ORIGINAL ARTICLE

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 at 20 minutes 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.

Arch Otolaryngol Head Neck Surg. 2004;130:63-67

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.

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,[1] including measurement of calcium levels,[2] gland vascularity,[3] and intraoperative parathyroid hormone (PTH) monitoring.[4] Early work[5] 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

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

Pathological Feature	Total Thyroidectomy Group	Completion Thyroidectomy Group
Multinodular goiter	34	5
Papillary carcinoma	36	8
Hashimoto thyroiditis	9	0
Follicular carcinoma	4	2
Graves disease	5	0
Medullary carcinoma	2	0
Lymphoma	1	0
Total	**91**	**15**

*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 5 minutes ($time_5$), 10 minutes ($time_{10}$), and 20 minutes ($time_{20}$) after the excision of the thyroid gland. The change in PTH levels was calculated as previously described.[5] Briefly, the change in PTH levels was determined by calculating the difference between $time_5$, $time_{10}$, and $time_{20}$ and the highest preexcision level (either postinduction or postisolation), referred to as $time_0$.

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 incisional 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,[6] 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[6] 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 (1.14-1.29 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.[7,8] 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 $time_0$ 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).

RESULTS

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-

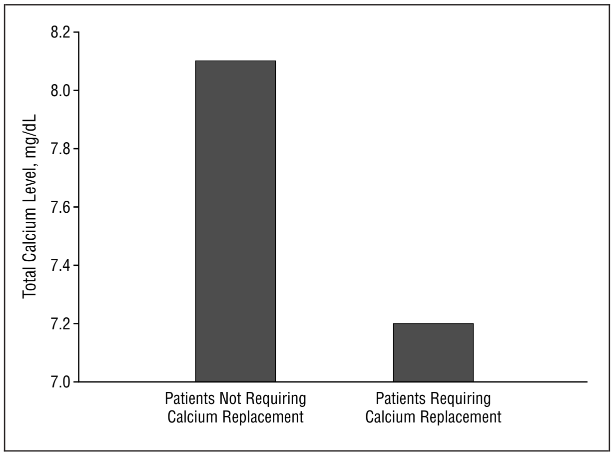

Figure 1. Lowest postoperative total calcium level. To convert total calcium to millimoles per liter, multiply by 0.25.

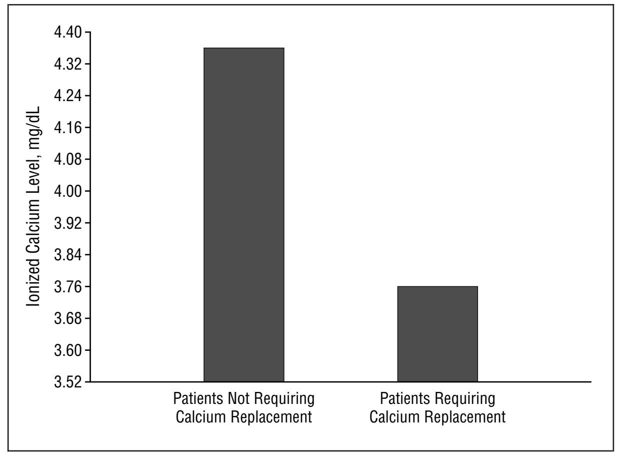

Figure 2. Lowest postoperative ionized calcium level.

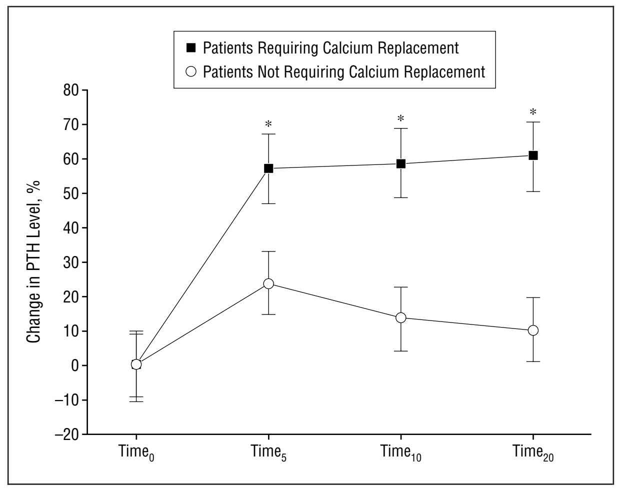

Figure 3. Change in parathyroid hormone (PTH) level before thyroidectomy ($time_0$) and 5, 10, and 20 minutes after thyroidectomy ($time_5$, $time_{10}$, and $time_{20}$, respectively). The asterisk indicates a significant ($P<.005$) difference.

