Risk factors of hypoparathyroidism after bilateral total thyroidectomy

Hypoparathyroidism after thyroidectomy

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Abstract

Aim: Hypoparathyroidism (HPP) is a complication after thyroid surgery that is difficult-to-treat in the long term. Our aim was to assess the outcomes of patients undergoing bilateral total thyroidectomy for thyroid disorders and to determine the incidence and risk factors of transient or permanent HPP. Material and Method: The outcomes of patients who underwent bilateral total thyroidectomy were evaluated. The patients were divided into three groups, namely those that did not develop hypocalcemia (Group 1), those that developed transient hypocalcemia (Group 2), and those that developed permanent hypocalcemia (Group 3). Results: The mean postoperative Ca and iPTH levels were 8.1±0.6 mg/dL and 37.1±17.8 pg/mL, respectively in Group 1; 7.6±0.5 mg/dL and 10.9±10.7 pg/mL, respectively in Group 2; and 7.4±0.7 mg/dL and 8.2±9.6 pg/mL, respectively in Group 3. Postoperative Ca and iPTH levels were significantly lower in Group 2 and Group 3 compared to Group 1 (p<0.01). An inter-group analysis with respect to mean excised nodule size revealed a mean nodule size of 20.1±14.3 mm in Group 1; 21.5±14.5 mm in Group 2; and 35.6±11.5 mm in Group 3. The mean excised nodule size of Group 3 was significantly greater than those of the other groups (p<0.05). Discussion: Female gender, low preoperative calcium level, the number of incidentally excised parathyroid glands, and nodule size were considered risk factors for developing postoperative HPP; thus, it is recommended to follow such patients closely in the postoperative period.

Keywords

Hypoparathyroidism; Thyroidectomy; Hypocalcemia; Parathormone

Introduction

Thyroid surgery is commonly performed for benign and malignant disorders of the thyroid gland. Bilateral total thyroidectomy is the preferred treatment modality for thyroid disorders such as thyroid malignancies and multinodular goiter [1]. Although recurrent laryngeal nerve injury is the most important complication of thyroid surgery, hypoparathyroidism (HPP) is another complication that is difficult-to-treat in the long term. Dissection, inadvertent excision of the parathyroid glands with the thyroid gland, or ligation of the thyroidal arteries during surgery may cause transient or permanent HPP [2]. The incidence of hypocalcemia following HPP has been reported at a range of 2% to 68% [3].

The aim of the present study was to assess the outcomes of patients undergoing bilateral total thyroidectomy for benign or malignant thyroid disorders and to determine the incidence and risk factors of transient or permanent HPP that developed in patients with symptoms of hypocalcemia during follow-up.

Material and Method

The outcomes of patients aged 18-60 years who underwent bilateral total thyroidectomy for thyroid diseases at our department between January 2012 and May 2018 were retrospectively evaluated. Patients with a history of thyroid surgery; those who underwent central or modified radical neck dissection; those with active thyroiditis; those who had Graves' disease or who underwent autotransplantation due to accidental parathyroidectomy during surgery were excluded from the study. Moreover, chronic renal disease, documented osteoporosis, hyperparathyroidism, or known hypocalcemia were the other exclusion criteria. This study was approved by Baskent University Institutional Review Board (Project no: KA 18/144) and supported by Baskent University Research Fund.

Serum calcium level was studied during the preoperative period and Ca and PTH levels on the morning of surgery. A serum calcium level below 8 mg/dl was considered hypocalcemia, and a PTH level below 12 pg/mL was considered hypoparathyroidism. Low calcium level for 6 months or longer in the postoperative period was considered permanent hypocalcemia while low calcium levels for less than 6 months were considered transient hypocalcemia.

All patients gave written informed consent in the preoperative period. All surgical interventions were performed by the same team that had expertise in thyroid surgery. Routine serum calcium and PTH level were studied on the morning of the surgery. Patients without hypocalcemia and with a normal PTH level were discharged one day later. Patients with hypocalcemia, low PTH level, or symptoms of hypocalcemia were kept at the hospital for an additional day to receive oral or intravenous calcium replacement. Patients whose symptoms of hypocalcemia improved were discharged with oral calcium replacement therapy. All patients were called for control visits at 7th, 15th, and 30th days, followed by monthly follow-ups. Patients who did not meet the follow-up criteria and those with missing data were excluded.

Patients meeting the criteria were assessed in terms of age, sex, preoperative diagnosis, preoperative Ca level, Ca and PTH levels on the morning of the surgery, pathology result, and the number of accidentally excised parathyroid glands detected in the pathology examination. The duration of hospital stays, calcium replacement administered during the hospital stay, and the duration of post-discharge calcium replacement therapy were evaluated. The patients were divided into three groups, namely those that did not develop hypocalcemia (Group 1), those that developed transient hypocalcemia (Group 2), and those that developed permanent hypocalcemia (Group 3), and the three groups were statistically compared with one another. SPSS v25.0 (SPSS, Chicago, IL, US) statistical software was used for statistical analysis. Normally distributed data weres presented as mean and standard deviation (SD), non-normally distributed data as median and interquartile range (IQR), and categorical data as frequencies and percentages. The Chi-Square test or the Fishers exact test was used to estimate the associations between categorical variables. ANOVA and the Kruskal–Wallis test was employed for comparison of two or more groups. The statistical significance level was set at 0.05.

