ORIGINAL RESEARCH

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Can the risk of hypocalcemia be detected with intact parathyroid hormone level after total thyroidectomy?

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Abstract

Objective: Nowadays, thyroidectomy is performed in patients with various indications. However, transient or permanent hypocalcemia occurs after surgery. In this case, the duration of hospitalization of the patients is prolonged. In this study, we aimed to detect hypocalcemia in the early phase with intact parathyroid hormone (iPTH), a biochemical marker.

Method: Hospital records of patients who had undergone standard bilateral total thyroidectomy for thyroid disease were retrospectively analyzed between September 2018 and April 2019 at the Department of General Surgery, Gaziantep University.

Results: Of the 114 patients included in the study, 91 were female (79.8%), and 23 were male (23%). Calcium levels of ≤8.5 mg/dL were found in 49 of 114 patients. Clinical symptoms of hypocalcemia were observed in 19 of these 49 patients. There was a significant correlation between the patients' iPTH levels at 3-6 hours postoperatively and the calcium values at 24 hours postoperatively ($p<0.05$). In addition, a significant, positive and weak correlation was found between the iPTH level and the iPTH level at 24 hours postoperatively and the Ca level at 24 hours postoperatively ($p<0.05$). The iPTH level measured between 3 and 6 hours postoperatively can predict hypocalcemia with a sensitivity of 77.5% and a specificity of 40.3%.

Conclusion: Postoperative hypocalcemia can be predicted with iPTH in the early period. The serum iPTH value has been concluded to be an effective parameter that can be used to predict postoperative hypocalcemia.

Keywords: Intact Parathyroid Hormone, Hypocalcemia, Thyroidectomy

INTRODUCTION

The thyroid gland is a vital endocrine organ that secretes thyroid hormones and is often operated on for many reasons (1). The most common complication following total thyroidectomy for thyroid disease is transient hypocalcemia (2). This clinical condition prolongs the patient's duration of hospitalization. Hypocalcemia may develop due to various factors, such as impaired blood supply to the parathyroid gland and injury to the parathyroid gland during dissection with the experience of the surgeon performing the surgery. However, thanks to developments in medicine, the risk of complications has been minimized through the use of advanced surgical instruments, good preoperative preparation of patients, and the development of anesthetic techniques. In parallel with these developments, the risk of morbidity, mortality, and complications in patients decreased.

Evaluating hypocalcemia with serum calcium value by looking at the clinical manifestation of the patients after surgery causes the diagnosis of hypocalcemia to be delayed and the duration of hospitalization to be prolonged. Hypocalcemia

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can be asymptomatic and sometimes lead to life-threatening clinical consequences (3). Early identification of risk factors for hypocalcemia is all the more important to reduce the potential risks and duration of hospitalization associated with hypocalcemia. Hypocalcemia can be predicted in the early postoperative period with iPTH (intact parathyroid hormone), which is tested immediately after surgery. This can also prevent prophylactic Ca (calcium) and vitamin D treatment in the early postoperative period (3).

Hypocalcemia and Hypoparathyroidism

Hypocalcemia that persists for less than one year after thyroidectomy is called transient hypocalcemia. If this condition persists for more than one year and requires calcium replacement, it is called persistent hypocalcemia.

The incidence of transient hypocalcemia is 3-80%, whereas permanent hypocalcemia occurs in society with an incidence of 0.4-13% (1,2).

Temporary hypocalcemia is not observed for a variety of reasons, such as complete ischemia or ischemic damage to the parathyroid glands due to thyroidectomy, hypothermia of the parathyroid glands, ET-1 (endothelin-1) secretion, hematomas formed adjacent to the parathyroid gland, calcitonin secretion due to surgical manipulation of the thyroid gland, fasting bone syndrome, hemodilution, hypothermia, decreased calcium absorption by the kidneys, removal of the parathyroid glands and necrosis due to vascular injury (4–9).

