)(0.693). \]

The spike in PTH during neck dissection, rather than variability of PTH half-life, can cause a false-negative test result.

RESULTS

Ten patients underwent parathyroidectomy with IOPTH monitoring. The clinical characteristics of the patients are indicated in Table 1. Four patients had a history of kidney stones, and 5 patients had evidence of osteopenia or osteoporosis. All patients had hypercalcemia, with a mean calcium level of 11.2 mg/dL (2.80 mmol/L). The average preoperative PTH level was 148 pg/mL (15.6 pmol/L). All patients underwent normalization of calcium and PTH, usually performed 1 to 2 weeks postoperatively. The mean postoperative calcium level was 9.0 mg/dL (2.23 mmol/L), and the postoperative PTH level was 37 pg/mL (3.9 pmol/L). The IOPTH values for the 10 patients are given in Table 2, these data are shown diagrammatically in Figure 1. A second postexcision value (PE2) was obtained in 3 patients. One of these patients (patient 5) had evidence of hyperplasia, which was identified by inspection of the ipsilateral gland. After excision of a 731-mg parathyroid adenoma, a PE1 value of 32 pg/mL (3.4 pmol/L) was obtained. A second enlarged gland of 166 mg was excised, and 10 minutes after this excision the IOPTH level fell to 23.2 pg/mL (2.4 pmol/L). In patient 6, the IOPTH value spiked from the BL1 value of 95.5 pg/mL (10.1 pmol/L) to a BL2 value of 751 pg/mL (79.1 pmol/L). After excision of a 2.23-g adenoma, the IOPTH value was 103 pg/mL (10.8 pmol/L); a PE2 of 53 pg/mL (5.6 pmol/L) was obtained 20 minutes after excision. As indicated in Table 2, the mean ± SD half-life for PTH based on 9 patients (excluding patient 10) was 3.93 ± 1.08 minutes.

Patient 10 was a 40-year-old man with primary hyperparathyroidism. He had preoperative localization studies with high-resolution ultrasound and a sestamibi scan. Both studies localized a single left lower parathyroid adenoma. At the time of operation, the left neck was explored first; a 318-mg parathyroid adenoma was identified as indicated by the localization tests. A normal left superior parathyroid gland was identified and confirmed by biopsy results. During the operation, the BL1 value was 83.5 pg/mL (8.8 pmol/L), and the BL2 level was 78 pg/mL (8.2 pmol/L); 10 minutes postexcision, the PE1 value was 71.5 pg/mL (7.5 pmol/L). At the time of the PE1 result, the incision had been closed and no further neck dissection had occurred since the value had been obtained. The results of previous studies indicate that the patient should have been cured by the operation. Given these findings, there was a suspicion that the elevated PE1 value might be a false-negative result. Therefore, a second postexcision value was obtained approximately 20 minutes after resection of the adenoma. While the result was being determined, the right side of the neck was explored. The right upper parathyroid gland was found to be normal and was later confirmed by frozen section. A PE2 level of 92 pg/mL (1.0 pmol/L) was obtained at that time, and the operation was concluded with no further exploration. One week postoperatively, the patient’s calcium level was 9.7 mg/dL (2.43 mmol/L) with an intact PTH level of 35 pg/mL (3.7 pmol/L).

Using the IOPTH values, it is possible to calculate this patient’s PTH half-life. The change in PTH value during the 10-minute interval between adenoma excision and the obtainment of the PE1 level would indicate a PTH

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Table 1. Clinical Characteristics of 10 Patients Undergoing Parathyroidectomy

<table>
<thead>
<tr>
<th>Sex, M:F</th>
<th>1:4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>53.8 ± 10.2</td>
</tr>
<tr>
<td>Medical history, No. of patients</td>
<td></td>
</tr>
<tr>
<td>Nephrolithiasis</td>
<td>4</td>
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<tr>
<td>Hypertension</td>
<td>2</td>
</tr>
<tr>
<td>Osteoporosis/osteopenia</td>
<td>5</td>
</tr>
<tr>
<td>Recurrence</td>
<td>1</td>
</tr>
<tr>
<td>Average calcium level, mg/dL†</td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>11.2 ± 0.85</td>
</tr>
<tr>
<td>Postoperative</td>
<td>9.0 ± 0.49</td>
</tr>
<tr>
<td>Average parathyroid hormone level, pg/mL‡</td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>148 ± 126</td>
</tr>
<tr>
<td>Postoperative</td>
<td>37 ± 21</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD unless otherwise indicated.
†To convert to SI units (mmol/L), multiply by 0.25.
‡To convert to SI units (pmol/L), multiply by 0.1053.

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The use of IOPTH provides a means to confirm that all physiologically hyperactive parathyroid tissue has been excised at the time of neck exploration for hyperparathyroidism. The test requires that the PTH value fall at least 50% from baseline as evidence of successful exploration. The assay has been reported to have an accuracy of 96% to 98% in predicting successful parathyroidectomy. A false-positive result is defined as a 50% reduction during surgery in a patient who has persistent hyperparathyroidism postoperatively or in whom additional hyperplastic glands are identified. In our series, patient 5 was noted to have a 166-mg hyperplastic gland during the operation. The IOPTH value is estimated to have been 556 pg/mL (58.5 pmol/L) at the time the adenoma was resected. This value is within the peak range observed in this group of patients.
remaining despite a significant decrease in PTH. The IOPTH assay has a false-positive rate of 3% to 24%, which is most often seen in the setting of hyperplasia.11,13,14 The occurrence of false-positive findings has fueled the debate about whether all enlarged parathyroid glands are functionally hyperactive.13 In an attempt to decrease the false-positive rate, some authors have recommended that the postexcision level fall to 70% of baseline as evidence of successful exploration.15

