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Early prediction of hypocalcemia after thyroidectomy by parathormone measurement in surgical site irrigation fluid

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ABSTRACT

Background: Improvements in surgical technique cannot eliminate the risk of hypocalcemia. We aimed to evaluate the accuracy of PTH levels in surgical site irrigation fluid (irPTH) in predicting patients at risk for postoperative hypocalcemia.

Methods: Prospective analysis of 160 consecutive patients undergoing thyroidectomy was performed. Patients were divided into 2 groups based on postoperative serum calcium levels. Patients with hypocalcemia were assigned to Group 1 ($n = 38$), while those with normocalcemia were assigned to Group 2 ($n = 122$). Preoperative and postoperative serum calcium levels and PTH level of surgical site irrigation fluid (irPTH), and the difference in serum calcium levels before and after thyroidectomy were determined.

Results: The difference in serum calcium levels and irPTH levels in Group 1 were significantly higher than those in group 2 ($p = 0.001$). There was a negative correlation between postoperative serum calcium level and irPTH level ($r = -0.641$, $p = 0.0001$). Patients who had irPTH level higher than 250 pg/mL had a 69-fold increased risk for postoperative hypocalcemia (OR = 69.88; 95% CI: 15.37–309.94).

Conclusions: High irPTH level is significantly associated with postoperative hypocalcemia. The irPTH assay is sufficient to identify hypocalcemia in the majority of patients and it is a sensitive tool to identify patients at risk of developing postoperative hypocalcemia.

1. Background

Thyroidectomy is one of the most frequent operations performed in iodine-deficient regions.[1–3] The most common complications of thyroidectomy include vocal cord palsy and hypocalcemia.[4,5] Hypocalcemia is frequently encountered after thyroidectomy and it continues to challenge even the experienced surgeon. The incidence of postoperative hypocalcemia is reported to vary from 1.6% to above 50%.[4–9] The etiology of hypoparathyroidism seems to be a multifactorial phenomenon but the most important factors can be listed as the iatrogenic surgical trauma and devascularization to parathyroid glands, the extent of surgery, the experience of the surgeon and the number of functioning glands left behind.[4,6,10,11] Although efforts were made to identify clinical and pathologic risk factors for the development of hypocalcemia after thyroidectomy, advancements so far lack an ideal perioperative assessment of parathyroid function.[12–14]

Recently, several studies investigated the reliability of intraoperative or postoperative serum parathormone (PTH) measurements in predicting hypocalcemia after thyroidectomy and decreased serum PTH levels were found early predictive of postoperative hypocalcemia.[15–22]

2. Aim of the study

The aim of this prospective clinical study is to evaluate the accuracy of PTH levels in surgical site irrigation fluid (irPTH) in predicting patients at risk for postoperative hypocalcemia. To our knowledge, this is the first prospective study performed to detect the irPTH level in predicting postoperative hypocalcemia.

3. Patients and methods

3.1. Patients

A total of 160 consecutive patients who underwent total thyroidectomy (TT) and near total thyroidectomy (NTT) in General

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Surgery Clinic at the Ataturk Training and Research Hospital between November 2007 and June 2008 were included prospectively in the present study.

The main indications for surgery included Graves disease, thyroid carcinoma, multinodular toxic goiter, and large goiter with a compressive effect. Patients with concomitant parathyroid disease, patients in whom accidental removal of one or more parathyroid glands occurred (either identified in the pathology report or identified intraoperatively), patients undergoing reoperative thyroid surgery and central neck and/or lateral neck lymph node dissection as well as those who refused to participate were excluded from the present study. None of the patients had signs or symptoms indicating metabolic bone disease and none of the patients were on medications known to affect serum calcium metabolism such as oral calcium/vitamin D supplementation, antiresorptive agents, hormone replacement therapy for postmenopausal women, anabolic agents, thiazide type diuretics and antiepileptic agents. The study plan was reviewed and approved by our institutional ethical committee, and informed consent was obtained from all patients.