Serious complications such as cataracts, calcifications in the basal ganglia of the brain and cerebellum, and papilledema may occur in hypocalcemic patients who have waited for a long time and are delayed (10). Therefore, in hypocalcemic patients, calcium measurement should be performed in the postoperative period, regardless of the clinical picture. In this study, we aimed to detect hypocalcemia in the early phase with intact parathyroid hormone (iPTH), a biochemical marker.

METHOD

Ethical permission was obtained from the Gaziantep University, Medical Faculty Clinical Research Ethics Committee for this study with date 09.01.2019 and number 2019/34, and Helsinki Declaration rules were followed to conduct this study. Hospital records of 114 patients over 18 years of age who had undergone standard bilateral total thyroidectomy due to thyroid diseases (Graves' disease, multinodular goiter, benign and malignant thyroid diseases) were retrospectively analyzed between September 2018 and April 2019 at the Department of General Surgery, Faculty of Medicine, Gaziantep University. With the joint council meetings held with general surgery, endocrinology, nuclear medicine, and pathology, surgery was decided for these patients. The surgeries of the patients were performed by the same surgical team. Patients who underwent central or lateral lymph node dissection during surgery, patients with recurrent multinodular goiter, patients with parathyroid disease, pregnant patients, and patients with renal failure were excluded from the study. In these patients, age, gender, comorbidities, preoperative calcium, and parathyroid hormone levels, and postoperative calcium and parathyroid hormone levels measured in the blood between 3-6 hours, and calcium and parathyroid hormone levels measured 24 hours later were. The normal calcium range was assessed to be 8.5-10.5 mg/dL (milligrams/deciliter) when analyzed. Hypocalcemia was defined as a calcium value below 8.5 mg/dL. The intact parathormone (iPTH) levels were measured using an autoanalyzer with the spectrophotometric and chemiluminescent methods (Beckman Coulter Unicel DxI 800). The normal serum iPTH value was considered to be in the range of 15-65 pg/mL. In the postoperative period, numbness in the body, hand or foot, numbness, muscle spasms, positive Chvostek or Trousseau findings and cardiac arrhythmia were accepted as symptoms of hypocalcemia. Patients in whom these symptoms were not observed and whose calcium levels were decreased were evaluated as asymptomatic hypocalcemic patients.

Statistical Analysis

The analyses were performed with the SPSS 22.0 program. Repeated measurements analysis of variance test was used to compare the differences of iPTH and calcium values obtained at different measurement times. In order to determine from which measurement time the statistically significant difference originates, the LSD (Least significant difference) test, one of the multiple comparison tests, was used. The relationship between iPTH and calcium values obtained at different measurement times was analyzed by Pearson correlation analysis. In addition, patients were divided into two groups as hypocalcemia and normocalcemia according to the postoperative 24th hour calcium value. The T test was used to test the difference between the post op 3-6 hour iPTH values of these two groups. ROC analysis was used to determine the cut-off point for the variables. In all analyses, $p<0.05$ was considered significant.

RESULTS

A total of 114 male and female patients aged 18-82 years who underwent standard bilateral total thyroidectomy for thyroid disease (Graves', multinodular goiter, benign and malignant thyroid diseases) were included in the study. Ninety-one of the patients were female (79.8%), and 23 were male (23%). The mean age of the patients was 48 years.

In the study, the pathology results of the thyroidectomy material of the patients included in the surgery were analyzed (Table 1). Pathological examination revealed follicular

adenoma in 1 patient (0.9%), follicular neoplasia in 3 patients (2.6%), Graves' disease in 9 patients (7.9%), nodular goiter in 1 patient (0.9%), suspected hurthle cell neoplasia in 2 patients (1.8%), hurthle cell neoplasia in 1 patient (0.9%), medullary thyroid carcinoma in 1 patient (0.9%), medullary carcinoma in situ in 1 patient (0.9%), multinodular goiter in 45 patients (39.5%), NIFTP in 1 patient (0.9%), papillary microcarcinoma in 27 patients (23.7%), and papillary carcinoma in 22 patients (19.3%).

