Intact Parathyroid Hormone (iPTH) as a Predictor of Symptomatic Hypocalcemia after Total Thyroidectomy; A Cross Sectional Study

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Abstract

Background: This study aimed to measure levels of intact parathyroid hormone (iPTH) following total or completion thyroidectomy, to evaluate its role in diagnosing symptomatic hypocalcemia in affected patients.

Methods: This cross-sectional study was conducted on patients who underwent total or completion thyroidectomy during 2014–2015. Serum iPTH and calcium levels were measured immediately after surgical wound closure. Hypocalcemia symptoms were assessed every 8 hours postoperatively. The relationship between serum calcium and iPTH levels was analyzed. Statistical tests included repeated measures ANOVA, t-test, Chi-square, Mann–Whitney U, and ANOVA. The optimal iPTH cut-off value was determined using receiver operating characteristic (ROC) curve analysis.

Results: Of 112 surgical patients, iPTH was measured in 100 cases. Twenty patients developed symptomatic hypocalcemia. There were no statistically significant differences among normocalcemic, asymptomatic hypocalcemic, and symptomatic hypocalcemic groups in terms of age, preoperative calcium levels, or length of hospitalization (P = 0.48, P = 0.46, and P = 0.6, respectively). iPTH levels differed across the groups, notably between asymptomatic and symptomatic hypocalcemic patients (P = 0.029). ROC analysis identified an optimal iPTH cut-off value of 18.9 pg/mL, with sensitivity and specificity of 90% and 56.52%, respectively.

Conclusions: iPTH measurement immediately following thyroidectomy shows utility in predicting symptomatic hypocalcemia and may play an important role in identifying patients at risk postoperatively.

Keywords: Total thyroidectomy, Hypocalcemia, iPTH, Predictive Factor

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Introduction

During thyroid surgeries—particularly total thyroidectomy—there is a significant risk of parathyroid gland injury, which can lead to temporary or permanent hypocalcemia. Hypocalcemia is the most common complication of total thyroidectomy, occurring in approximately 30% of cases. While most instances are asymptomatic, symptomatic hypocalcemia can present as a medical emergency requiring intravenous (IV) calcium administration [1]. Due to this risk, patients typically remain hospitalized for at least 48 hours for calcium level monitoring [2,3].

Measuring intact parathyroid hormone (iPTH) levels after thyroid surgery is considered a reliable method for identifying patients at risk of developing hypocalcemia. Although intraoperative PTH (ioPTH) levels are routinely measured during parathyroidectomy, they are not commonly assessed during thyroidectomy [4]. The etiology of postoperative transient hypoparathyroidism is generally attributed to ischemic injury of the parathyroid glands [1]. Active PTH has a short

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biological half-life of 2–4 minutes, primarily due to rapid hepatic and renal clearance. Consequently, measuring iPTH levels immediately after thyroid surgery may offer a dependable tool for predicting patients at high risk for symptomatic hypocalcemia [5–7].

Various approaches have been employed to determine the optimal timing for measuring PTH levels following thyroidectomy. Some studies assessed PTH intraoperatively, while others focused on postoperative evaluations. Hypocalcemia is also a key contributor to prolonged hospital stays after thyroidectomy [8,9].

Although numerous recent investigations have explored the utility of iPTH as a predictor of postoperative symptomatic hypocalcemia, the clinical relevance of this relationship remains under discussion [10]. Importantly, early identification of high-risk patients could facilitate timely prophylactic supplementation and potentially enable earlier discharge [11].

This study was designed to assess the predictive accuracy of postoperative iPTH levels for symptomatic hypocalcemia in patients who underwent total or completion thyroidectomy.

Materials and Methods

This cross-sectional study was conducted on patients referred to the General Surgery Clinic of Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran, who underwent total or completion thyroidectomy between April 2014 and March 2015. A total of 112 patients were evaluated for thyroidectomy. Serum iPTH levels were measured for 100 patients; 12 were excluded—seven due to inconclusive laboratory results, three due to a history of calcium supplementation, and two due to preference to withdraw from the study. The study was approved by the ethics committee of Tehran University of Medical Sciences, and written informed consent was obtained from all participants.

Demographic characteristics, including age and sex, were collected. Renal failure and parathyroid adenoma were ruled out using relevant laboratory criteria. Vitamin D and albumin levels were not routinely assessed preoperatively or postoperatively.

Total and completion thyroidectomy procedures were performed using standard techniques by an attending surgeon and a senior surgical resident, with careful identification of the recurrent laryngeal nerve and parathyroid glands. Blood samples for measuring iPTH and serum calcium were obtained immediately following surgical incision closure.

