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Predictors of Hypocalcemia Occurring After a Total/Near Total Thyroidectomy

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Abstract

Purpose. The aim of this study was to identify the predictors of early postoperative hypocalcemia after a total/near total thyroidectomy in order to select patients for prompt treatment to prevent symptomatic hypocalcemia.

Methods. Patients with hypocalcemia within 24 h of surgery were identified as Group I and normocalcemic patients as Group II. The perioperative serum total calcium (tCa, ionized calcium (iCa) and intact parathormone (iPTH) were measured perioperatively. Skin closure (SC) was accepted as the reference time point. Data are expressed as the mean ± SEM.

Results. The study included 73 patients. Hypocalcemia (Group I) was detected in 40 patients (54%) within the first 24 h postoperatively. Symptomatic hypocalcemia was detected in 40% of the patients in Group I. Intact parathormone values at 10 min of SC were significantly lower in Group I ($P = 0.001$). IPTH measurement at 10 min of SC showing a ≥30% decrease had a 92.3% sensitivity and 92.6% specificity in predicting hypocalcemia after a total/near total thyroidectomy. The postoperative day 15 mean tCa, iCa, and iPTH values were similar in both groups of patients. The mean iPTH level was 16.79 ± 2.5 pg/dl at 10 min after SC in patients who developed symptomatic hypocalcemia.

Conclusions. Intact parathormone measurement 10 min after SC is helpful to predict early postoperative hypocalcemia. An IPTH decrease ≥30% at this time point estimates the risk of postoperative hypocalcemia.

Key words Thyroidectomy · Hypocalcemia · Parathormone

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Introduction

Hypocalcemia is the most frequent metabolic complication of a thyroidectomy.[1–3] Devascularization or excision of the parathyroid glands, excretion of endothelin 1, venous stasis as a result of surgical dissection, and hematoma are the causes of hypocalcemia associated with a thyroidectomy. The rate of hypocalcemia following a bilateral subtotal thyroidectomy is reported to be in the range of 0.3%–23%, with a 0.6% rate of permanent hypocalcemia.[4] The frequency of this complication is increased after a total/near total thyroidectomy in the range of 19%–59% with 2.8% developing permanent hypocalcemia.[5–8] The visual identification of at least two parathyroid glands has been reported to prevent permanent hypocalcemia.[9]

The aim of this prospective study was to develop a novel method of predicting early postoperative hypocalcemia after a total/near total thyroidectomy by perioperative monitoring of the intact parathormone (iPTH), ionized calcium (iCa), and serum total calcium (tCa).

Patients and Methods

A prospective analysis of the patients who underwent surgery between May 2006 and March 2008 was performed. The normal range of iPTH was accepted as 15–88 pg/ml. Hypocalcemia was defined tCa <8.5 mg/dl and iCa <1.120 mmol/dl. Perioral paresthesia and/or hand, foot paresthesia, the presence of Chvostek's sign, tetany, and muscle cramps were accepted as indications of symptomatic hypocalcemia. Patients with hypocalcemia within 24 h of surgery were classified as Group I and normocalcemic patients during the given period as Group II. The surgical procedure involved an exploration of the parathyroid glands and bilateral recurrent laryngeal nerves before initiating the thyroidectomy.

The specimens were macroscopically controlled in the operating room for detection of accidentally removed parathyroid glands as well as a histopathological examination. Demographic data, preoperative magnesium, phosphorus, albumin, creatinine, operative indications, surgical technique, postoperative complications, and preoperative thyroid function tests were evaluated. Perioperative monitoring of tCa and iCa were done preoperatively on the day of surgery, 5, 10, and 15 min, and 24 h after skin closure (SC), and on postoperative day (POD) 15 and 30. In addition, the tCa levels were measured 12 h postoperatively. The serum iPTH values were drawn preoperatively, 10 min after SC, and on POD 15 and 30. The perioperative time point for blood drawing for iPTH levels was selected according to the short half life (2–5 min) of circulating iPTH in order to estimate the earliest possible surgical impact on the parathyroid glands. Previous reports show that 10 min after SC is optimal for the detection of any change in the circulating iPTH related to surgical trauma.[10] Blood samples were drawn from a peripheral vein and stored in dry tubes for analysis of tCa, and in heparinized syringes with 80 IU of heparin for the analysis of serum iCa and pH. Heparinized syringes were transferred in the dry ice box at an estimated temperature of 40°C. Serum iPTH, tCa, and iCa analysis were carried out using a chemiluminescent immunometric assay (Beckman Coulter, High Wycombe, UK), *o*-cresolphthalein method (Dade Behring, Dimention RxL-Max, Eschborn, Germany), and ion selective analyzer (Radiometer ABL 800 Flex, Bronshoj, Denmark), respectively. The statistical analysis was done using the SPSS version 10.0 software package for Windows. Student's *t*-test, Chi-square analysis, and receiver operating characteristics analyses were performed and the statistical significance was accepted as $P < 0.05$. All data are expressed as the mean ± SEM.