All thyroid procedures were performed by experienced surgeons and by 4th year residents in training under the supervision of an experienced surgeon using the conventional clamp-and-tie technique. Vessel sealing systems including ultrasonic dissectors, electrothermal bipolar vessel sealers, and titanium clips were not used. Total thyroidectomy was performed by extracapsular dissection. Near total thyroidectomy was performed by the capsular dissection method, and less than 1 g of remnant tissue was left around the Berry ligament. For the remnant tissue, we estimated that 1 cm^3 equaled 1 g. Recurrent laryngeal nerves were carefully identified and dissected. All parathyroid glands identified and preserved with meticulous dissection for their blood supply.

The surgical site was irrigated by saline solution (50 ml/patient) after thyroidectomy. The irrigant was aspirated by sterile syringe (10 ml). PTH level of the surgical site irrigation fluid (irPTH) was measured. Serum calcium and PTH levels were determined the day before surgery and serum calcium was measured 24 h postoperatively. Serum calcium concentration was adjusted for serum albumin. The difference in serum calcium levels before and after thyroidectomy was calculated. Fifty patients were assigned to a control group. Before thyroidectomies were performed, surgical site was irrigated by saline solution (50 ml/patient). irPTH was also measured. The surgical indications of control group also included Graves disease, thyroid carcinoma, multinodular toxic goiter, and large goiter with a compressive effect.

One hundred sixty patients were divided into two groups according to postoperative calcium level. Patients in Group 1 ($n = 38$) had postoperative serum calcium level $\leq$8 mg/dL, whereas patients in Group 2 ($n = 122$) had serum calcium level >8 mg/dL. Hypocalcemia was defined as serum calcium concentration $\leq$8 mg/dL. Asymptomatic hypocalcemia was determined with laboratory findings alone whereas laboratory findings accompanied by clinical symptoms were referred to as symptomatic hypocalcemia. Presence of clinical symptoms or signs of hypocalcaemia were reported and included as facial paresthesia, positive Chvostek's signs, and muscular spasm. Serum calcium levels of hypocalcemic patients were measured every 12 h until the day they were stabilized. Patients who developed asymptomatic hypocalcemia were treated with oral calcium (3–6 g/day), while those with symptomatic hypocalcemia were treated with parenteral calcium and an oral 1,25-dihydroxy vitamin D3 (calcitriol) supplementation of 1–1.5 μg/day. Patients with asymptomatic hypocalcemia were discharged on oral calcium, whereas patients with symptomatic hypocalcemia were discharged on oral calcium and/or calcitriol at doses modified in relation to serum calcium concentration and were followed up weekly until their serum calcium and PTH levels were normalized.

3.2. Biochemical analysis

Serum calcium levels were determined by auto-analyzer (Cobas Integra 800, Roche Diagnostics, Basel, Switzerland). Serum PTH and surgical site irrigation fluid PTH levels were determined by immunoradiometric assay using commercially available kits—the PTH-120 min-IRMA kit (BioSource Europe S.a, Nivelles, Belgium). Normal ranges of biochemical parameters were 8.5–10.5 mg/dL for serum calcium and 10–65 pg/mL for serum PTH concentrations.

3.3. Statistics

Data were analyzed using SPSS 11.0 for Windows. Results were expressed as mean ± SD. Comparisons of data were performed by Mann–Whitney-U, Wilcoxon, Student-*t* and chi-squared tests. Receiver operating characteristic (ROC) curves were designed to identify the cut-off values for irPTH level and the difference of serum calcium level before and after thyroidectomy. Correlation analysis of continuous variables was performed using Spearman's rank test. Results were considered statistically significant when the two-tailed p value was less than 0.05.

4. Results

4.1. Patients

The mean ± SD age was 46.4 ± 12 years (range, 20–77 years) for 160 patients. The female to male ratio was 9:1 ($n = 144$ and 16, respectively). The mean ± SD for preoperative serum calcium and PTH levels, postoperative serum calcium, irPTH, and the postoperative drop in serum calcium level were 9.3 ± 0.4 mg/dL, 37.7 ± 13 pg/mL, 8.2 ± 0.6 mg/dL, 290.56 ± 409 pg/mL (median; 116 pg/mL), and 0.9 ± 0.7 mg/dL, respectively. Mean postoperative serum calcium level was lower than mean preoperative serum calcium level (9.3 ± 0.4 mg/dL vs. 8.2 ± 0.6 mg/dL, $p < 0.001$).

