The Role of Intraoperative Rapid Parathyroid Hormone Monitoring for Predicting Thyroidectomy-Related Hypocalcemia

Kevin M. Higgins, MD; David L. Mandell, MD; Satish Govindaraj, MD; Eric M. Genden, MD; Jeffrey I. Mechanick, MD; Donald A. Bergman, MD; Edward J. Diamond, PhD; Mark L. Urken, MD

Objective: To determine if the intraoperative rapid parathyroid hormone (PTH) assay can be used to accurately predict postoperative calcium levels following total or completion thyroidectomy.

Design: A prospective study.

Setting: Tertiary care referral center.

Patients: One hundred four patients following a total or completion thyroidectomy.

Intervention: Intraoperative rapid plasma PTH levels were determined for patients undergoing a total or completion thyroidectomy.

Main Outcome Measures: Parathyroid hormone levels were recorded after the induction of anesthesia, before excision, and 5, 10, and 20 minutes after thyroidectomy. Postoperative calcium levels were monitored every 6 hours until hospital discharge. Intraoperative PTH levels were correlated with postoperative calcium levels and clinical symptoms of hypocalcemia.

Results: Twenty-two patients (21.2%) required short-term postoperative calcium supplementation, and 2 (1.9%) required long-term calcium replacement. There was a statistically significant difference between those patients requiring calcium replacement and those who did not require calcium supplementation, for postoperative total calcium level (7.2 vs 8.1 mg/dL [1.8 vs 2.0 mmol/L]; \( P < .001 \)) and ionized calcium level (3.76 vs 4.36 mg/dL [0.94 vs 1.09 mmol/L]; \( P < .001 \)). In addition, the PTH changes from baseline demonstrated statistically significant differences at 5, 10, and 20 minutes after the excision between the 2 groups (\( P < .005 \)). In those patients requiring calcium supplementation, 14 (64%) of 22 demonstrated a change in PTH level of greater than 75% from baseline, and in those patients who did not require postoperative calcium supplementation, 61 (74%) of 82 demonstrated a change in PTH level of less than 75% from baseline (\( P < .005 \)).

Conclusion: Intraoperative PTH monitoring may be a useful tool in identifying patients who will not require postoperative calcium supplementation following total or completion thyroidectomy.


PARATHYROID DYSFUNCTION following a total or completion thyroidectomy is not uncommon, and may be associated with significant patient morbidity. A concerted effort has been made to identify risk factors for postoperative hypocalcemia, including measurement of calcium levels, gland vascularity, and intraoperative parathyroid hormone (PTH) monitoring. Early work has suggested that intraoperative PTH monitoring may represent a promising method to predict postoperative hypocalcemia. The ability to successfully identify patients who are at risk for postoperative hypocalcemia could potentially limit morbidity by instituting early replacement therapy and by identifying patients who could be safely discharged from the hospital. This study determines if intraoperative PTH monitoring could accurately identify patients at risk for postoperative hypocalcemia following total or completion thyroidectomy.

METHODS

One hundred four patients undergoing a total or completion thyroidectomy at the Department of Otolaryngology–Head and Neck Surgery, Mount Sinai Hospital, New York, were preoperatively enrolled in this study from July 12, 2000, through August 8, 2002. Following informed consent, all of the operations were performed by one of us (E.M.G. or M.L.U.). The study was approved by the Institutional Review Board, and was in accordance with the ethical standards of the Mount Sinai School of Medicine.

From the Division of Endocrinology (Drs Mechanick, Bergman, and Diamond), the Department of Otolaryngology (Drs Higgins, Mandell, Govindaraj, Genden, and Urken), and the Center for Clinical Laboratories (Dr Diamond), Mount Sinai School of Medicine, New York, NY. The authors have no relevant financial interest in this article.
Predicting hypocalcemia was previously examined with a pilot study. The product moment correlation coefficient between the rapid PTH assay and the standard 2-hour hospital immunochemiluminometric assay was established (Pearson 1.75 mmol/L) and the normal range of ionized calcium is 4.56-5.16 mg/dL. The variables for calcium supplementation were based on prior studies.

Asymptomatic patients with normal total and ionized calcium levels did not receive calcium supplementation. Patients who demonstrated signs and/or symptoms of postoperative hypocalcemia (perioral and/or acral paresthesias, a positive Chvostek sign, and frank tetany) underwent testing for total and ionized calcium levels, and intravenous calcium replacement was initiated. Intravenous therapy was maintained until the total calcium level was 7.5 mg/dL or greater or the ionized calcium level was 3.84 mg/dL or greater. Following intravenous calcium replacement, oral calcium replacement was initiated. At hospital discharge, patients who did not receive postoperative calcium replacement were given a prescription for oral calcium replacement and instructed to contact the attending endocrinologist (J.I.M. or D.A.B.) in the event that perioral or acral paresthesias occur. They were instructed to have total and ionized calcium levels drawn before initiating calcium replacement therapy. If a patient was administered calcium during the first postoperative week before having blood drawn for total and ionized calcium levels, the patient was excluded from the study.