Results

The study included 73 patients. The mean age of the patients was 48.3 ± 2.5 years (range: 25–72). The male-to-female ratio was 0.14. Patient characteristics are summarized in Table 1. Groups I and II were comparable with regard to the demographics. Preoperative serum albumin, creatinine, magnesium, phosphorus and thyroid function tests, and serum pH measured at 10 min after SC were similar between the two groups ($P > 0.05$). A total thyroidectomy was performed in 25 patients (35%) and near-total thyroidectomy in 48 patients (65%). There were no accidentally removed parathyroid glands detected in either the perioperative specimen controls or histopathological examinations. Hypocalcemia (Group I) was detected biochemically in 40 patients within the first postoperative 24 h (54%). Symptomatic hypocalcemia was detected in 16 patients (21%) in Group I. Postoperative complications included hematoma in 3 patients ($n = 1$ in Group I, $n = 2$ in Group II) which were managed conservatively. Unilateral recurrent nerve injury was detected in 1 patient in group I. The histopathological analysis revealed, multinodular goiter in 47 patients (64.4%), Hashimoto thyroiditis in 13 (17.8%), papillary carcinoma in 7 (9.6%), follicular adenoma in 5 (6.8%), and undifferentiated carcinoma in 1 patient (1.4%). Four patients with papillary thyroid carcinoma and one patient with undifferentiated carcinoma were diagnosed preoperatively by fine-needle aspiration (FNA) cytology whereas 3 patients with occult papillary carcinoma were preoperatively diagnosed with a benign colloidal nodule by FNA. The distribution of the preferred surgical techniques and histopathological examination results of specimens were similar in both groups ($P > 0.05$). Serum tCa drawn preoperatively and immediately after SC at 5, 10, and 15 min were similar in both groups. The mean tCa levels

Table 1. Patient characteristics

	n	Group I (*n* = 40)	Group II (*n* = 33)	*P*
Age (years)	73	47 ± 10.6	49 ± 11.14	>0.05
Female/male	64/9	37/3	27/6	>0.05
Diagnosis				
Multinodular goiter	47	25	22	0.062
Hashimoto thyroiditis	13	6	7	—
Papillary carcinoma	7	5	2	—
Follicular adenoma	5	3	2	—
Undifferentiated carcinoma	1	1	—	—
Surgical technique				
Total thyroidectomy	25	17	8	>0.05
Near total thyroidectomy	48	23	25	>0.05
Complications				
Bleeding/hematoma	3	1	2	
Unilateral recurrent laryngeal nerve injury	1	1	—	

at 12 h of SC were 7.89 ± 0.38 mg/dl (range: 7–8.5 mg/dl) in Group I and 8.85 ± 0.32 mg/dl (range: 8.4–10 mg/dl) in Group II (P = 0.0001; Fig. 1). The sensitivity and specificity of tCa at 12 h to predict symptoms of hypocalcemia was 97.3% and 98.4%, respectively. Serum iCa measurements at 10 min of SC detected a statistically significant difference between the two groups (mean iCa; 1.063 ± 0.057 and 1.112 ± 0.079 mmol/l in Groups I and II, respectively, P = 0.004; Fig. 2). Sensitivity and specificity of iCa levels <1.079 mmol/l after 10 min of SC to predict the postoperative hypocalcemia was 60% and 75%, respectively. Intact parathormone values at 10 min of SC were; 26.3 ± 4.3 pg/dl (range: 5–42) in Group I, 60.5 ± 4.4 pg/dl (range: 22–138) in Group II, and