In histopathogic evaluation, papillary cancer was detected in 26 patients (16%), of whom 20 (76%) had papillary microcarcinoma (<1 cm). Mean ± SD size of all tumors was 6.5 ± 4.3 mm (range 2–17 mm).

The mean ± SD age was 47.1 ± 13 years (range, 25–75 years) for control group. The female to male ratio was 7.3:1 ($n = 44$ and 6,

Table 1
A comparison of demographic and laboratory features in patients with control and study group.

		Study group ($n = 160$)	Control group ($n = 50$)	p
Demographic and clinical features	Age	46.4 ± 12	47.1 ± 13	NS
	F:M	9:1	7.3:1	NS
	Preoperative serum Ca level (mg/dL)	9.3 ± 0.4	9.2 ± 0.3	NS
	Preoperative serum PTH level (mg/dL)	37.7 ± 13	36.6 ± 12	NS
	The ratio of total thyroidectomy	69%	70%	NS
	Experienced endocrine surgeon	87.5%	80%	NS
Surgical indications	Multinodular goiter	41.8%	38%	NS
	Multinodular toxic goiter	29.3%	28%	NS
	Graves disease	13.7%	20%	NS
	Carcinoma	15%	14%	NS

Abbreviations: F: female, M: male, PTH: parathormone.

respectively). The mean ± SD for preoperative serum calcium and PTH levels were 9.2 ± 0.3 mg/dL, 36.6 ± 13 pg/mL, respectively. No significant difference was found in terms of demographic features, surgical indications, and preoperative serum calcium and PTH levels between the study group and control group (Table 1).

There was no operative mortality. The incidence of transient vocal cord paralysis was 4.3% (7/160). Persistent vocal cord paralysis and hypoparathyroidism were not encountered in our series.

4.2. Postoperative hypocalcemia

In 38 (23.7%) out of 160 patients, serum calcium level was found to be lower than 8 mg/dL at the postoperative 24th h. Patients in Group 1 were significantly older than those in Group 2 ($p = 0.001$). No significant difference was found in terms of preoperative serum calcium and PTH levels between Group 1 and Group 2 ($p > 0.05$). Postoperative serum calcium level in Group 1 was significantly lower than that in Group 2 ($p = 0.001$). The postoperative drop in serum calcium level and irPTH levels in Group 1 were significantly higher than those in Group 2 ($p = 0.001$) (Table 2). The irPTH level in control group (8.3 ± 3.6 pg/mL) was significantly lower than that in Group 1 and Group 2 (803.26 ± 515 pg/mL and 130.87 ± 174 pg/mL).

Of 38 patients, 27 (71%) developed symptomatic hypocalcemia and 11 (29%) developed asymptomatic hypocalcemia. The postoperative drop in serum calcium level and irPTH level in patients with symptomatic hypocalcemia (2.3 ± 0.3 mg/dL and 1010 ± 486 pg/mL, respectively) were significantly higher than those in patients with asymptomatic hypocalcemia (1.1 ± 0.3 mg/dL and 293 ± 122 pg/mL, respectively) ($p = 0.001$). Hospital stay was significantly longer in Group 1 (3.6 ± 1.1 days, range 2–6 days) compared with that in Group 2 (1.3 ± 0.4 days, range 1–2 days) ($p = 0.001$).

4.3. Correlations

There was a negative correlation between age and postoperative serum calcium level ($r = -0.236$, $p = 0.033$) whereas a positive correlation was found between age and irPTH level ($r = -0.212$, $p = 0.007$) and postoperative drop in serum calcium level ($r = -0.239$, $p = 0.002$). There was a negative correlation between irPTH level and postoperative serum calcium level ($r = -0.641$, $p = 0.0001$) while a positive correlation was found between irPTH level and postoperative drop in serum calcium level ($r = 0.781$, $p = 0.0001$) (Fig. 1).