A telephone survey coupled with a comprehensive medical record review was performed to determine if patients received the required calcium supplementation during the postoperative course.

A 1-way analysis of variance was applied to analyze the difference between the time0 and postexcision values. If the analysis of variance demonstrated significance (P<.005), then specific group mean comparisons were performed for that variable using a post hoc Tukey test to correct for multiple comparisons and to maintain an overall α level of .05. All statistical tests were 2-tailed and calculated using statistical software (Statistica, version 5.1; StatSoft Inc, Tulsa, Okla).

One hundred four patients completed the study (81 female and 23 male patients); they were a mean age of 48.5 years at surgery (range, 14-84 years). A total thyroidectomy was performed in 84 patients and a completion thyroidectomy was performed in 20. General anesthesia was used in 102 patients. There were 52 patients with malignant disease, and 28 underwent paratracheal lymph node dissections for central compartment nodal disease (Table 1). The average preoperative total serum calcium level was 8.9 mg/dL (2.22 mmol/L) (range, 7.8-10.2 mg/dL [1.95-2.55 mmol/L]), and the average preoperative serum albumin and serum creatinine levels were 4.2 g/dL (range, 3.3-4.8 g/dL) and 0.9 mg/dL (80 µmol/L) (range, 0.4-1.5 mg/dL [35-133 µmol/L]), respectively. There were no significant differences in preoperative calcium, serum albumin, or serum creatinine levels between the 2 groups (P = .08). Patients were contacted for follow-up at a mean of 4.9 months (range, 4-19 months). The postoperative calcium replacement protocol was adhered to in all 104 patients.

Twenty-two patients (21.2%) received postoperative calcium supplementation; 19 were asymptomatic, but received oral calcium because of a postoperative total serum calcium level of less than 7.5 mg/dL and/or a postoperative serum ionized calcium level of less than 3.84 mg/dL. The calcium nadir in these patients occurred be-

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**Table 1. Pathological Features in Patients Who Underwent a Total Thyroidectomy or a Completion Thyroidectomy**

<table>
<thead>
<tr>
<th>Pathological Feature</th>
<th>Total Thyroidectomy Group</th>
<th>Completion Thyroidectomy Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multinodular goiter</td>
<td>34</td>
<td>5</td>
</tr>
<tr>
<td>Papillary carcinoma</td>
<td>36</td>
<td>8</td>
</tr>
<tr>
<td>Hashimoto thyroiditis</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Follicular carcinoma</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Graves disease</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Medullary carcinoma</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>91</strong></td>
<td><strong>15</strong></td>
</tr>
</tbody>
</table>

*Data are given as number of patients in each group. Some patients had more than 1 pathological feature.*

Medicine. Informed consent was obtained from all subjects before enrollment into the study. The following information was obtained for each patient: age at surgery; sex; preoperative serum albumin, creatinine, and total serum calcium levels; type of anesthesia (general vs local); and total number of parathyroid glands visualized. Patients with evidence of renal failure and/or coexisting parathyroid gland pathologic features were excluded from the study.

In all patients, blood was drawn intraoperatively for the rapid PTH assay from either a peripheral intravenous line or a radial arterial line at the following times: after the induction of anesthesia (postinduction), just before the removal of the thyroid gland (postisolation), and 3 minutes (timeR), 10 minutes (time10), and 20 minutes (time20) after the excision of the thyroid gland. The change in PTH levels was calculated as previously described. Briefly, the change in PTH levels was determined by calculating the difference between time0, time10, and time20 and the highest preexcision level (either postinduction or postisolation), referred to as timeC.

Patients who demonstrated a profound decline in PTH levels during surgery underwent examination of the parathyroid glands. The vascularity of the gland was evaluated by performing an incisonal biopsy. If there was bright red bleeding, the operative case was concluded; however, if there was no bright red bleeding, parathyroid autotransplantation was performed in the sternocleidomastoid muscle. Rapid intraoperative PTH levels were determined using a commercially available immunochemiluminometric assay (Quick-IntraOperative Intact PTH Kit; Nichols Institute Diagnostics, San Juan Capistrano, Calif). The assay was performed and completed by a technician in approximately 12 minutes. In a prior study, a correlation between the rapid PTH assay and the standard 2-hour hospital immunochemiluminometric assay was established (Pearson product moment correlation coefficient r = 0.83, P <.01).