Postoperatively, patients were monitored every eight hours for symptoms of hypocalcemia, including perioral numbness and tingling, limb paresthesia, Chvostek sign, and Trousseau sign. Based on previous studies, a serum calcium threshold of 8.5 mg/dL was used to define hypocalcemia.

Patients were categorized into three groups according to calcium levels and presence of hypocalcemic symptoms: normocalcemic patients (NC), transient asymptomatic hypocalcemic patients (AH), and symptomatic hypocalcemic patients (SH). Oral or intravenous calcium was administered if serum calcium was below 8.5 mg/dL or if symptoms were present.

According to the reference range of the contracting laboratory, iPTH levels below 15 pg/mL and above 65 pg/mL were considered abnormal. iPTH was measured using the Electrochemiluminescence (ECL) method (Roche 410E).

Data were analysed using Stata Software [Stata Corp. 2009. Stata Statistical Software: Release 11. College Station, TX: Stata Corp LP]. Frequency and relative frequency were calculated for qualitative variables, while means and standard deviations were computed for quantitative variables. To examine the association between independent variables and the main outcomes (symptomatic/asymptomatic), depending on the type of variable, we used t-test, Chi-Square, Mann-Whitney, and ANOVA tests. A mixed between-within subjects analysis of variance (repeated measures ANOVA) was conducted to assess patients' calcium levels in the two hypocalcemic groups (symptomatic/asymptomatic) across eight calcium measurements after the operation. Additionally, a receiver operating characteristic (ROC) curve was used to determine the optimal cut-off point for iPTH levels in diagnosing symptomatic and asymptomatic patients. Alongside sensitivity and specificity performance measures, the predictive values—positive predictive value (PPV) and negative predictive value (NPV)—were calculated. A p-value less than 0.05 (<0.05) was considered statistically significant.

Results

112 patients underwent surgery. The iPTH test was performed for 100 patients, and 12 patients were excluded. Based on the results obtained from this study, 21 percent of cases were male, and the mean age of men and women was 47.57 ± 14.36 and 40.46 ± 12.75 years, respectively [The total mean age: 41.96 ± 13.35 years; age range: 14–74 years]. According to the results, 20 patients had symptomatic hypocalcemia (Table 1). The results also showed that the age, calcium level before the operation, and the length of hospitalization were not different between normocalcemic and the two types of hypocalcemic

Table 1: The average levels of calcium in each of the regarding checkpoints.

Variables	Levels	Serum calcium			P-value
		Normocalcemic	Hypocalcemia		
			Asymptomatic hypocalcemia	Symptomatic hypocalcemia	
Patients, n(%)	N(%)	11 (11%)	20 (20%)	69 (69%)	---
Age	Mean± SD	41.45 ± 14.55	42.94 ± 13.26	38.85 ± 13.21	0.48
Calcium	Mean± SD	8.13 ± 0.40	7.91 ± 0.63	7.85 ± 0.56	0.46
iPTH	Mean± SD	31.91 ± 25.77	27.82 ± 22.08	14.35 ± 13.94	0.029
Length of hospitalization (Days)	Mean± SD	2.27 ± 2.00	3.15 ± 0.93	2.83 ± 2.60	0.60
Gender	Male (No.)	5	11	5	0.07
	Female (No.)	6	58	15	
iPTH Category	Normal (No.) (15- 65pg/dl)	6	37	5	0.07
	Abnormal (No.) (<15, >65 pg/dl)	5	32	15	

Table 2: descriptive statistics of patients' calcium in two groups of hyoocalcemia (with and without symptoms) eight times after operation.

Follow up Time	Hypocalcemia			
	Symptomatic hypocalcemia		A symptomatic hypocalcemia	
	n	Mean ± SD	n	Mean (SD)
Time 1	20	8.23 (0.89)	69	8.47 (0.856)
Time 2	20	8.33 (1.08)	69	8.25 (0.87)
Time 3	20	8 (0.77)	66	8.09 (0.70)
Time 4	20	7.86 (0.65)	58	8.34 (0.90)
Time 5	15	7.95 (0.71)	52	8.35 (0.74)
Time 6	14	7.95 (0.71)	38	8.38 (0.73)
Time 7	11	8.1 (1.33)	21	8.39 (0.86)
Time 8	10	7.94 (0.87)	11	8.81 (0.72)

Time1: Immediately after closing the surgical incision. Time2, Time3, …, Time8: Time intervals (every 8-hours) after operation in which serum calcium levels were assessed.

groups (P = 0.48, P = 0.46, and P = 0.6, respectively). There was also no difference in the distribution of gender and iPTH categories (normal/abnormal) (P = 0.07 and P = 0.07, respectively). However, there was a significant difference in iPTH levels between the normocalcemic and the two hypocalcemic groups (asymptomatic/symptomatic) (P = 0.029). Bonferroni's post-hoc pairwise comparison showed a significant difference in iPTH levels between the symptomatic and asymptomatic hypocalcemia groups (P = 0.04) (Table 1).