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 $time_{20}$ 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 $time_5$ (57.20%), $time_{10}$ (58.68%), and $time_{20}$ (60.86%) when compared with patients who did not require calcium replacement at $time_5$ (24.05%), $time_{10}$ (13.57%), and $time_{20}$ (10.41%) ($P<.005$) (**Figure 3**). The $time_{20}$ value was the most predictive: in those patients requiring calcium supplementation, 14 (64%) of 22 demonstrated a change in the PTH $time_{20}$ 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 $time_{20}$ value of less than 75% from baseline. However, the Pearson product moment correlation coefficient demonstrated a weak correlation between change in PTH level at $time_5$ (0.29), $time_{10}$ (0.33), and $time_{20}$ (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.

COMMENT

Abnormalities of the thyroid gland are common, affecting approximately 10% of the general population.[9,10] More than 80 000 thyroidectomy procedures are performed each year in the United States.[11] Postoperative hypocalcemia after total thyroidectomy has been reported to range from 1.3% to 35%[12,13] (**Table 2**). Sasson et al[15] reported on a 9-year series of 141 thyroidectomies (69 total thyroidectomies), with a 13% incidence of hypocalcemia. A recent retrospective series by Bhattacharyya and Fried[9] identified 517 patients who underwent a total thyroidectomy in whom thyroid malignancy and goiter accounted for more than 73.9% of the cases. Thirty-two patients (6.2%) developed postoperative hypocalcemia. The pathogenesis of postoperative hypoparathyroidism is likely multifactorial.[16] Some researchers[15,17] have identified para-

Table 2. Incidence of Hypocalcemia After Total Thyroidectomy

Source	No. of Patients	Incidence of Hypocalcemia, %	
		Temporary	Permanent
Pappalardo et al,[13] 1998	141	35	3
Mishra et al,[12] 1999	232	28	1.3
Bergamaschi et al,[14] 1998	150	20	4

thyroid reimplantation as a risk factor for postoperative hypocalcemia, while others[15] 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,[18] efforts to identify risk factors for postoperative hypocalcemia have been disappointing.[1,19] Kuhel and Carew[3] 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 immunochemiluminometric assay has yielded several studies[4,20] suggesting the usefulness of intraoperative PTH monitoring to predict postoperative hypocalcemia following thyroidectomy. Lo et al[20] 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 a 75% decline in the quick PTH level after thyroidectomy accurately identified normocalcemic patients during surgery, and the reported correlation coefficient was 0.6974 (r^2=0.028).[20] Similarly, Warren et al[4] retrospectively reviewed 23 patients in whom PTH levels were assayed before surgery and at $time_{10}$, and found that intraoperative PTH levels of greater than 15 pg/mL (>15 ng/L) after a total or completion thyroidectomy demonstrated a low risk of postoperative hypocalcemia. Postoperative total calcium levels had a statistically significant positive correlation with postoperative PTH levels (r=0.70, P=.001) and a negative correlation with percentage of decrease in PTH levels (r=−0.75, P<.01).

In our study, no statistically significant association could be demonstrated between the occurrence of hypocalcemia and sex, indication for surgery, presence of nodal dissection, or parathyroid reimplantation. We found that patients who required calcium replacement demonstrated a significantly elevated PTH level at $time_5$, $time_{10}$, and $time_{20}$ vs patients who did not require postoperative calcium supplementation. In contrast to the studies by Lo et al[20] and Warren et al,[4] 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 $time_{20}$ 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 $time_0$ PTH levels are 20 pg/mL or less (≤20 ng/L), the quick PTH assay is unable to accurately predict postoperative calcium homeostasis. When $time_0$ PTH values are greater than 20 pg/mL, the predictability and correlation are significantly improved, with 13 study patients having $time_0$ 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 $time_{20}$ 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 $time_0$ PTH levels are 20 pg/mL or less, the assay is unreliable in predicting postoperative calcium levels.

Submitted for publication April 17, 2003; final revision received June 16, 2003; accepted July 14, 2003.

