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Original Article

Intact parathormone measurement 1 hour after total thyroidectomy as a predictor of symptomatic hypocalcemia

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Abstract: Objective: Postoperative iPTH assay may predict significant hypocalcemia after thyroid surgery. The present study aimed to evaluate the ability of iPTH assay to monitor parathyroid function and to identify the risk of postoperative hypocalcemia in patients underwent thyroid surgery. Materials and methods: One hundred patients participated in the study (7 male and 93 female). Hypocalcemia was defined as a serum calcium concentration less than 8.0 mg/dL and symptoms of hypocalcemia. Concomitant serum calcium and iPTH levels were measured before operation and at 1st h for iPTH, 24th h for calcium after thyroidectomy. Results: Postoperative hypocalcemia was observed in 31 patients. The mean postoperative serum calcium concentration in normocalcemic patients was 8.8 ± 0.5 mg/dL, whereas it was 7.6 ± 0.3 mg/dL in hypocalcemic patients. The mean postoperative 1st hour iPTH of patients in the hypocalcemia group was 9.1 ± 4.9 pg/mL, whereas patients of the normocalcemia group had a mean postoperative iPTH of 35.8 ± 20.2 pg/mL. Conclusion: Postoperative 1st hour iPTH < 8 pg/mL with drop in iPTH level ≥ 81.5% together showed the highest diagnostic accuracy in predicting postoperative hypocalcemia.

Keywords: Hypocalcemia, intact parathyroid hormone, thyroid surgery

Introduction

Postoperative hypocalcemia is one of the most common complications of thyroid surgery ranging from 1 to 50% with a transient condition occur in up to 50% of patients and a permanent condition about 1% of patients [1, 2]. Prolonged hospitalization to monitor serum calcium concentrations is considered as the standard care by many surgeons in the absence of any reliable predictors of hypocalcemia because of the possibility of symptomatic hypocalcemia by postoperative 5th day. On the other hand there has been renewed interest for faster discharge with the increasing preference in hypocalcemia after thyroidectomy [3-5].

The benefit of postoperative iPTH measurement for determining which patient will become significantly hypocalcemic after thyroid surgery has gained acceptance among surgeons. Both absolute levels and percentage decline can be used with similar accuracy [6-8]. Recently, concomitant or combined postoperative iPTH and serum calcium measurement are deemed to be better than serum calcium or serum iPTH measurement alone in early prediction of hypocalcemia [7, 9]. In this study we aimed to evaluate the ability of the iPTH assay to monitor parathyroid function 1st hour after thyroid surgery and to identify patients at risk for postoperative hypocalcemia.

Materials and methods

Study design

All consecutive patients undergoing total thyroidectomy at Ankara Training and Research Hospital, Department of General Surgery between September 2008 and September 2010 were considered eligible for the present study. Patients were enrolled in a prospective longitudinal study focusing on the search for those

Table 1. Demographic and operative features of the patients

	Hypocalcemic	Normocalcemic	*P value*
Number of patient	31	69	-
Age (*years*; *range*)	49 ± 11	53 ± 12	0.74
Gender (*Male/Female*)	2/29	5/64	0.85
Thyroid Disease (*n*)			
●→*Malignant*	3	7	NS
●→*Bening*	28	62	
Operation (n)			
●→*Total thyroidectomy*	27	60	NS
●→*Completion thyroidectomy*	4	9	
Operative time (minute)	90 ± 34 (*26-168*)	88 ± 31 (*24-161*)	NS

Data are given as mean ± SD (range). NS means not significant.

parameters predicting early postoperative hypocalcemia. Exclusion criteria included concomitant parathyroid diseases (adenoma or carcinoma), medications of oral calcium and/or vitamin D before operation and renal failure. All eligible patients provided informed consent to be included in the study. Approval for this study was obtained from the Institutional Review Board of our hospital.

Hypocalcemia was defined as serum calcium concentration less than 8.0 mg/dL and symptoms of hypocalcemia (facial paresthesia, positive Chvostek's or Trousseau's signs, and muscular spasm) [10]. All other patients were considered normocalcemic. Concomitant serum calcium and iPTH levels were measured before operation and at 1st h for iPTH, 24th h for calcium after thyroidectomy. All the blood samples were obtained from peripheral venipuncture. Serum iPTH level has been measured by the chemiluminescent, immunometric assay (Beckman Coulter®, Brea, CA, USA). Normal range for iPTH assay of our institution is between 12 and 65 pg/mL [11]. Serum concentrations of calcium were determined by routine colorimetric assay (Olympus System Reagent®). When patients had a calcium level less than 8.0 mg/dL and developed symptoms of hypocalcemia, they were started on oral calcium and/or vitamin D supplements. Intravenous calcium gluconate was administered for severe hypocalcemia with clinically significant symptoms.