4.4. Evaluation of cut-off values for irPTH based on hypocalcemia and the difference in serum calcium level

The optimal cut-off value for irPTH based on hypocalcemia (sensitivity: 94%; specificity: 81%) was 250 pg/mL. An irPTH level higher than 250 pg/mL significantly correlated with postoperative hypocalcemia ($p = 0.03$) (Fig. 2A). The optimal cut-off value for the postoperative drop in serum calcium level based on hypocalcemia (sensitivity: 94%; specificity: 81%) was 1 mg/dL. An irPTH level higher than 250 pg/mL significantly correlated with the postoperative drop in serum calcium level ($p = 0.03$) (Fig. 2B).

According to ROC analysis, when the irPTH level was more than 250 pg/mL, hypocalcemia was detected in 94% of patients. False positive high PTH level ratio was 6%. Of 38 patients with hypocalcemia, 36 patients had PTH level higher than 250 pg/mL and 2 patients had PTH level lower than 250 pg/mL. Although the irPTH level was not increased in these 2 patients, the postoperative hypocalcemia was detected.

The postoperative drop in serum calcium level was found to be above 1 mg/dL in all of these patients. Patients who had an irPTH level higher than 250 pg/mL had a 69-fold increased risk for postoperative hypocalcemia (OR = 69.88; 95% CI:15.37–309.94).

The positive predictive value (PPV), negative predictive value (NPV) and overall accuracy of irPTH in postoperative hypocalcemia and the postoperative drop in serum calcium level were 61%, 99%, and 84%, respectively.

4.5. Evaluation of cut-off values for irPTH based on symptomatic hypocalcemia

The optimal cut-off value for irPTH based on symptomatic hypocalcemia (sensitivity: 96%; specificity: 90%) was 450 pg/mL. The PPV, NPV and overall accuracy of irPTH in postoperative symptomatic hypocalcemia were 96%, 92%, and 97%, respectively.

5. Discussion

We investigated the predictive value of irPTH level in developing postoperative hypocalcemia after thyroidectomy and found that high irPTH level was significantly associated with postoperative hypocalcemia. The irPTH level in patients with hypocalcemia was significantly higher than that in patients with normocalcemia. When the irPTH level was higher than 250 pg/mL hypocalcemia was detected in 94% of patients. The postoperative PTH assay in the irrigation fluid was sufficient to identify hypocalcemia in the majority of patients.

We suggest that irPTH levels are based on indirect evaluations of postsurgical residual parathyroid gland function. The exact mechanism of increase in irPTH levels in surgical site is not yet clear. The irPTH level in control group was found as 8.3 ± 3.6 pg/mL (before thyroid dissection and thyroidectomy). After thyroidectomy, mean irPTH level in patients with normocalcemia was 130.87 ± 174 pg/mL, whereas mean irPTH level in patients with hypocalcemia was 803.26 ± 515 pg/mL. The irPTH level in patients with normocalcemia was significantly higher than that in control group. irPTH level slightly increased in patients who even did not develop hypocalcaemia after thyroidectomy. Postoperative hypocalcemia was not detected in these patients despite a slight

Table 2
A comparison of laboratory features in patients with hypocalcemia and patients with normocalcemia.

Features	Patients with hypocalcemia ($n = 38$)	Patients with normocalcemia ($n = 122$)	p
Age	54.2 ± 13	45.5 ± 15	0.001
F/M	38/4	106/12	0.44
Preoperative serum calcium level (mg/dL)	9.4 ± 0.3	9.2 ± 0.4	0.08
Preoperative serum PTH level (pg/dL)	39.7 ± 12	37.1 ± 13	0.22
Postoperative serum calcium level (mg/dL)	7.4 ± 0.4	8.7 ± 0.4	0.001
Irrigation fluid PTH level (pg/mL)	803.26 ± 515	130.87 ± 174	0.001
The postoperative drop in serum calcium level (pg/mL)	2 ± 0.6	0.5 ± 0.4	0.001

Abbreviations: F: female, M: male, PTH: parathormone.