Table 1. Pathology diagnoses of patients after surgery

Pathology Pieces	n	%
Follicular Adenoma	1	0.9
Follicular Neoplasia	3	2.6
Graves	9	7.9
Nodular Goiter	1	0.9
Hurthle Cell Neoplasia Suspicious	2	1.8
Hurthle Cell Neoplasia	1	0.9
Medullary Carcinoma	1	0.9
Medullary Carcinoma in situ	1	0.9
Multinodular Goiter	45	39.5
NIFTP	1	0.9
Papillary Microcarcinoma	27	23.7
Papillary Thyroid Carcinoma	22	19.3
Total	114	100.0

NIFTP: noninvasive follicular thyroid neoplasm with papillary-like nuclear features, n: number of patients

A calcium level of ≤8.5 mg/dL was found in 49 of 114 patients included in the study. Clinical symptoms of hypocalcemia were observed in 19 of these 49 patients. However, although the calcium value was >8.5 mg/dL, hypocalcemia symptoms were observed in 4 patients. Calcium replacement was performed in 19 patients with symptoms of hypocalcemia. In addition, although the calcium value was >8.5 mg/dL, calcium replacement was performed in 4 patients who developed hypocalcemia in the clinic.

Table 2. Age and hypocalcemia relationship

Calcium	n	Average age	Standard deviation	p value
≤ 8.5 mg/dL	49	47.76	11.60	0.815
> 8.5 mg/dL	65	48.34	14.14	

n: number of patients, p<0.05

When the data between the age of 114 patients included in the study and hypocalcemia were analyzed, the mean age of 49 patients with Ca≤8.5 mg/dL in the postoperative period was 47.7, while the mean age of 65 patients with Ca>8.5 mg/dL was 48.3 (Table 2). No significant correlation was found between age and hypocalcemia (p>0.05).

The relationship between sex and calcium studied in the postoperative period was analyzed. While Ca ≤8.5 mg/dL in 4 (17.4%) of 23 male patients, the number of males with Ca>8.5 mg/dL was 19 (82.6%). While Ca≤8.5 mg/dL was detected in 45 (49.5%) of 91 female patients included in the study in the postoperative period, Ca >8.5 mg/dL was detected in 46 (50.5%) female patients (Table 3). The risk of hypocalcemia in females was found to be higher than that in males and was found to be statistically significant (p<0.05).

Table 3. Gender and calcium relationship

			Calcium (mg/dL)		Total	p value
			Ca≤8.5 mg/dL	Ca>8.5 mg/dL		
Gender	M	n	4	19	23	0.006*
		%	17.4%	82.6%	100.0%	
	F	n	45	46	91	
		%	49.5%	50.5%	100.0%	
Total		n	49	65	114	
		%	43%	57%	100.0%	

P<0.05, Ca: calcium, M: male, F: female, n: number of patients

Patients' preoperative and postoperative 3-6 h and 24 h iPTH levels were analyzed (Table 4). The preoperative iPTH levels were found to be higher than postoperative iPTH levels that measured between 3-6 hours and 24th hours. Statistical analysis revealed that the preoperative and postoperative iPTH levels were statistically significant compared to the measurement times (p<0.05).

Table 4. Comparison of iPTH values according to measurement times.

Sample Time:	n	Mean ± standard deviation	p
Preoperative iPTH	114	53.64±26.25	0.001*
Postoperative iPTH (3-6 hours)	114	32.66±23.99	
Postoperative iPTH (24th hour)	114	33.39±25.83	

*p<0.05, n: number of patients, iPTH: intact parathyroid hormone, t-test

The patients' preoperative and postoperative Ca levels were analyzed at 3-6 hours and 24 hours (Table 5). The preoperative Ca values were higher than postoperatively 3-6 hours Ca levels and 24th hours Ca levels. Statistical analysis revealed that the preoperative and postoperative Ca levels were significant compared to the measurement times (p<0.05).

Patients' iPTH levels were analyzed between 3-6 hours postoperatively, and the calcium levels were analyzed at 24 hours postoperatively (Table 6). Patients who were found

to have hypocalcemia at the 24th hour postoperatively were also found to have low iPTH levels between 3-6 hours postoperatively. There was a significant correlation between the iPTH levels of the patients at 3-6 hours postoperatively and the calcium levels at 24 hours postoperatively ($p<0.05$).

