Original Article: Investigating the Risk Factors of Hypoparathyroidism after Total Thyroidectomy

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<u>ABSTRACT</u>

Introduction: The aim of this study was to determine the outcome of low PTH after surgery and to monitor parathyroid recovery times in patients who underwent total thyroidectomy. Material and Methods: A commercially available PTH (iPTH) test was used to monitor iPTH levels on days 1 and 4. PTH levels were negative. It is determined by the same blood test as the sCa level. To exclude vitamin D deficiency, we first measured 25-hydroxyvitamin D and 1,25dihydroxyvitamin D levels in all patients Postoperative hypoparathyroidism was defined as postoperative albumin-adjusted sCa levels below 1.9 mmol/L (Convert to mg/dL, divide) with 0.25 (range of use, 2.10-2.60 mmol/L) symptoms of hypocalcemia (response to neuromuscular stress including paresthesias, muscle spasms, tetany or seizures) or sCa levels lower than results (1.9-2.1 mmol/L) with neuromuscular symptoms during the first 4 days after surgery. Results: In a multivariate logistic regression model, we found that patients who received an autograft of parathyroid tissue during surgery were more likely to have low PTH immediately after surgery (OR = 2.6; 95% CI, 1.8-3.8). Additionally, patients with parathyroid tissue who showed negative parathyroid tissue removal on the final pathology report were more likely to have postoperative PTH <10 pg/mL (OR = 2.2; 95% CI, 1.5 -3.3). Parathyroid tissue was the only risk factor for permanent hypoparathyroidism in the pathology report (OR = 3.6, 95% CI, 1.1-11.5). **Conclusion:** This study suggests that drug therapy should be considered in addition to PTH measurement, as 50% of patients with persistent hypoparathyroidism have elevated PTH levels to $\geq 10 \text{ pg/mL}$, but still want more help to avoid hypoparathyroidism. Symptoms of calcemia. In addition, 12 months may be the most appropriate time to define persistent hypoparathyroidism, as 5% of patients with low PTH resolve 6-12 months after treatment.

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Introduction

atrogenic injury of the parathyroid glands is a rare side effect of total thyroidectomy. Measurement of serum - PTH immediately after surgery is a sensitive and specific method to assess parathyroid function and identify patients at risk for hypocalcemia [1-3]. If postoperative PTH levels are low, administration of calcium and vitamin D (calcitriol) may reduce the incidence of hypocalcemia symptoms [4].

In the literature, the incidence of low PTH after total thyroidectomy varies between 7% and 37%. Part of this change is related to the different methods used to identify this issue. Because surgeons know this is a potential risk of surgery, many patients are treated with calcium supplements or calcitriol to try to relieve symptoms [5-7]. While these supplements may help reduce symptoms in patients, it can be difficult determine to who has hypoparathyroidism and who does not based on calcium levels, symptoms, or needs [8]. An objective criterion, and perhaps the most concise way to describe the development of hypoparathyroidism, is to look at PTH levels immediately after surgery before starting additional drug therapy. In this study, we evaluated a person with PTH <10 pg/mL as a thyroid gland replacement [9-11].

Most people with parathyroid disease do not return to normal function within a few weeks or a month of thyroidectomy [12]. However, there is no consensus in the literature on how best to define parathyroid function. Some studies consider euparathyroidism when the patient's serum PTH returns to at least 10 pg/mL in the absence of symptoms of hypocalcemia. When patients do not need calcium or calcitriol supplementation to prevent hypocalcemic symptoms, another focus on drug therapy to restore parathyroid function should be considered [13-15]. A third method of determining recovery of parathyroid function is to determine when serum PTH levels are within the normal range and when calcium or calcitriol supplementation is discontinued [16].

In addition, different definitions are used to determine when postoperative hypoparathyroidism should be classified. Some think that thyroid damage that does not work within 6 months after surgery is permanent, while others think that it is permanent for up to 1 year after surgery [17-19].

Postoperative hypocalcemia, reported to occur in 1.6% to 50% of patients, is the most common and sometimes serious complication after total thyroidectomy. Therefore, patients should be carefully monitored and checked frequently after surgery [20].

Postoperative hypoparathyroidism is caused by rupture of the parathyroid blood due to proximity to the thyroid capsule during surgery, the presence of one or more tumors, destruction of the tumor in the parathyroid (RLS) artery, or parathyroid insufficiency. Because hematoma. Created [21].

How to best estimate the clinical and biochemical effect and timing of the development of postoperative temporary or permanent hypoparathyroidism has become a problem in the documentation. Some authors have suggested that clinical use or early measurement of parathyroid hormone (PTH) activity is helpful, and daily serum calcium (sCa) testing is challenging until it is high. Others recommend measuring sCa concentrations only in selected patients or within the first 24 hours after surgery [22-24].