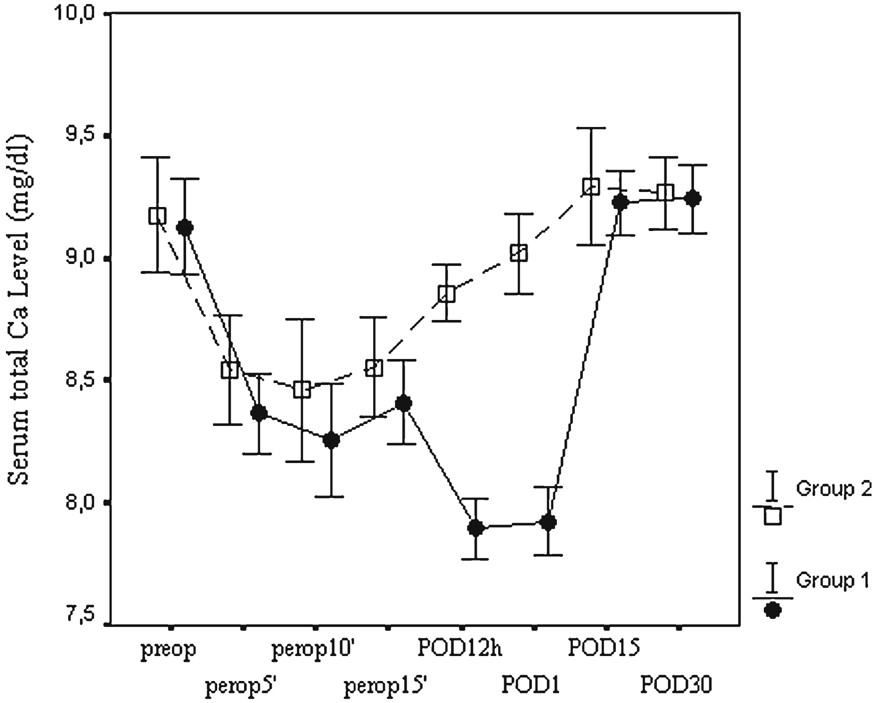

Fig. 1. Perioperative serum total calcium levels in Groups I and II. *Preop*, preoperative value; *perop 5′*, *10′*, *15′*, 5, 10, 15 min after skin closure; *POD12h*, postoperative 12 h after skin closure; *POD*, postoperative day