Statistical analysis

Patient's demographic characteristics, pathological findings, operative and postoperative results as well as all serum measurements were recorded. Categorical variables were compared using chi-square tests; continuous variables were compared using Student's T-test. Normally distributed continuous variables were declared as mean ± SD. Preoperative and postoperative 1st hour iPTH measurements compared with Student's t test. The predictive ability hypocalcemia of the iPTH were tested with receiver operating characteristics (ROC) curve. ROC curves used to test predictive ability of the level of both postoperative iPTH and the percent change in iPTH after surgery. The area under the curve (AUC) was calculated. Sensitivity and specificity of the full range of threshold values for both postoperative iPTH and percent change in PTH were analyzed. The *P* value was reported as significant when $P < 0.05$. SPSS statistical software was used for statistical analysis (SPSS, version 14, Chicago IL, USA).

Results

One hundred patients participated in the study (7 male and 93 female). Patient mean age was 51 ± 11 years. Indication for thyroidectomy was benign thyroid disease in 90 patients and malignant in 10 patients. At an average follow-up of 12 months, only 1 patient had persistent hypocalcemia requiring supplementation with calcium and vitamin D. Postoperative hypocalcemia was observed in 31 patients. There was no difference between normocalcemia patients and hypocalcemia patients for age, sex, type of operation and pathological findings (**Table 1**). All patients had normal preoperative serum calcium concentrations with a mean value of 9.5 ± 0.7 mg/dL. The mean postoperative serum calcium concentration in normocalcemic patients was 8.8 ± 0.5 mg/dL, whereas in hypocalcemic patients, it was 7.6 ± 0.3 mg/dL (**Table 2**). Patients in the hypocalcemia group had a significantly lower postoperative iPTH than patients in the normocalcemic group (**Table 2**). The mean postoperative 1st hour iPTH of patients in the hypocalcemia group was 9.05 ± 4.9 pg/mL, whereas patients of the normocalcemia group had a mean postoperative iPTH of

Table 2. Comparison of perioperative serum calcium and iPTH values between normocalcemic and hypocalcemic patients

Variable	Hypocalcemia	Normocalcemia	*P value*
Preoperative calcium, mean ± SD	9.4 ± 0.6	9.5 ± 0.4	*NS*
1st day Postoperative calcium, mean ± SD	7.6 ± 0.3	8.8 ± 0.5	< 0.001
Preoperative iPTH, pg/mL, mean ± SD	54.13 ± 19.94	58.48 ± 25.79	*NS*
1st hour after operation iPTH, pg/mL, mean ± SD	9.05 ± 4.91	35.8 ± 20.2	< 0.001
Mean percentage change PTH	81.5%	52.7%	< 0.001

Data are given as mean ± SD. NS means not significant.