The incidence of low PTH after total thyroidectomy varies. While low PTH levels are observed after surgery, the long-term effect on the patient has not been clearly defined. When will they heal and how will they result in permanent hypoparathyroidism? The aim of this

study was to determine the outcome of low PTH after surgery and to monitor parathyroid recovery times in patients who underwent total thyroidectomy [25].

Material and Methods

Study Design: 115 consecutive patients undergoing primary total thyroidectomy were followed over an 18-month period and the subsequent function of the thyroid gland was evaluated. Of these, 59 (34.7%) were men and 85 (65.3%) were women, with a ratio of men to women of 1:1.9. The mean (SD) patient age was 52.9 (16.3) (median, 55; range, 12-86). According to the study, the duration of hospital stay was 4 (mean 4; range 4-7) days. All patients gave informed consent to participate in this study. Between January 2018 and December 2020. 115 patients underwent total thyroidectomy or total thyroidectomy at UW. 1054 patients had PTH blood test within 24 hours after surgery and were included in this study. The normal range for PTH analysis at our center is between 10 and 72 pg/mL. Low PTH was defined as PTH <10 pg/mL measured immediately after surgery.

Inclusion And Exclusion Criteria : The patients were followed for 1 year. We determined that parathyroid function was good when serum PTH ≥ 10 pg/mL and patients did not need calcitriol or calcium supplements >2000 mg per day to avoid symptoms of hypocalcemia. If the patient does not fully recover within 1 year, it is considered as permanent hypoparathyroidism.

Methods: A commercially available PTH (iPTH) test (Elecsys 1010; Roche Diagnostics, Mannheim, Germany) was used to monitor iPTH levels on days 1 and 4. PTH levels were negative. It is determined by the same blood test as the sCa level. To exclude vitamin D deficiency, we first measured 25-hydroxyvitamin D and 1,25-

dihydroxyvitamin D levels in all patients Postoperative hypoparathyroidism was defined as postoperative albumin-adjusted sCa levels below 1.9 mmol/L (Convert to mg/dL, divide) with 0.25 (range of use, 2.10-2.60 mmol/L) symptoms of hypocalcemia (response to neuromuscular stress including paresthesias, muscle spasms, tetany or seizures) or sCa levels lower than results (1.9-2.1 mmol/L) with neuromuscular symptoms during the first 4 days after surgery. All hypoparathyroid patients received two 500 to 1000 mg oral calcium supplements (calcium mono- and di-citrate [Maxi-Kalz; Viatris Pharma, Hamburg. Germany]) and a 0.25 microgram vitamin D analogue (calcitriol [Rocaltrol; Roche Diagnostics]). twice a day, regardless of symptoms. Intravenous calcium therapy is not required in these patients. Postoperative hypoparathyroidism patients were discharged when the recorded sCa level was above 2.0 mmol/L. In these patients, sCa and iPTH levels

Ethical Considerations: This study was carried out after being approved by the ethics committee of Tabriz University of Medical Sciences. All study participants signed the informed consent form. No fees were charged to the patients. All complications were resolved in the shortest possible time by the research team.

were measured 4 weeks after surgery and 2 days

after discontinuation of calcium and calcitriol

therapy. Final measurements of sCa and iPTH

levels were made 6 months after thyroidectomy.

Hypoparathyroidism is classified as permanent

if the sCa level returns to normal within 6 months; in any case it is classified as security.

Data Analysis : All collected data were analyzed using the Statistical Package for the Social Sciences Software Version 20 (SPSS; IBM Corporation, Armonk, NY). Data are presented as mean, standard deviation, median, minimum and maximum, percentage and number. The Shapiro-Wilk W test was performed when the sample size of the continuous variable was <50; When the value is >50, the Kolmogorov-Smirnov test is performed. When the distribution between two independent groups was given, the independent sample t-test was used;

Results

All patients underwent total thyroidectomy and both RLNs were microdissected from the entire neck. Neuromonitoring was not used. Benign thyroid disease was the indication for surgery in 98 patients (57.6%), including 89 patients with thyroid function and 9 patients with thyrotoxic nodular goiter. 72 holes (42.4%) showed various types of thyroid cancer, including differentiated thyroid carcinoma in 71 cases and lymphoma in 1 case. Bilateral (n=57) or unilateral (n=45) central lymph node dissection (CND) was performed in 102 patients (60.0%) before total thyroidectomy. Ninety-eight operations (57.6%) endocrine surgery (thyroid) (B.N.), 5 patients (2.9%) were treated by specialists, 67 patients (39.4%) were treated by senior doctors (B.N.). Identify the parathyroid gland macroscopically and make a detailed analysis of the thyroid gland. Every effort is made to identify and protect all parathyroid glands. There were 4 parathyroid glands in 116 patients (68.2%) and 3 parathyroid glands in 41 patients (24.2) (Figure 1).