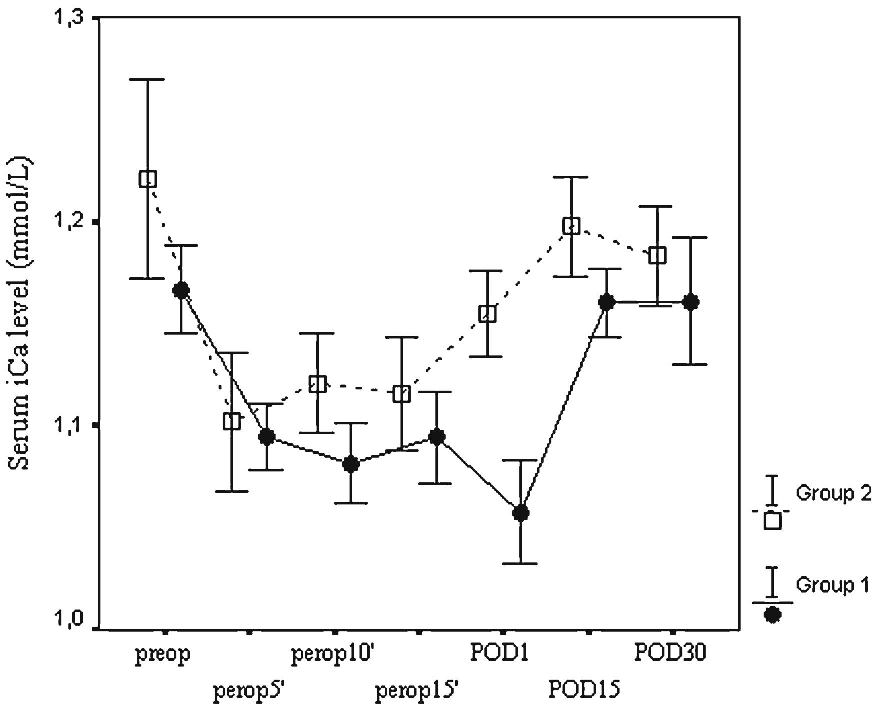

Fig. 2. Perioperative serum ionized calcium levels in Groups I and II. *Preop*, preoperative value; *perop 5′*, *10′*, *15′*, 5, 10, 15 min after skin closure; *POD*, postoperative day

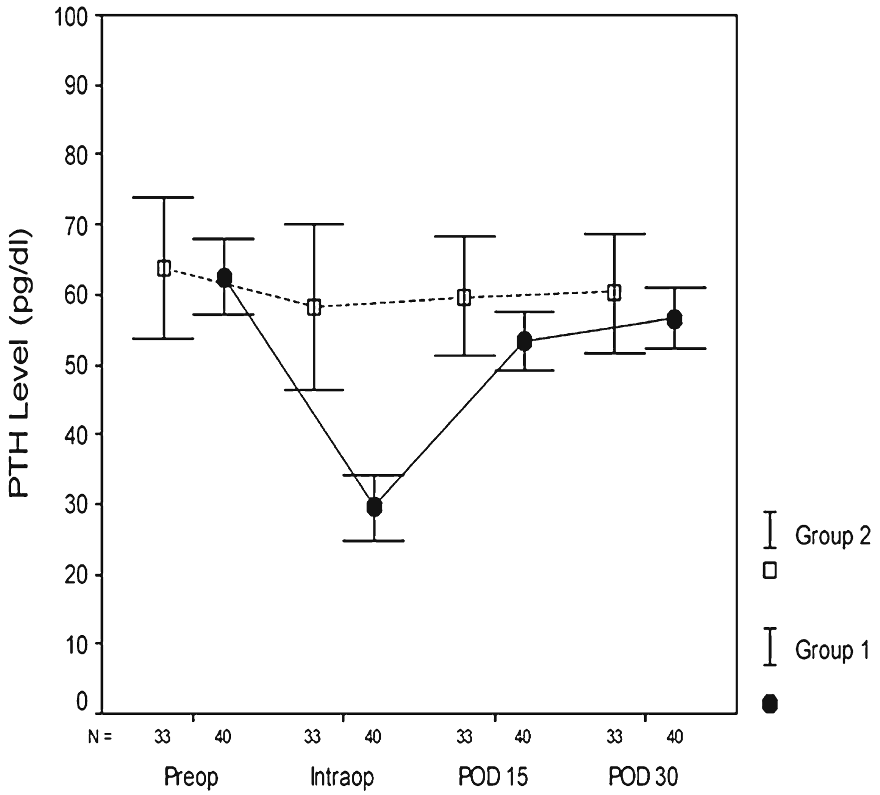

Fig. 3. Perioperative intact parathormone levels in Groups I and II. *Preop*, preoperative value; *Intraop*, 10 min after skin closure; *POD*, postoperative day