Results of the repeated measures ANOVA revealed that there was no significant interaction between hypocalcemia type and time of detection (P = 0.2547). There was also no substantial main effect for time (P = 0.06), indicating that both groups showed no reduction or increase in their calcium levels across the eight time-point measurements (Table 2).

The total score of the iPTH scale did not conform to a normal distribution (median score: 15.8; range: 4–95). Using ROC analysis, the optimal cut-off score of the iPTH diagnostic scale was determined to be 18.9 (Figure 1). At this cut-off, the sensitivity, specificity, PPV, and NPV of the diagnostic scale were 90.00%, 56.54%, 37.54%, and 95.11%, respectively. The area under the curve (AUC) was 0.727 [95% confidence interval (CI): 0.622–0.816]. The level of iPTH in both symptomatic and asymptomatic groups was significantly different (P = 0.002). Assessment of iPTH played a significant role in the prediction of symptomatic hypocalcemia (P < 0.001). In the present study, there were no substantial missing data, as the entire process was conducted under the direct supervision of researchers.

Discussion

Nowadays, checking serum iPTH levels after total thyroidectomy is increasingly used to identify patients at risk for postoperative hypocalcemia [9]. Thyroidectomy patients who are discharged from the hospital earlier than usual may be at risk of severe

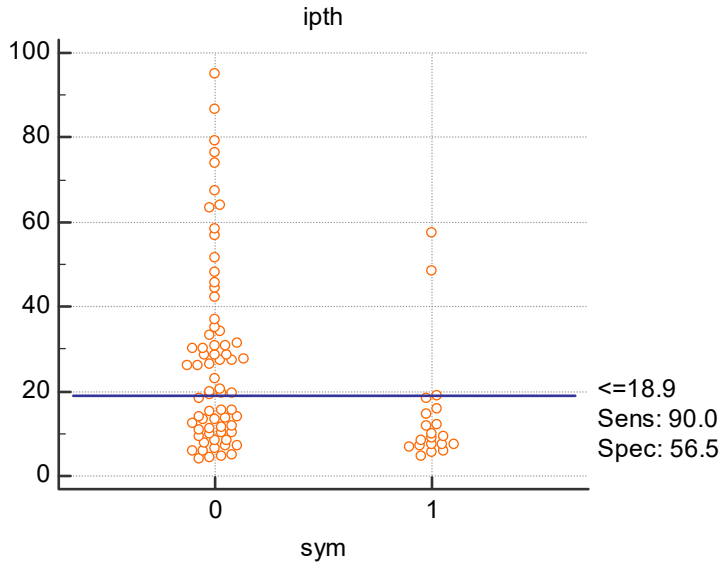

Fig. 1: ROC curve showing iPTH optimum cut-off value

hypocalcemia. Calcium supplements are routinely prescribed in most cases, although these patients may not require them (over-treatment). On the other hand, undiagnosed hypocalcemia after discharge can lead to delayed treatment (under-treatment). Therefore, prediction, diagnosis, and prevention of hypocalcemia in patients undergoing thyroidectomy appear to be imperative issues.

In our study, 21 patients were male (21%) and 79 patients were female (79%), all of whom were examined and assessed. The mean age in males was approximately 46.48 ± 14.32 years, and 40.76 ± 12.91 years in females (P = 0.089). Based on the findings of the linear regression model, there was a significant relationship between decreasing serum calcium levels and low iPTH levels. Specifically, at the T4 and T5 checkpoints, the mean serum calcium level was statistically different between the normal and abnormal groups. This indicates that patients with lower levels of serum iPTH immediately after surgery have a higher likelihood of developing symptomatic hypocalcemia within 24 hours. This result aligns with findings from other researchers, who demonstrated that low postoperative PTH levels can be associated with hypocalcemia [12].

To improve the accuracy of the study, serum PTH levels may be assessed immediately after surgery or within 1 to 8 hours thereafter. A study by Calis et al. showed that measuring PTH 20 minutes postoperatively offers better accuracy for predicting early postoperative hypocalcemia than measuring calcium or PTH at 4 or 24 hours post-surgery [13]. The timing of PTH measurement can markedly enhance the sensitivity and specificity of the test in predicting hypocalcemia following total thyroidectomy. In light of the sensitivity (90%) and specificity (56.52%) reported in this study, checking the iPTH level after surgery may be beneficial.

The results of this study revealed that 20 patients had symptomatic hypocalcemia. This outcome was determined based on clinical symptoms and a decrease in serum calcium levels during the first two days after surgery (<8.5 mg/dl).