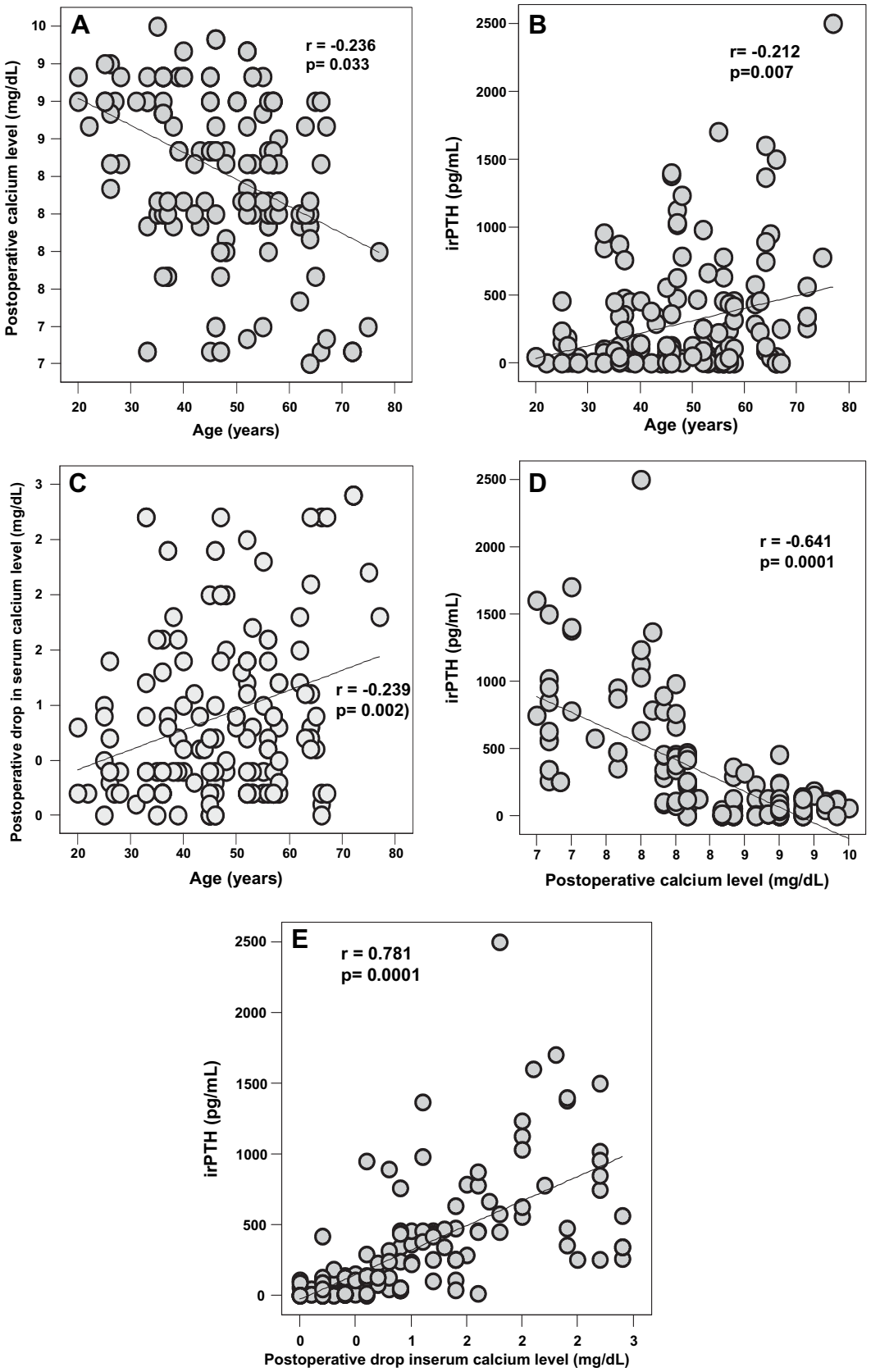
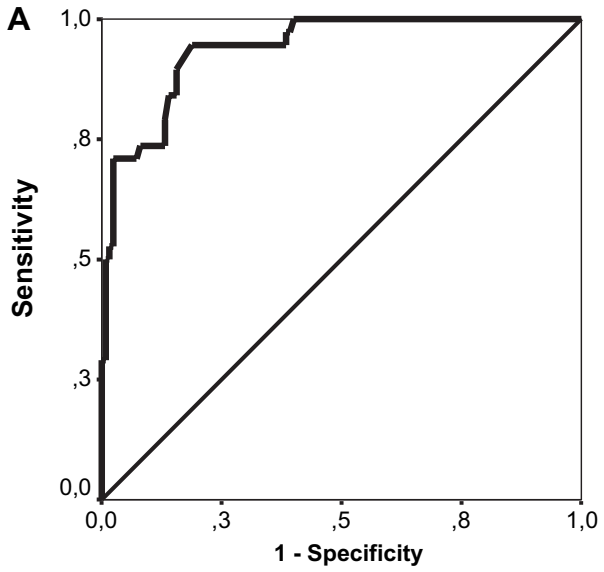
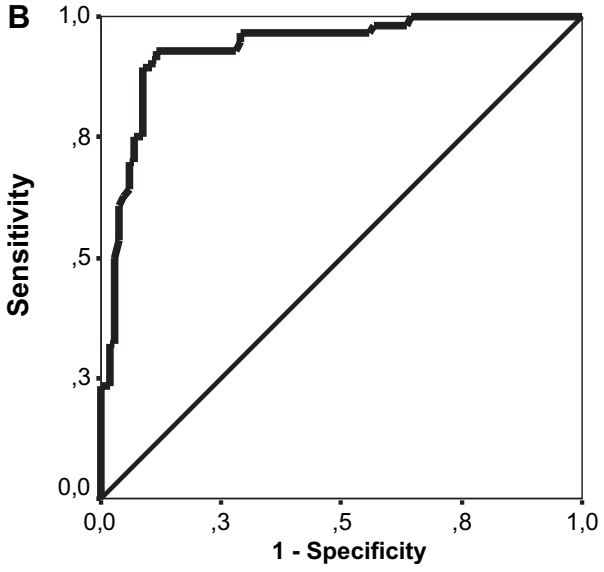