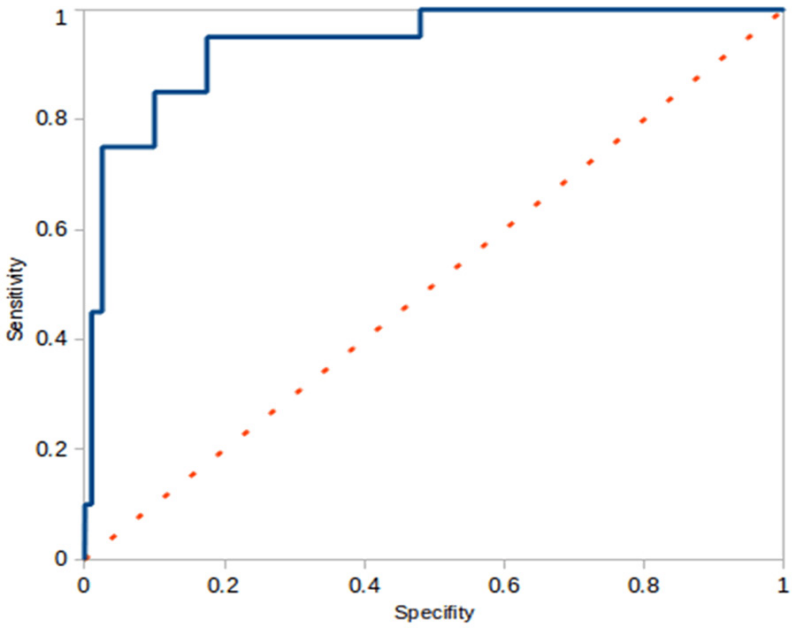

Figure 1. Receiver operating characteristic (ROC) analysis for prediction of hypocalcemic symptoms, based on 1-hour post thyroidectomy iPTH values. For 1-hour iPTH < 8 pg/dL, specificity is 95.8% and sensitivity is 93.7%. Area under curve = 0.937.

35.8 ± 20.2 pg/mL (P < 0.001). This represented a percent change in iPTH from the preoperative level of 52.7% in the normocalcemia group versus 81.5% in the hypocalcemia group (P < 0.001).

The ROC curve for change in percentage of iPTH and postoperative 1st hour iPTH predict hypocalcemia shown in **Figure 1**. The area under the ROC curves were 0.937 (95% confidence interval [CI] 0.902-0.979) and 0.931 (95% CI 0.896-0.978) for postoperative 1st hour iPTH and the percent change in iPTH absolute, respectively (**Figures 1**, **2**). The maximum sum of sensitivity and specificity for percent change PTH as a test to predict hypocalcemia occurred at 81.5% reduction in iPTH. The maximum sum of sensitivity (93.7%) and specificity (95.8%) for postoperative 1st hour iPTH level as a test for predicting hypocalcemia occurred at a PTH level of 8 g/mL (**Table 3**).

Discussion

The incidence of hypocalcemia after total thyroidectomy ranges between 1 to 50% [2]. It is difficult to predict which patients will develop hypocalcemia after total thyroidectomy based on surgical events [1]. Currently, there is no consensus regarding what is considered adequate monitoring for hypocalcemia development after thyroid surgery. Different approaches have been proposed to achieve early prediction of postoperative hypocalcemia. Some authors suggested thatnomonitorandstartroutinecalciumsupplementation, some of them treating only symptomatic patients, others measure postoperative iPTH, calcium levels and percentage change of iPTH [5, 12-15]. The aim of this prospective study was to evaluate reliability of postoperative 1st hour iPTH assessment and percentage change of iPTH for predicting clinically relevant post-thyroidectomy hypocalcemia to allow for the safe early discharge of patients.

The utility of postoperative iPTH measurement with or without drop percentage of iPTH for determining which patient will become significantly hypocalcemic after thyroid surgery has gained acceptance among surgeons [6-8]. Studies performed by Lam and Kerr [6] and Payne [8] first showed the utility of postopera-

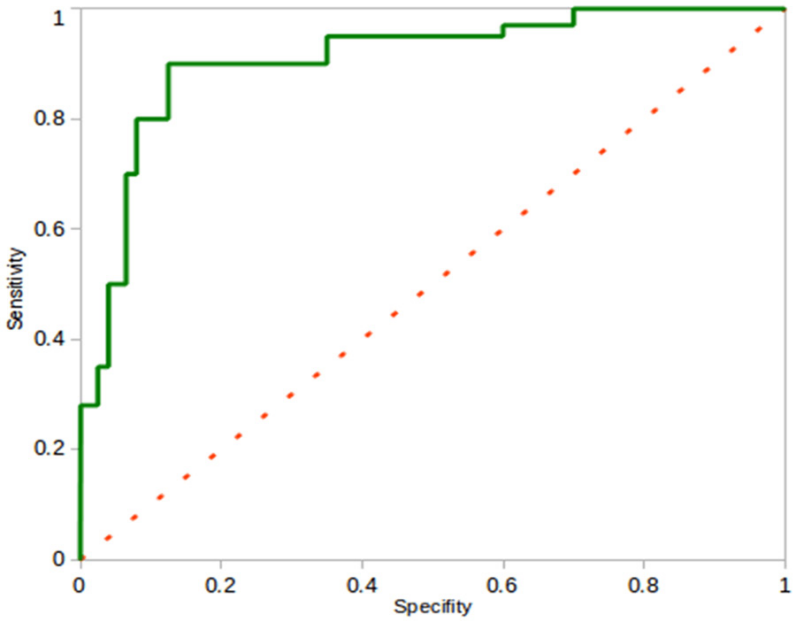

Figure 2. Receiver operating characteristic (ROC) analysis for prediction of hypocalcemic symptoms, based on persent change in iPTH. For change in iPTH, specificity is 95.2% and sensitvity is 93.1%. Area under curve = 0.931.