Figure 1: PTH rate after surgery

11 patients had 2 tumors (6.5%). One patient did not have parathyroid disease and the remaining patient had 5 tumors. If parathyroid vascularization cannot be preserved along branches of negative vessels in the thyroid gland, the gland is resected and the sample sent for frozen section analysis. The remains were stored in cold isotonic sodium chloride solution, dissected, and autografted to the sternocleidomastoid muscle at the end of the procedure(Figure 2).



Figure 2: Recovery time in PTH after thyroidectomy

Parathyroid autotransplantation was performed in 16 (50.0%) of 85 patients. 64 (75.3%) autologous transplantation cases of 1 tumor, 19 cases (22.4%) of 2 tumors and 2 cases of 3 tumors (2.4%). Complications other than postoperative hypoparathyroidism were seen in 31 (18.2%) patients. Postoperative transient unilateral RLN palsy was noted in 18 patients (10.6%) and 1 patient (0.6%). Focal hematomas or seromas developed in 11 patients (6.5%) that did not require further intervention. Pulmonary embolism was suspected in 1 patient in the hospital and radiologically. According to the prospective method, albumin-adjusted total sCa levels were measured on days 1 to 4, before and once daily between 6 and 7 am(Figure 3).



Figure 3: Senility and Specificity results

Patients with postoperative hypoparathyroidism and whose parathyroid function improved within one year were compared with patients with permanent hypoparathyroidism. Patients with improved parathyroid function have a preoperative PTH measurement. In patients with persistent hypoparathyroidism, the final pathology report found higher calcium levels in less than 2 weeks and a higher incidence of parathyroid tissue in thyroid samples. In a multivariate logistic regression model, we found that patients who received an autograft of parathyroid tissue during surgery were more likely to have low PTH immediately after surgery (OR = 2.6; 95%) 1.8-3.8). Additionally, CI. patients with parathyroid tissue who showed negative parathyroid tissue removal on the final pathology report were more likely to have postoperative PTH <10 pg/mL (OR = 2.2; 95%) CI, 1.5 -3.3). Parathyroid tissue was the only risk

factor for permanent hypoparathyroidism in the pathology report (OR = 3.6, 95% CI, 1.1–11.5). Age, gender, neck surgery, thyroiditis and malignancy were not associated with postoperative low PTH or persistent hypoparathyroidism. The validity of the multiple logistic regression model was tested using the likelihood ratio chi-square test with a p value of 0.03 for the model.

Discussion

In addition to RLS palsy, clinically recognized postoperative hypoparathyroidism is a serious and sometimes serious complication after total thyroidectomy [26-28]. There is debate about the most important factors responsible for the development of postoperative temporary or permanent hypoparathyroidism [29]. A decrease in total sCa levels measured on the 1st postoperative day was observed in 97.6% of the patients. This phenomenon is often controversial and is often explained by blood thinning after surgery [30-32].

However, the decrease in sCa levels in the first 3 days after surgery may be due to the surgery used in this study, for example, extensive resection of the RLS in all patients to prevent paralysis of the RLS. Although performed by microdissection, the procedure can block blood flow to the parathyroid gland, leading to adverse reactions [33]. There is also no additional risk associated with CND in these patients, as the number of patients with and without hypocalcemia was not significantly different when comparing patients with and without CND. This contradicts findings from others. In addition, surgeons involved in thyroid surgery did not influence the incidence of postoperative hypocalcemia [34-36].

the literature, In postthyroidectomy hypoparathyroidism has been defined differently, mostly according to total sCa levels. Recently, it has been shown that iPTH levels should be measured intraoperatively, perioperatively, or immediately after surgery to clearly distinguish and predict postoperative hypoparathyroidism [37-39]. Depending on the definition, the incidence of hypoparathyroidism after thyroidectomy ranges from 1.6% to 50%, which appears high and should not be seen in specific endocrine surgeries [40-42].

In this study, postoperative hypoparathyroidism was defined as a total sCa level of less than 1.90 mmol/L, with or without neuromuscular symptoms. In addition, patients with subnormal sCa levels and symptoms were classified as hypoparathyroidism patients [43-45]. An initial iPTH level of less than 15 pg/mL is used for better interpretation. By definition, hypoparathyroidism changes were recorded in 41 (24.1%) of 170 patients after total thyroidectomy. Permanent hypoparathyroidism developed in 2 additional patients (1.2%) [46].

There is debate about the most important parameters for predicting postoperative or permanent hypoparathyroidism and the best time to judge them. Several studies have identified a decrease in sCa levels within 48 hours of surgery as a safe indicator of postoperative hypoparathyroidism [47-49].

Unlike these studies, we found that only the total sCa level measured in the first 2 days after surgery did not predict changes in hypoparathyroidism [50].