Fig. 1. Correlations between age and postoperative serum calcium level (A), and irPTH (B), postoperative drop in serum calcium level (C), postoperative serum calcium level and irPTH level (D), postoperative drop in serum calcium level (E).



	Area	Std. Error	p	95% CI
irPTH	0.939	0.019	0.001	0.902 – 0.977



	Area	Std. Error	p	95% CI
irPTH	0.933	0.02	0.001	0.892 – 0.974

Fig. 2. (A). ROC curve for the PTH levels of the surgical site irrigation fluid predicting postoperative hypocalcemia; (B). ROC curve for the PTH levels of the surgical site irrigation fluid predicting the postoperative drop in serum calcium level. "cut-off values of irPTH = 250 pg/mL; cut-off values of postoperative drop in serum calcium level 1 mg/dL".

increase in PTH level. One explanation could be that parathyroid glands may be subjected to surgical trauma during thyroidectomy.

Thyroidectomy carries potential risk to all four parathyroid glands and both recurrent laryngeal nerve.[4–6] Postoperative hypocalcemia is one of the most frequent complications after thyroidectomy. Biochemical hypocalcemia has been reported in as many as 50% of cases, but symptomatic hypocalcemia is seen much less frequently.[4–8] Improvements in surgical technique cannot eliminate the risk of hypocalcemia; therefore, hypocalcemia may occur even in the hands of the more experienced thyroid surgeons.[5–10] The causes of hypocalcemia after TT are multifactorial, and some of the factors involve iatrogenic surgical trauma to parathyroid glands, inadvertent removal of parathyroid glands, the number of functioning glands left behind, the extent of surgery, the experience of the surgeon, hyperthyroidism, retrosternal goiter, concomitant neck dissection, and thyroid carcinoma.[4–7,23–29]