Table 5. Comparison of calcium values according to measurement times

Sample Time:	n	Mean ± standard deviation (mg/dl)	p
Preoperative Ca	114	9.50±0.59[a]	0.001*
Postoperative Ca (3-6 hours)	114	8.51±0.97[b]	
Postoperative Ca (24th hour)	114	8.69±0.70[b]	

*p<0.05, n: number of patients, Ca: blood calcium level, t-test

Table 6. 3-6/h iPTH-postoperative and 24/h calcium relationship in the postoperative period

n	Postoperative 24th hour calcium value(mg/dl)	Postoperative 3-6/h iPTH mean Values	p value
49	≤8 5	27.31	0.038*
65	>8.5	36.72	

p<0.05, n: number of patients, h: hour, iPTH: intact parathyroid hormone

Table 7. Relationship between iPTH and calcium values

		Preoperative Ca p value	Postoperative Ca 3-6 hours p value	Postoperative Ca 24th hour p value
Preoperative iPTH	Pearson Correlation	-0.029	-0.051	0.016
	Sig. (2-tailed)	0.759	0.592	0.863
	n	114	114	114
Postoperative iPTH 3-6 hours	Pearson Correlation	0.060	0.079	0.287**
	Sig. (2-tailed)	0.529	0.402	0.002*
	n	114	114	114
Postoperative iPTH 24th hour	Pearson Correlation	0.122	0.053	0.308**
	Sig. (2-tailed)	0.197	0.577	0.001*
	n	114	114	114

P<0.05, n: number of patients, iPTH: intact parathyroid hormone, Ca: calcium, Pearson correlation analysis

The relationship between preoperative and postoperative iPTH and calcium levels was investigated using Pearson correlation analysis (Table 7). Accordingly, a statistically significant, positive and weak relationship was found between the iPTH level measured between 3-6 hours postoperatively and the iPTH level measured at 24 hours postoperatively and the Ca level measured at 24 hours postoperatively ($p<0.05$). Hypocalcemia can be predicted in the 24th postoperative hour by examining the iPTH level in the 3-6 hours postoperatively.

When the relationship between the iPTH level measured in the 3rd to 6th postoperative hour and hypocalcemia was investigated, the ROC diagram obtained for the postoperative iPTH level is shown in Figure 1. This is the 39.6 pg/ml cut-off point for the postoperative iPTH level. The area under the ROC curve for the iPTH level measured between 3-6 hours postoperatively was 0.611, and the iPTH level measured between 3-6 hours postoperatively was significant in predicting hypocalcemia (95% confidence interval: 63.4-88;

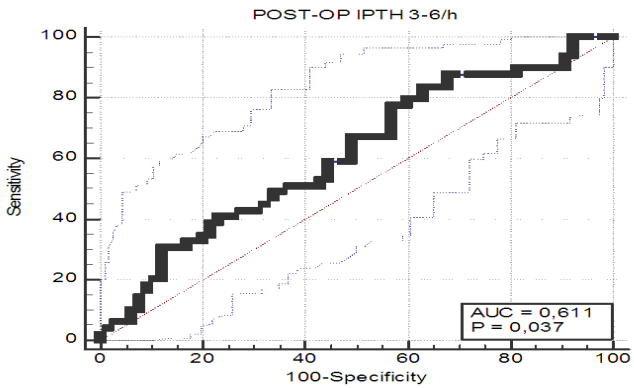

Figure 1: ROC curve obtained for iPTH value at 3-6 hours postoperatively

$p<0.05$). When the serum iPTH value was below 39.6 pg/ml between 3 and 6 hours postoperatively, it was found that it could predict hypocalcemia with a sensitivity of 77.55% and specificity of 40.3%.