demonstrated a significant difference ($P = 0.001$; Fig. 3). Intact PTH measurement at 10 min of SC showing a ≥30% decrease in comparison to preoperative values had a 92.3% sensitivity and 92.6% specificity in predicting symptomatic hypocalcemia after total/near total thyroidectomy. During the postoperative period, asymptomatic ($n = 24$) and symptomatic ($n = 16$) hypocalcemia were detected in Group I. Intact parathormone measurements 10 min after SC in patients with symptomatic and asymptomatic hypocalcemia were 16.79 ± 2.5 pg/dl (range:5–21) and 32.6 ± 0.8 pg/dl (range:25.4–42.5; P = 0.002), respectively (Fig. 4). The mean tCa values in patients with symptomatic and asymptomatic hypocalcemia at 24 h of SC was 7.46 ± 0.33 mg/dl (range: 6.80–7.9) and 8.22 ± 0.13 mg/dl (range: 8.0–8.4; P = 0,001), respectively. Patients with symptomatic hypocalcemia ($n = 16$) were treated with oral and intravenous calcium replacement and vitamin D administration. Patients with asymptomatic hypocalcemia were followed and tCa levels returned to normal levels within 2.5 ± 0.4 days. Sixteen patients were discharged with oral calcium and vitamin D supplementation. The mean serum iPTH levels were 42.1 ± 2.1 pg/dl (range: 30.8–73) in asymptomatic patients and 32.8 ± 2 pg/dl (range: 15.8–48.6) in symptomatic patients ($P = 0.001$) at the time of discharge. The mean hospital stay was 3.5 ± 1.3 days in Group I and 1.33 ± 0.5 days in Group II ($P = 0.001$). Postoperative day 15 mean tCa, iCa, and iPTH values were similar between the two groups. Patients discharged with calcium replacement (n = 16) demonstrated iPTH values comparable to preoperative values at POD 15 and the calcium replacement treatment was discontinued. None of the patients discharged with calcium replacement treatment needed further retreatment after discontinuing the calcium replacement at POD 15. Postoperative day 30 values revealed comparable iPTH values to preoperative measurement in both groups. There was no case of permanent hypocalcemia among both groups. Both groups showed a similar level of tCa, iCa, and iPTH at POD 30, and no mortality occurred.

Discussion

The incidence of hypocalcemia after either a total or near total thyroidectomy is reported to be between 1.6% and 59%.[5,6,11] Most of the patients with hypocalcemia after a thyroidectomy are asymptomatic and recover without any need of treatment.[11] It is important to initiate medical treatment before the onset of the symptoms and thus prevent symptomatic hypocalcemia. According to the current results, intraoperative iPTH measurement at 10-min intervals of SC is the best perioperative parameter to predict early postoperative hypocalcemia. Nahas et al. reported that serum Ca levels tend to

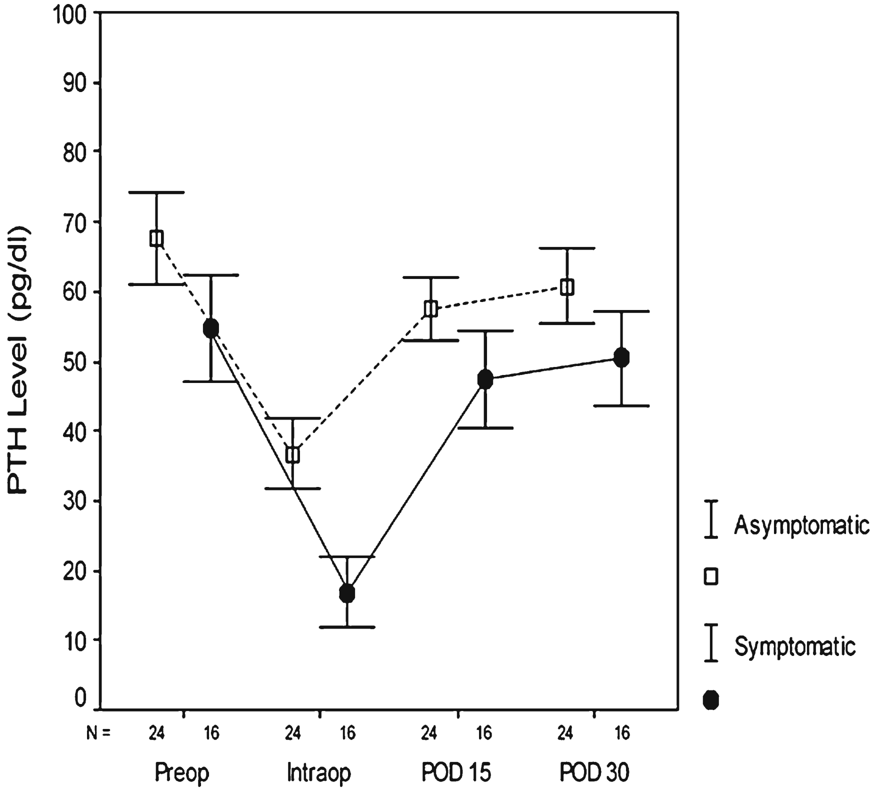

Fig. 4. Perioperative intact parathormone levels in Group I (symptomatic hypocalcemic patients vs asymptomatic patients). *Preop*, preoperative value; *Intraop*, 10 min after skin closure; *POD*, postoperative day