Hypocalcemia is the principal factor that determines length of hospital stay after thyroid surgery. Identifying patients with low risk of hypocalcaemia may facilitate early discharge. The symptoms of hypocalcemia usually manifest 24–48 h after the thyroid operations.[10,11] Close monitoring of serum calcium levels is commonly used to identify postoperative hypocalcemia, however, there is no consensus about the optimal postoperative time.[30,31]

An intraoperative or postoperative serum PTH assay has been increasingly adopted to monitor the identification of patients who are at risk for hypocalcemia.[15–20] Investigators evaluated the applicability of intraoperative PTH (ioPTH) assay to identify postoperative hypocalcemia compared with postoperative serum calcium monitoring.[17,19,32] Both the ioPTH assay and consecutive early calcium measurements are accurate in predicting postoperative normocalcemia.[17,19,32] However, the ioPTH assay is available within 15–20 min after operation, but serum calcium monitoring requires at least 24 h.[17,19] The ioPTH assay monitors parathyroid function during thyroidectomy and identify patients at risk of clinically significant hypocalcemia much earlier than serum calcium monitoring.[15–22,32]

The accuracy of low intraoperative and postoperative serum PTH levels in predicting biochemical and symptomatic postoperative hypocalcemia was effective.[15–22] In addition to its clinical usefulness in identification of patients to be treated, serum PTH assay may also be cost-effective by reducing postoperative hospital stay and the need for expensive postoperative serum calcium monitoring. The sensitivity of the ioPTH level in predicting postoperative hypocalcemia is 70–80%.[15–18] In several studies, low serum PTH levels 8 and 12 h after operation were found to be the most accurate (98%) predictors of postoperative hypocalcemia.[19–22] On the contrary, Lombardi et al.[33] evaluated the reliability of PTH levels 4 h after thyroidectomy as a predictor of hypocalcemia in a large series of patients. In this study, false-negative results were observed in %13.4 of the patients. They found that low 4 h-PTH levels alone did not accurately predict clinically-relevant postoperative hypocalcemia.

In previous studies, the use of the intraoperative and postoperative serum PTH assay provided a way to assess overall parathyroid function during thyroidectomy.[19,22,34–36] Although efforts have been made for the use of perioperative PTH level in predicting postoperative hypocalcemia, findings on the accuracy of serum PTH monitoring and the optimal postoperative time remained obscure. To our knowledge, our study is the first prospective study performed to detect the value of irPTH level in predicting postoperative hypocalcemia after thyroidectomy.

PTH is made by the parathyroid gland and is critical to calcium and phosphorus balance. Parathyroid gland dysfunction results in low serum PTH and calcium levels. The most probable cause is certainly postoperative hypocalcemia secondary to trauma and devascularization during thyroidectomy.[7,10,11] Therefore we suggest that parathyroid gland destruction by surgical trauma contributes to the release of PTH to the surgical site and irPTH assay can identify patients at risk of hypocalcemia much earlier than perioperative PTH monitoring. In our study, we didn't compare the predictive value of postoperative hypocalcemia of irPTH and ioPTH, however, recent studies showed that the sensitivity of ioPTH level in predicting postoperative hypocalcemia is 70% to 80%. For this reason, we consider that the predictive value of irPTH level could be higher than ioPTH level. A study for comparing the predictive value of irPTH with ioPTH is currently being conducted in our clinic. In our study, irPTH was strongly useful to predict hypocalcemia after

thyroidectomy. Based on the results of the study, we recommend that patients with irPTH levels higher than 250 pg/dL should immediately be placed on oral calcium and, if necessary, vitamin D supplementation in order to prevent symptomatic hypocalcemia.

6. Conclusion

irPTH assay is a sensitive tool in predicting postoperative hypocalcemia and identifying patients at risk of developing postoperative hypocalcemia.

Conflict of interest
None declared.

Funding
We have no conflict interest.

Ethical approval
Local ethical committee, Istanbul medical Faculty.

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