DISCUSSION

Thyroidectomy is the most commonly performed endocrine surgical procedure worldwide. Thyroidectomy procedures can lead to various complications. The most common complication is hypocalcemia. Due to these complications, the medical treatments of the patients are prolonged, and the duration of hospitalization is prolonged. Accordingly, many biochemical and hormonal tests are required. While the rate of transient hypocalcemia is 10-50%, the rate of permanent hypocalcemia lasting more than 6 months is 0.5-2% (11–13). A total of 114 patients were included in our study, and 49 (42.3%) of these patients had transient hypocalcemia. The rate of development of hypocalcemia is similar to the literature (11–16).

The cause of hypocalcemia after thyroidectomy is not fully known. However, it was thought that there were reasons such as impaired blood supply to the parathyroid glands due to manipulations during surgery, the development of ischemia in the glands or accidental removal of the glands during surgery. Therefore, the physician performing thyroid surgery should have sufficient information about the anatomy of

the parathyroid glands and the changes in the parathyroid glands. The surgeon should stay away from interventions that will affect the blood supply to the glands. In many studies in the literature, it has been suggested that postoperative hypocalcemia may be due to surgical technique (11,17,18). In a prospective study conducted by Acun et al. (19), it was reported that there was no difference between experienced surgeons and residents in terms of damage to the parathyroid gland during surgery and related hypocalcemia. Since all the surgeries included in our study were performed with the same surgical team and the same surgical technique by the same residents, hypocalcemia that may occur due to surgical technique was standardized.

In the statistical analysis conducted for the relationship between hypocalcemia and gender, we observed a statistically significant higher susceptibility to hypocalcemia among females. A study by Bove et. al (8) similarly reported an increased risk of hypocalcemia associated with the female gender.

Early detection of the risk of hypocalcemia is important to avoid prophylactic medical treatment so that patients can be discharged early and avoid the risk of hypocalcemia that may occur. Calcium metabolism is slow and shows no signs and symptoms in postoperative early hour measurements. These findings occur at 24-72 hours postoperatively (20). The half-life in intact PTH blood is 2-5 minutes. Because of the short half-life of PTH, its drop in the early postoperative period has been used as a marker for transient hypocalcemia (14–16,21,22). In some studies, measurement of postoperative parathyroid hormone levels has been shown to reduce the incidence of hypocalcemia and the duration of hospitalization with early calcium replacement therapy by predicting hypocalcemia (14,23,24). In various studies conducted to predict hypocalcemia in the early period, the timing of iPTH measurement, the method and the thresholds obtained have been presented (16,23,25).

As the most common complication after total thyroidectomy is transient hypocalcemia, many centers prophylactically administer low-dose calcium and vitamin D to patients. However, studies have shown that low-dose calcium prophylaxis does not prevent the symptoms of hypocalcemia (20,26). According to these studies, more than 50% of the patients received unnecessary Ca prophylaxis, which caused an increase in health expenses. However, in our study, calcium replacement was performed at the appropriate dose according to the calcium values at the 24th postoperative hour and in patients with hypocalcemia symptoms. By comparing the iPTH and calcium levels examined in patients between the postoperative 3-6 hours before and after the surgery and at the postoperative 24th hour, we aimed to determine the relationship between the changes that may occur in the iPTH levels and the changes that may occur in the calcium levels and to predict hypocalcemia at a much earlier time. The aim was to prevent the symptoms of hypocalcemia that may develop by initiating early medical treatment in patients with postoperative hypocalcemia and to shorten the patients' duration of hospitalization.

In our study, the cut-off value was determined to be 39.6 pg/mL (picogram/milliliter) according to the ROC curve for the iPTH level measured between 3-6 hours postoperatively. When the iPTH value measured between the postoperative 3-6 hours was less than 39.6 pg/ml, the risk of hypocalcemia at the 24th hour was predicted with an accuracy of 77.5% and a specificity of 40.3%. Many similar studies are available in the literature. In a study of 260 patients published by Davide Inversini et al. (25) in 2016, the iPTH cut-off value of 10.0 pg/ml was shown to have a sensitivity of 76% and a specificity of 83% for the assessment of postoperative hypocalcemia. In this study, it was shown that there was a statistically strong relationship between iPTH and serum calcium levels at the 24th and 48th postoperative hours. In a prospective study conducted by Montana Suwannasarn et al. (26) in 2017 involving 65 patients, preoperative and postoperative 4th-hour iPTH values of the patients were measured, and hypocalcemia was detected in 25 (38.5%) patients. When the postoperative 4th-hour iPTH value was below 12.5 pg/mL and the iPTH decrease was above 72%, hypocalcemia was predicted in patients with a sensitivity of 92%, specificity of 87.5%, and accuracy of 82.1%.