The utility of rapid intraoperative PTH monitoring in predicting hypocalcemia was previously examined with a pilot study undertaken by Mandell et al at our institution. This preliminary work highlighted the importance of a strict calcium supplementation protocol that could be prospectively applied to each patient. This study population consisted of an entirely new cohort wherein this well-defined protocol was followed to determine the need for calcium replacement in each patient. Postoperatively, total and ionized calcium levels were drawn every 6 hours until hospital discharge. Hospital discharge was contingent on normal total and normal ionized calcium levels. According to the hospital assay used in our institution, the normal range of total serum calcium is 8.5 to 11.0 mg/dL (2.12-2.75 mmol/L) and the normal range of ionized calcium is 4.56 to 5.16 mg/dL (1.43-1.29 mmol/L). Oral calcium replacement was initiated for a postoperative total calcium level of less than 7.5 mg/dL (<1.88 mmol/L) (normal range, 8.5-11.0 mg/dL) and/or an ionized calcium level of less than 3.84 mg/dL (<0.96 mmol/L) (normal range, 4.56-5.16 mg/dL). The variables for calcium supplementation were based on prior studies.

Asymptomatic patients with normal total and ionized calcium levels did not receive calcium supplementation. Patients who demonstrated signs and/or symptoms of postoperative hypocalcemia (perioral and/or acral paresthesias, a positive Chvostek sign, and frank tetany) underwent testing for total and ionized calcium levels, and intravenous calcium replacement was initiated. Intravenous therapy was maintained until the total calcium level was 7.5 mg/dL or greater or the ionized calcium level was 3.84 mg/dL or greater. Following intravenous calcium replacement, oral calcium replacement was initiated. At hospital discharge, patients who did not receive postoperative calcium replacement were given a prescription for oral calcium replacement and instructed to contact the attending endocrinologist (J.I.M. or D.A.B.) in the event that perioral or acral paresthesias occur. They were instructed to have total and ionized calcium levels drawn before initiating calcium replacement therapy. If a patient was administered calcium during the first postoperative week before having blood drawn for total and ionized calcium levels, the patient was excluded from the study.

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tween 12 and 24 hours after surgery. Three patients required calcium replacement for symptomatic hypocalcemia. The onset of symptoms occurred between 24 and 48 hours. After calcium supplementation, total and ionized serum calcium levels normalized and all signs and symptoms resolved. Two patients (1.9%) requiring long-term calcium supplementation were considered to have permanent hypoparathyroidism, with absolute PTH values of less than 5 pg/mL (<5 ng/L) at 5 and 16 months.

There was no demonstrable correlation between the requirement for postoperative calcium and patient age, sex, histopathological features, paratracheal node dissection, albumin levels, or creatinine levels. A total of 28 single-gland and 8 two-gland autotransplantations were performed. Interestingly, both patients requiring long-term calcium replacement had single glands autotransplanted after demonstrating a profound intraoperative change in PTH level at time20 of greater than 75% in each case. There were statistically significant differences between those patients requiring calcium replacement and those who did not require calcium supplementation, for postoperative total calcium level (7.2 vs 8.1 mg/dL [1.8 vs 2.0 mmol/L]; P<.001) and ionized calcium level (3.76 vs 4.36 mg/dL [0.94 vs 1.09 mmol/L]; P<.001) (Figure 1 and Figure 2, respectively). Patients who required calcium replacement demonstrated a significantly higher change in PTH level at time0 (57.20%), time10 (58.68%), and time20 (60.86%) when compared with patients who did not require calcium replacement at time0 (24.05%), time10 (13.57%), and time20 (10.41%) (P<.005) (Figure 3). The time20 value was the most predictive: in those patients requiring calcium supplementation, 14 (64%) of 22 demonstrated a change in the PTH time20 value of greater than 75% from baseline. In those patients who did not require postoperative calcium supplementation, 61 (74%) of 82 demonstrated a change in the PTH time20 value of less than 75% from baseline. However, the Pearson product moment correlation coefficient demonstrated a weak correlation between change in PTH level at time0 (0.29), time10 (0.33), and time20 (0.37) and the lowest postoperative ionized calcium level, limiting the ability to generate a significant positive predictive value. These data suggest that while there is a statistically demonstrable difference between the calcium-requiring patients and the non–calcium-requiring patients for PTH level (P=.08), a statistically significant correlation could not be demonstrated for the magnitude of the change in PTH level.