A false-negative test result is defined as a result in which the IOPTH value does not demonstrate an appropriate decline after successful parathyroidectomy. This was apparent in the case in patient 10, who failed to have an appropriate decline in IOPTH level after the excision of a single adenoma. The IOPTH assay has a false-negative rate of 2% to 10%.11,13,14,16 A recent article by Libutti et al16 attributed a spike in the PTH level seems more likely in this patient. This conclusion is supported by the fortuitous findings in patient 6, in whom a spike from a baseline of 95.5 pg/mL (10.1 pmol/L) to a peak of 751 pg/mL (79.1 pmol/L) was recorded. We presume that a spike occurred in patient 10 after the BL2 was obtained. Although variability of half-life may account for a false-negative result in some cases, a spike in the PTH level seems more likely in this patient. Because the PTH half-life is 1 to 4 minutes,10,16 the protocol used in this series was not devised to accurately assess this measure. Rather, this protocol measures the PTH level 3 to 10 half-lives after excision and is designed to determine a new postexcision PTH baseline. These data can provide an estimate of the PTH half-life, however; the values determined in our study were within the range for half-lives reported in other series. Therefore, we feel confident that a PTH spike rather than variability in half-life explains the occurrence of this patient’s false-negative result.

A spike in hormone levels during mobilization of hormonally active tumors has been noted in other tissues. Pheochromocytomas are notorious for releasing large amounts of vasoactive metabolites during resection and have led to the practices of limiting palpation during resection and attempting to ligate the venous drainage as soon as it becomes feasible.17,18 Although other series have reported more modest increases in PTH during neck exploration,11 the potential for misleading results was not mentioned. Our data establish that parathyroid mobilization can cause a spike in IOPTH values that may go unrecognized based on current protocols for IOPTH monitoring.

The recognition that a spike in PTH can affect the interpretation of the assay underscores the importance of standardizing the time when blood samples are drawn. A review of the published protocols from various institutions is presented in Table 3. Most institutions report drawing a single baseline value, the exact timing of which is not usually described except that it occurs before resection of the adenoma. In some cases this baseline was obtained immediately after induction of anesthesia, which would clearly miss a spike in PTH that could occur during dissection. Some investigators used a BL2, the time of which was also variable and occurred before ligation of the vascular pedicle. Postexcision values were determined at various times after resection as indicated; some investigators obtained these values 30 minutes after resection. The longer the interval between resection and checking a postexcision value, the more likely that a plateau will be achieved. However, PTH half-life is 1 to 4 minutes, and protocols with longer postexcision times will lengthen the time of operation. The protocol used for obtaining baseline and postexcision values in our study was similar to that in the series by Garner and Leight.11

Because of the recognition that mobilization of a parathyroid adenoma can create a spike in the IOPTH level, we have altered our protocol for obtaining samples. The BL1 is obtained after induction of anesthesia at the time of neck incision. The BL2 is obtained immediately after

Table 3. Protocols for Intraoperative Parathyroid Hormone Assay From Various Institutions

<table>
<thead>
<tr>
<th>Authors</th>
<th>Institution</th>
<th>Timing of Baseline Values</th>
<th>Timing of Postexcision Values, min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nussbaum et al1 (1988)</td>
<td>Massachusetts General Hospital</td>
<td>From internal jugular vein just before ligation of vascular pedicle</td>
<td>15 and 30</td>
</tr>
<tr>
<td>McHenry et al14 (1990)</td>
<td>University of Toronto</td>
<td>Immediately after induction of anesthesia</td>
<td>20</td>
</tr>
<tr>
<td>Irvin et al12 (1994)</td>
<td>University of Miami</td>
<td>1. After induction but before incision 2. After dissection but before tumor excision</td>
<td>10 and 20</td>
</tr>
<tr>
<td>Weber and Ritchie15 (1999)</td>
<td>Emory University School of Medicine</td>
<td>Before resection of parathyroid</td>
<td>10</td>
</tr>
<tr>
<td>Gordon et al14 (1999)</td>
<td>University of Texas</td>
<td>After induction but before incision</td>
<td>5, 10, and 20</td>
</tr>
<tr>
<td>Libutti et al16 (1999)</td>
<td>National Institutes of Health</td>
<td>Before excision</td>
<td>5 and 10</td>
</tr>
</tbody>
</table>

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resection of the adenoma and represents time zero \((t_0)\) after adenoma resection. A postexcision value is obtained 10 minutes after resection of the adenoma. This approach serves 2 purposes. First, it standardizes the time at which the samples are drawn. Second, it avoids misleading results caused by a spike in PTH that may occur during mobilization of the adenoma. Whereas persistent elevation of the IOPTH or morphologic evidence of hyperplasia will necessitate bilateral neck exploration, determining the PTH level immediately after adenoma resection will eliminate false-negative results caused by a spike in PTH levels. Our data provide additional evidence that the IOPTH assay is a useful test to help the surgeon determine when an adequate resection has been performed. However, the test is not a substitute for sound clinical judgment, and the recognition of false-positive and false-negative results requires that the data be interpreted in the context of the clinical situation.

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REFERENCES