In a study of 112 patients conducted by Adolfo Pisanu et al. (23) between 2010 and 2011, it was observed that the preoperative serum iPTH level decreased by 80.2% at the 6th postoperative hour and increased by 37% at the 48th postoperative hour in 33 patients who developed hypocalcemia. This difference was found to be significant in repeated iPTH measurements. As a result of the studies, a treatment algorithm was established with serum iPTH and calcium levels at the 6th and 24th postoperative hours (23). In our study, it was found that there was a statistically significant difference between the iPTH values of the groups formed according to the calcium value on the first postoperative day between 3 and 6 hours postoperatively ($p<0.05$). It was found that the iPTH levels of hypocalcemic patients were lower than those of normocalcemic patients between 3 and 6 hours postoperatively. We aimed to establish a hypocalcemia treatment algorithm with appropriate treatment by predicting postoperative hypocalcemia with iPTH between 3-6 hours postoperatively and at the 24th postoperative hour.

In a multicenter prospective study conducted by Saleh F. Al-Dhahri et al. (27) between 2009 and 2012, 168 patients were evaluated. The decrease in PTH value at the first postoperative hour was found to be significant in terms

of predicting hypocalcemia. Patients with symptoms of hypocalcemia had a greater reduction in PTH than those without. A positive correlation was found between the length of hospital stay and a decrease in PTH value of more than 73% postoperatively. In another study conducted by Azmi Lale et al. (28), 818 adult patients were discussed. The length of hospital stay of patients who developed postoperative hypocalcemia was found to be longer than that of normal patients. In our study, we aimed to reduce the duration of hospitalization of the patients by predicting the hypocalcemic picture that developed postoperatively with the decrease in iPTH and initiating appropriate calcium replacement on time.

In a study conducted by A. Bove et al. (29) examined preoperative PTH, postoperative 1st-hour PTH and postoperative 24th-hour serum calcium values in 96 patients between 2012 and 2013. The serum PTH level at the 1st postoperative hour was found to be 39.8 pg/dl for the detection of postoperative hypocalcemia and was found to predict hypocalcemia with a sensitivity of 50% and a specificity of 87%. Similar to this study, the cut-off value for iPTH measured between 3-6 hours postoperatively in our study was also 39.6 pg/ml. Thus, when the iPTH level was below 39.6 pg/ml, hypocalcemia could be predicted with a sensitivity of 77.55% and a specificity of 40.3%.

Limitations of The Study

The limitation of our study is that the long-term results of these patients are not known.

CONCLUSION

Postoperative hypocalcemia can be predicted with iPTH in the early period. Performing the necessary treatment at the appropriate time by predicting hypocalcemia early with the iPTH value measured from the blood between 3-6 hours postoperatively and at the 24th hour postoperatively shortens the length of hospital stay. There was a statistically significant relationship between the iPTH value measured from the blood between 3-6 hours postoperatively and at 24 hours postoperatively and the serum calcium levels of patients who developed hypocalcemia. Serum iPTH level was found to be an effective parameter for predicting postoperative hypocalcemia. Further comprehensive studies are needed to predict hypocalcemia in the early postoperative period.

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Both externally and internally peer reviewed.

Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article.

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Ethical Declaration:

Ethical permission was obtained from the Gaziantep University, Medical Faculty Clinical Research Ethics Committee for this study with date 09.01.2019 and number 2019/34, and Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept: AA, Design: AA, AH, NB, Supervising: AA, AH, LY, AB, Financing and equipment: AA, LY, Data collection and entry: AH, AA, NB, Analysis and interpretation: AA, LY, NB, AB, Literature search: AH, AA, AB Writing: AH, AA, NB, Critical review: AA, LY, AB

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