decrease during the first 6 h after a thyroidectomy and return to normal levels at 12 h.[12] A minimal decrease of tCa levels was detected intraoperatively in comparison to preoperative values. However, that decrease in tCa levels was not predictive for postoperative hypocalcemia. Serum tCa levels returned to normal values in Group II at 12 h postoperatively while patients in Group I demonstrated a steady decline in tCa levels. Postoperative 12-h tCa measurement predicted hypocalcemia with a sensitivity and specificity of 97.3% and 98.4%, respectively. As a result, measuring the perioperative iPTH levels is helpful in recognizing group of patients at high risk to develop hypocalcemia between the completion of the procedure and 12th postoperative hour.

The physiological functions of calcium are produced by ionized calcium which represents 45% of the serum total calcium. It is demonstrated that renal tubules reabsorb less iCa as a result of decreased iPTH following thyroidectomy and cause hypocalcemia.[13] The iCa level ≤1.079 mmol/l measured at 10 min of SC demonstrated a sensitivity and specificity of predicting postoperative hypocalcemia 60% and 75%, respectively. However, iCa measured at a given time point did not correlate with the prediction of postoperative symptomatic hypocalcemia. There is substantial data concerning the predictive value of perioperative iPTH measurement for postoperative hypocalcemia.[14–18] The current findings support the predictive value of intraoperative iPTH measurement after 10 min of SC. The detection of a ≥30% decrease of iPTH at given time point has a 92.3% sensitivity and 92.6% specificity in predicting postoperative hypocalcemia. Series with large numbers of patients have reported that an intraoperative iPTH level ≤15 pg/ml is associated with postoperative hypocalcemia.[2,19–24] The current series with a limited number of patients in comparison to the reported literature detected a threshold of intraoperative iPTH measurement as 14.8 pg/dl to predict postoperative symptomatic hypocalcemia, with a sensitivity of 60% and specificity of 98%. This should be a warning sign for the surgeon in the case of detection of intraoperative iPTH decreasing ≥30% in comparison to preoperative levels. Medical treatment could be initiated during the immediate postoperative period for those demonstrating iPTH ≤15 pg/ml intraoperatively. None of the current patients with a normal tCa level at 12 h after SC developed hypocalcemia and all were discharged on POD 1. Asymptomatic hypocalcemic patients regained normocalcemic levels after an average of 2.5 postoperative days without any need of calcium replacement treatment. Therefore it is also safe to discharge these patients on POD 1 on a regular basis. Funahashi et al. reported that in case of a surgical trauma to the parathyroid glands or autoimplantation, the iPTH level returns back to normal level within 15–28 days.[24–26] In the current study, all patients with either symptomatic or asymptomatic hypocalcemia demonstrated normal iPTH levels at POD 15 and therefore calcium replacement treatment was stopped.

In conclusion, there is a 20% chance that patients demonstrating hypocalcemia after a total/near total thyroidectomy will require calcium replacement treatment. It is important not to delay the decision to start calcium replacement. It would be helpful to accept ≥30% iPTH decrease detected after 10 min of SC after a thyroidectomy in comparison to the preoperative levels as the close follow-up criteria during the immediate postoperative period. Although the sensitivity was lower, possibly due to the limited number of patients in the present series, prompt calcium replacement in patients demonstrating an iPTH level of <14.8 pg/dl at a given time point would decrease the number of patients who would develop symptomatic hypocalcemia. The measurement of intraoperative iCa levels with a threshold of 1.079 mmol/l may also be helpful to predict postoperative hypocalcemia, though with less sensitivity and specificity in comparison to iPTH measurements. It is safe to stop calcium replacement treatment for the patients demonstrating normal iPTH levels at POD 15 following a total/near total thyroidectomy. Further studies with a larger number of patients would define a better threshold of the perioperative iPTH level to start calcium replacement immediately in order to prevent the onset of symptomatic hypocalcemia.

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