This study was presented at the annual meeting of the American Head and Neck Society; May 5, 2003; Nashville, Tenn.

Corresponding author and reprints: Mark L. Urken, MD, Department of Otolaryngology, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, NY 10029.

REFERENCES

1. McHenry CR, Speroff T, Wentworth D, Murphy T. Risk factors for postthyroidectomy hypocalcemia. *Surgery.* 1994;116:641-648.
2. Husein M, Hier MP, Al-Abdulhadi K, Black M. Predicting calcium status post thyroidectomy with early calcium levels. *Otolaryngol Head Neck Surg.* 2002;127:289-293.
3. Kuhel WI, Carew JF. Parathyroid biopsy to facilitate the preservation of functional parathyroid tissue during thyroidectomy. *Head Neck.* 1999;21:442-446.

4. Warren FM, Andersen PE, Wax MK, Cohen JI. Intraoperative parathyroid hormone levels in thyroid and parathyroid surgery. *Laryngoscope.* 2002;112:1866-1870.
5. Irvin GL 3rd, Dembrow VD, Prudhomme DL. Clinical usefulness of an intraoperative "quick parathyroid hormone" assay. *Surgery.* 1993;114:1019-1023.
6. Mandell DL, Genden EM, Mechanick JI, Bergman DA, Diamond EJ, Urken ML. The influence of intraoperative parathyroid hormone monitoring on the surgical management of hyperparathyroidism. *Arch Otolaryngol Head Neck Surg.* 2001;127:821-827.
7. Adams J, Andersen P, Everts E, Cohen J. Early postoperative calcium levels as predictors of hypocalcemia. *Laryngoscope.* 1998;108:1829-1831.
8. Bentrem DJ, Rademaker A, Angelos P. Evaluation of serum calcium levels in predicting hypoparathyroidism after total/near-total thyroidectomy or parathyroidectomy. *Am Surg.* 2001;67:249-252.
9. Bhattacharyya N, Fried MP. Assessment of the morbidity and complications of total thyroidectomy. *Arch Otolaryngol Head Neck Surg.* 2002;128:389-392.
10. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. *Arch Intern Med.* 2000;160:526-534.
11. Harness JK, Organ CH Jr, Thompson NW. Operative experience of US general surgery residents in thyroid and parathyroid disease. *Surgery.* 1995;118:1063-1070.
12. Mishra A, Agarwal G, Agarwal A, Mishra SK. Safety and efficacy of total thyroidectomy in hands of endocrine surgery trainees. *Am J Surg.* 1999;178:377-380.
13. Pappalardo G, Guadalaxara A, Frattaroli FM, Illomei G, Falaschi P. Total compared with subtotal thyroidectomy in benign nodular disease: personal series and review of published reports. *Eur J Surg.* 1998;164:501-506.
14. Bergamaschi R, Becouarn G, Ronceray J, Arnaud JP. Morbidity of thyroid surgery. *Am J Surg.* 1998;176:71-75.
15. Sasson AR, Pingpank JF Jr, Wetherington RW, Hanlon AL, Ridge JA. Incidental parathyroidectomy during thyroid surgery does not cause transient symptomatic hypocalcemia. *Arch Otolaryngol Head Neck Surg.* 2001;127:304-308.
16. Wilson RB, Erskine C, Crowe PJ. Hypomagnesemia and hypocalcemia after thyroidectomy: prospective study. *World J Surg.* 2000;24:722-726.
17. Walker RP, Paloyan E, Kelley TF, Gopalsami C, Jarosz H. Parathyroid autotransplantation in patients undergoing a total thyroidectomy: a review of 261 patients. *Otolaryngol Head Neck Surg.* 1994;111(pt 1):258-264.
18. Brennan J, Moore EJ, Shuler KJ. Prospective analysis of the efficacy of continuous intraoperative nerve monitoring during thyroidectomy, parathyroidectomy, and parotidectomy. *Otolaryngol Head Neck Surg.* 2001;124:537-543.
19. Strickland PL, Recabaren J. Are preoperative serum calcium, parathyroid hormone, and adenoma weight predictive of postoperative hypocalcemia? *Am Surg.* 2002;68:1080-1082.
20. Lo CY, Luk JM, Tam SC. Applicability of intraoperative parathyroid hormone assay during thyroidectomy. *Ann Surg.* 2002;236:564-569.