Sixty (47.2%) of 127 patients without postoperative hypoparathyroidism and 35 (81.4%) 43 patients of classified as parathyroidism postoperative due to neuromuscular symptoms Hypoptotic patients showed subnormal sCa levels on the first postoperative day. Eight of 127 (6.3%) patients had mild symptoms (paresthesias) on the first day after surgery, but all sCa levels were recorded. Therefore, clinical signs will not be related to biochemical tests [51-53].

Using the total sCa level as an indicator of the risk of postoperative temporary or permanent hypoparathyroidism, we found that the total sCa level was less than 1.9 mmol/L at postoperative day 3, with the highest (72.1%) and specificity (92.9%)) we found that it has., PPV is 77. The decrease may be explained by the fact that some patients developed symptoms on the third and fourth day and took calcium and calcitriol. Postoperative sCa levels are planned as a function of time, and positive (no postoperative hypoparathyroidism risk) and negative results (high postoperative hypoparathyroidism risk9) Ca slopes do not improve postoperative thyroid hypoparathyroidism [54-56]. The precision of the sCa measurement for the first or second day and the second or third day after work is 88.4% and 67.0%, respectively; except 35.4% and 64.6%, respectively; and PPV were only 31.7% and 39.2%, respectively [57-59].

Perhaps the most reliable way to define transient or permanent hypoparathyroidism is

measurement after iPTH. All but 1 of 43 patients with transient or permanent hypoparathyroidism had iPTH levels below 15 pg/mL. While the iPTH level was 15.2 pg/mL on the first postoperative day in one patient, it decreased to 8 pg/mL on the fourth day. iPTH levels were below 15 pg/mL in four (3.1%) of 127 patients without hypoparathyroidism.

The sensitivity of iPTH measurement (97.7%) did not differ from the first day to the fourth postoperative day. Specificity and PPV increased from 65% to 82.6% to 96.1%. 6% to 87.5%, respectively.

Some authors recommend the rapid use of iPTH to monitor the body's function or function by predicting parathyroid function after surgery. 5,6,11,14 Although Lindblom et al5 found no significant difference between iPTH level measurement and sCa concentration measurement, monitoring the intraoperative iPTH level on the first day afterward to predict long-term hypoparathyroidism can predict which patients will be present. The first 24 hours after surgery requires intravenous calcium. None of the 170 consecutive patients in this series required additional calcium injections.

However, most studies recommend intraoperative monitoring of iPTH levels, levels below the normal range at the end of or just after surgery are associated with postoperative pain. Endocrine (Thyroid) Surgery Centers can easily monitor iPTH levels during thyroidectomy. However, most patients with thyroid problems are treated in a small operating room. Therefore, monitoring of iPTH levels intraoperatively can be a logistical issue and increase the cost. As a reliable tool, measuring iPTH level on the first day after surgery appears to be more useful, with an accuracy of up to 100%, to identify patients at risk of developing persistent or persistent hypoparathyroidism.

Autologous parathyroid replacement is recommended to avoid permanent hypoparathyroidism. Zedenius et al found that none of the 100 consecutive patients who underwent total thyroidectomy developed persistent hypoparathyroidism after routine grafting of at least 1 parathyroid gland into the sternocleidomastoid muscle. Lo and Lam shared similar experiences. In our series, parathyroid autotransplantation was performed as needed. Two patients with permanent hypoparathyroidism underwent thyroid autotransplantation.

Parathyroid function usually returns within 4 weeks. After stopping calcium and calcitriol supplementation, sCa and iPTH levels were measured 4 weeks or 6 months later in 2 of 43 patients whose iPTH levels were below 15 pg/mL on the first or fourth postoperative day. Always. Thus, hypoparathyroidism was consistently classified in these 41 patients. After 6 months, 2 hypoparathyroidism patients with iPTH levels below 15 pg/mL were classified as patients with persistent hypoparathyroidism, and these patients had sCa levels at hypocalcemic levels without supplementation of calcium and Calcitriol.

However, due to the large study sample of 1054 patients, it seems that these results could be generalized to a larger population. Additionally, at the university where this study was conducted, patients were given calcium and calcitriol as a measure of diabetes PTH. Some of these patients may not need additional medication to prevent symptoms of hypocalcemia. Therefore, we cannot control the of occurrence symptoms of hypoparathyroidism. Finally, the time to hypoparathyroidism is directly proportional to the frequency with which PTH levels are measured.

Conclusion

This study suggests that drug therapy should beconsidered in addition to PTH measurement, as50%ofpatientswithpersistent

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hypoparathyroidism have elevated PTH levels to ≥ 10 pg/mL, but still want more help to avoid hypoparathyroidism. Symptoms of calcemia. In addition, 12 months may be the most appropriate time to define persistent hypoparathyroidism, as 5% of patients with low PTH resolve 6-12 months after treatment.

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