Abnormalities of the thyroid gland are common, affecting approximately 10% of the general population. More than 80000 thyroidectomy procedures are performed each year in the United States. Postoperative hypocalcemia after total thyroidectomy has been reported to range from 1.3% to 35% (Table 2). Sasson et al identified 517 patients who underwent a total thyroidectomy in whom thyroid malignancy and goiter accounted for 1.3% to 35% (Table 2). Some researchers have identified para-

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**Figure 1.** Lowest postoperative total calcium level. To convert total calcium to millimoles per liter, multiply by 0.25.

**Figure 2.** Lowest postoperative ionized calcium level.

**Figure 3.** Change in parathyroid hormone (PTH) level before thyroidectomy (time0) and 5, 10, and 20 minutes after thyroidectomy (time5, time10, and time20, respectively). The asterisk indicates a significant (P<.005) difference.

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thyroid reimplantation as a risk factor for postoperative hypocalcemia, while others have found that total thyroidectomy for malignancy was associated with higher rates of postoperative hypocalcemia, highlighting the multifactorial nature of the problem.

The 2 most common complications of thyroidectomy include recurrent laryngeal nerve injury and postoperative hypocalcemia. While recurrent laryngeal nerve monitoring has been implemented in some institutions to identify and prevent potential nerve injury, efforts to identify risk factors for postoperative hypocalcemia have been disappointing. Kuhel and Carew studied the reliability of parathyroid gland color as a means of assessing parathyroid gland function. They performed incisional biopsies in 14 consecutive cases. Of the 34 parathyroid glands that were histologically confirmed, 17 appeared nonviable, with either no bleeding or minimal venous oozing. However, only 5 glands were severely discolored (black), with the other 12 having normal coloration, concluding that the absence of discoloration was not a reliable way to determine whether the parathyroid blood supply is intact. Subsequently, the introduction of the 2-site immunoradiometric assay and the 2-site antibody immunoluminometric assay has yielded several studies suggesting the usefulness of intraoperative PTH monitoring to predict postoperative hypocalcemia following thyroidectomy. Lo et al examined 100 patients and 20 control subjects using the intraoperative quick PTH assay to monitor parathyroid function. They found that a normal PTH level or less than 20 pg/mL, the predictability and correlation are significantly improved, with 13 study patients having time, levels below this threshold.

While we demonstrated that the quick PTH assay may be an effective tool for identifying those patients who are at risk for postoperative hypocalcemia following a total thyroidectomy; however, when time, PTH levels are 20 pg/mL or less, the assay is unreliable in predicting postoperative calcium levels.

**Table 2. Incidence of Hypocalcemia After Total Thyroidectomy**

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Patients</th>
<th>Incidence of Hypocalcemia, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pappalardo et al.1998</td>
<td>141</td>
<td>35</td>
</tr>
<tr>
<td>Mishra et al.1999</td>
<td>232</td>
<td>28</td>
</tr>
<tr>
<td>Bergamaschi et al.1998</td>
<td>150</td>
<td>20</td>
</tr>
</tbody>
</table>

The Pearson product moment correlation coefficient did not support a statistically significant positive or negative correlation between the PTH level and postoperative calcium levels. However, we did find that in those patients who did not require postoperative calcium supplementation, 61 (74%) of 82 demonstrated a change in the PTH time value of less than 75% from baseline.

While we demonstrated that the quick PTH assay can be used to aid in predicting the need for postoperative calcium supplementation, the inability to derive a strong correlation between a change in the PTH level and postoperative calcium levels may highlight the limitations of the current assay for detecting more subtle PTH level changes. In particular, we found that when time, PTH levels are 20 pg/mL or less (<20 ng/L), the quick PTH assay is unable to accurately predict postoperative calcium homeostasis. When time, PTH values are greater than 20 pg/mL, the predictability and correlation are significantly improved, with 13 study patients having time, levels below this threshold.

The cost incurred related to the performance of the intraoperative assay is $280 per patient, while the overall costs related to an overnight stay at our institution approach $3000. A formal cost-effectiveness survey will be undertaken after the initial peer review process examining our method is completed. It is anticipated that this survey would be included in a forthcoming clinical efficacy study in which our clinical practice patterns would be modified according to the variables established in this article, whereby those patients with an intraoperative change in PTH time, decrease of greater than 75% receive calcium and cholecalciferol supplementation immediately, while those with a decrease of less than 75% would be considered for same-day discharge.

In conclusion, the quick PTH assay may be an effective tool for identifying those patients who are at risk for postoperative hypocalcemia following a total thyroidectomy; however, when time, PTH levels are 20 pg/mL or less, the assay is unreliable in predicting postoperative calcium levels.

**REFERENCES**


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