Table 3. Sensitivity, specificity, positive predictive value and negative predictive value for 1st hour postoperative iPTH

Variable	Cut off Levels	AUC (95% CI)	SN (%)	SP (%)	PPV (%)	NPV (%)
1st hour postop iPTH	8	0.937 (0.902-0.979)	93.7	95.8	84.62%	96.77%

Abbreviations: AUC, Area Under Curve; SN, Sensitivity; SP, Specificity; PPV, Positive predictive value; NPV, Negative predictive value.

tive iPTH for predicting hypocalcemia after thyroid surgery. In the study by Lam and Kerr, postoperative 8 pg/mL iPTH had 100% sensitivity for identifying those patients at highest risk for the development of hypocalcemia. The study reported by Payne in 2003 [8], demonstrated that the combination of an iPTH level 28 pg/mL (3 pmol/L) along with an albumin-corrected serum calcium level 2.14 mmol/L, both measured 12 hours after thyroid surgery, was 100% specific for identifying those individuals who were at low risk for developing hypocalcemia. Higgins [13] state that in their study 75% drop in PTH predict hypocalcemia. We suggest two methods for predicting postthyroidectomy hypocalcemia using serum iPTH levels, percent change in PTH and the postoperative 1st h iPTH. Both appear to be good predictors of postoperative hypocalcemia as demonstrated by the area under the ROC curves (**Figures 1**, **2**).

There is no consensus regarding what is considered the gold standard testing timing of PTH sampling [16]. Roh and Park [17] examined quick PTH levels preoperative and at 10 min, 1 h, and 24 h postoperatively. Hypocalcemia developed in patients with who had significantly lower postoperative 10 minutes PTH than normocalcemic patients. Sywak [18] studied patients who underwent thyroidectomy and measured PTH at 4 and 24 h. They concluded that a single PTH level at postoperative 4 h accurately predicted hypocalcemia. Study conducted by Marcin [19], iPTH samples were taken in each patient preoperatively, at the end of surgery and 4 hours postoperatively for predicting post thyroidectomy hypocalcaemia. It was concluded that iPTH serum level less than 10 pg/mL at 4 hours postoperative had the highest accuracy. The largest prospective study by Lombardi [7] evaluating the utility of postoperative PTH measurements at a variety of times after thyroidectomy. They found the samples taken at 4 and 6 h postoperatively to be most accurate and in identifying those patients who may be safely discharged early from the hospital.

Given the results of the current study and short half-life and rapid clearance of iPTH, the absolute iPTH value measured 1 hour after the completion of thyroid surgery may be a clinically useful parameter. The present study, 1-hour postoperative serum iPTH value of < 8 pg/mL, has a sensitivity of 93.7% and sensitivity of 95.8% for predicting patients at risk for developing post total thyroidectomy symptomatic hypocalcemia.

Our study has some limitations. Asymptomatic patients who had a serum calcium level below

8 mg/dL were not evaluated. In our practice, these patients are started empiric calcium supplementation, and thus these patients are actually treated in our practice as if they are going to be hypocalcemic. Starting these patients on supplementation could certainly treat potential symptoms before they develop and misclassify these patients into the normocalcemia group. Nevertheless, it would be desirable to identify risky patients very clearly in the postoperative period so that early supplementation of calcium is possible to prevent the development of symptoms. Given that the threshold iPTH of 8 pg/mL and drop in iPTH level ≥ 81.5% identified all patients at increased risk of hypocalcemia with/without symptom, empiric calcium supplementation given to everyone who falls below this threshold represents a reasonable approach.

Conclusion

Postoperative 1st hour iPTH < 8 pg/mL with drop iPTH level ≥ 81.5% together showed the highest diagnostic accuracy in predicting postoperative hypocalcemia. This result allowed us to identify these patients eligible for both early and safe discharge on postoperative day one or early start supplementation treatment.

Disclosure of conflict of interest

None.

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