The main objective of this study was to evaluate the predictive value of the iPTH test for early diagnosis of the hypocalcemia. First, serum iPTH and serum calcium were measured immediately after surgery. Furthermore, calcium levels were measured for seven times consecutively (every 8 hours). The relationship between iPTH and total serum calcium level was statistically significant. This was consistent with previous studies in this field (5, 8, 9). Lim et. al. demonstrated that an iPTH ≤ 7.5 one hour after the surgery can identify people who prone to Symptomatic- Hypocalcemia (11). Matteo Angelo showed that an iPTH ≤ 12.5 4 hour after thyroidectomy could predict patients who are prone to symptomatic hypocalcemia (12). Therefore, researchers recommend early calcium intake in patients who undergoes thyroid surgery to reduce the risk of symptomatic hypocalcemia.

Land et al. studied 117 patients who underwent total and completion thyroidectomy. Of these, 17 patients had symptomatic hypocalcemia, and calcitriol supplements were prescribed upon hospital discharge. They concluded that PTH-SC is a reliable and precise factor for predicting the likelihood of clinical hypocalcemia. Discharging patients with

PTH >1 pmol/L on the day of surgery appears to be a reasonable approach [14]. Our results showed a lower level of iPTH in the subgroup of patients with symptomatic hypocalcemia compared to the other subgroups. Based on the obtained results, the sensitivity and specificity of iPTH for predicting hypocalcemia in patients immediately after surgery were 90% and 56.52%, respectively. The accuracy of the study was 72%, which closely aligns with similar studies. For example, Lang et al. showed that PTH-SC (≤1 or >1 pmol/L) had higher specificity (95.0%) and area under the curve (AUC = 0.887) than serial calcium monitoring or PTH-D1 alone. Although 3.98% of patients with PTH-SC >1 pmol/L required calcium supplements upon discharge, they only required the minimum amount needed to maintain normocalcemia. PTH-SC is an accurate and reliable method for predicting clinically relevant hypocalcemia [14, 15].

However, some studies have reported differing results. For instance, in a prospective study [16], serum iPTH levels were measured before surgery, immediately after closing the surgical incision, and four hours postoperatively. The results showed that 39 patients (28.8%) developed symptomatic hypocalcemia. These patients had significantly lower iPTH levels and serum calcium levels following surgery ($P < 0.001$). The sensitivity, specificity, and overall accuracy of iPTH for predicting hypocalcemia in this study were 97.4%, 65.9%, and 76.4%, respectively. The authors concluded that the reduction in iPTH was more accurate than the absolute iPTH level and could reliably predict hypocalcemia after thyroidectomy. They recommended that patients with normal iPTH could be safely discharged on the first day after surgery without calcium supplementation, which is consistent with findings from similar studies [14].

It should be noted that in some cases with PTH levels below the normal range, hypocalcemia cannot be predicted with certainty. According to this study, measuring PTH levels immediately after surgery may help identify patients at high risk for hypocalcemia. Although vitamin D and albumin levels have recently been measured at our institute (39% of patients had vitamin D <30 ng/dL and 25.8% had albumin <3.5 g/dL) [17], we lack these data for the current patient cohort, and this is considered a limitation of our study.

Conclusion

Taking into account, we conclude that checking iPTH immediately after the operation can be useful for predicting patients at risk for hypocalcemia. Regarding the remarkable sensitivity of this test, we expect to predict the majority of patients with symptomatic hypocalcemia after total or completion thyroidectomy. However, more comprehensive studies are needed to prove this theory.

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Ethics Approval and Consent to Participate

This study was conducted after obtaining approval from the relevant Ethics Committee [Code: TUMS.REC.1394.127].

Consent for Publication

The authors give their consent for the publication of this manuscript.

Availability of Data and Supporting Materials

Please contact the corresponding author for data requests.

Competing Interests

The authors declare that they have no competing interests.

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Authors' Contributions

AY: Contributed to the conception and design of the work, conducting the study, acquisition, analysis, and interpretation of data, drafting and revising the manuscript, approval of the final version, and agreed to all aspects of the work. AM: Contributed to complete revision and technical corrections. AGH-A and RE: Contributed to the conception and design of the work, revising the manuscript, approval of the final version, and agreed to all aspects of the work. AGH-A: Contributed to the design of the work, revising the manuscript, approval of the final version, and agreed to all aspects of the work. SHN: Contributed to the design of the work, revising the manuscript, approval of the final version, and agreed to all aspects of the work. AM and BN: Contributed to the design of the work, revising the manuscript, approval of the final version, and agreed to all aspects of the work. AY: Contributed to the design of the work, revising the

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Abbreviations

PTH: parathyroid hormone, iPTH: intact parathyroid hormone, IV: intravenous, ECL: electrogenerated chemiluminescence, PPV: positive predictive value, NPV: negative predictive value.

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