Results

A total of 182 patients of whom 136 (74.7%) were female were enrolled between January 2012 and May 2018. Among the study participants, HPP more commonly developed in women ($p < 0.05$). The mean patient age was 51.05±13.6 years, and the mean ASA score was 1.69±0.5. Among the study participants, 95 (52.2%) were operated for benign causes and 82 (47.8%) for malignant causes. One hundred and forty-seven (80.8%) patients did not develop postoperative hypoparathyroidism (Group 1), twenty-seven (14.8%) patients developed transient hypoparathyroidism (Group 2), and 8 (4.4%) patients developed permanent hypoparathyroidism (Group 3). The demographic properties of the patients were summarized in Table 1.

The mean postoperative Ca and iPTH levels were 8.1±0.6 mg/dL and 37.1±17.8 pg/mL, respectively in Group 1; 7.6±0.5 mg/dL and 10.9±10.7 pg/mL, respectively in Group 2; and 7.4±0.7 mg/dL and 8.2±9.6 pg/mL, respectively in Group 3. Postoperative Ca and iPTH levels were significantly lower in Group 2 and Group 3 compared to Group 1 ($p < 0.01$). The benign and malignant causes of operation were 77 and 70, respectively in Group 1; 4 and 4 in Group 2, respectively; and 14 and 13 in Group 3, respectively, and there was no significant difference between the groups ($p > 0.05$). The mean number of parathyroid glands on pathology examination was 0.1±0.4 in Group 1; 0.25±0.7 in Group 2; and 0.75±0.7 in Group 3. The number of parathyroid glands on pathology examination was significantly correlated to developing hypoparathyroidism ($p < 0.05$). An inter-group analysis with respect to mean excised nodule size revealed a mean nodule size of 20.1±14.3 mm in Group 1; 21.5±14.5 mm in Group 2; and 35.6±11.5 mm in Group 3. The mean excised nodule size in Group 3 was significantly greater than those in the other groups ($p < 0.05$). Compression the results between the three groups were summarized in Table 2.

Discussion

HPP following total thyroidectomy has been reported at variable rates. In our patient population, transient HPP developed in 14.8% of the patients and permanent HPP in 8 (4.4%). HPP development following iatrogenic parathyroid injury was reported

Table 1. Demographic findings.

Gender		
	Female	136
	Male	46
Age (years)		51.05±13.6
ASA		1.69±0.5
Diagnosis		
	Benign	95 (52.2%)
	Malign	82 (47.8%)
Result		
	Normo-parathyroidism	147 (80.8%)
	Transient hypoparathyroidism	27 (14.8%)
	Permanent hypoparathyroidism	8 (4.4%)

Table 2. Compression between the groups.

	Group 1	Group 2	Group 3	p
Number of patients	147 (80.8%)	27 (14.8%)	8 (4.4%)	
Pathology				>0.05
Benign	70	4	14	
Malign	77	4	13	
Po Ca (mg/dL)	8.1±0.6	7.6±0.5	7.4±0.7	<0.01
Po iPTH (pg/mL)	37.1±17.8	10.9±10.7	8.2±9.6	<0.01
Pathological parathyroid number	0.1±0.4	0.25±0.7	0.75±0.7	<0.05
Mean nodule size (mm)	20.1±14.3	21.5±14.5	35.6±11.5	<0.05

at a rate of 18%, with permanent HPP developing in 1.9% of patients [4]. Female patients were found to have a greater rate of transient or permanent HPP development. Female gender has been shown to be a risk factor for developing postoperative hypocalcemia [5]. Although this risk factor has not been fully explained, vitamin D effect or a small surgical field increasing the risk of HPP are held responsible [6,7]. A greater number of female patients in the patient group developing HPP can be interpreted as a type 1 statistical error due to a greater number of women operated in the sampling group.

Our study found a significant correlation between preoperative Ca level and postoperative hypocalcemia development. The link between a low preoperative Ca level and hypocalcemia risk could not be clearly explained. In a multicenter study on 3660 patients, a low preoperative Ca level was found to be a risk factor for developing postoperative hypocalcemia, although a clear cut-off level was not provided [8]. However, several studies have refuted a relationship between preoperative Ca level and postoperative hypocalcemia development [9]. Hallgrimsson et al. showed a 2-3% decrease in preoperative Ca level was linked to the risk of developing postoperative hypocalcemia [10]. Although that relationship has been shown by various other studies, it is still unclear why patients with lower preoperative calcium levels develop postoperative hypocalcemia. However, it is well known that, as our study demonstrated, measurement of postoperative serum calcium level plays an active role in predicting hypocalcemia development and determining treatment. Low PTH levels at postoperative period are known to be a risk factor for developing hypocalcemia. HPP may develop as a result of dissection of parathyroid glands, malignancy, ligation of the thyroidal arteries remote from the thyroid gland, or inadvertent excision of the parathyroid glands [11,12]. Our study demonstrated a link between inadvertent parathyroid gland excision and developing hypocalcemia. The number of excised parathyroid glands was particularly higher in the HPP develop-

ing group than the other groups. As expected, these patients have low serum PTH level in the postoperative period.

Lymph node dissection and malignancy have been reported as risk factors for developing HPP [13]. It has been reported by various studies that central lymph node dissection impairs blood supply of the parathyroid glands or inadvertently causes the performance of parathyroidectomy or autotransplantation during surgery [14]. Our study revealed that malignancy did not form a risk factor for developing HPP. This was attributed to the absence of patients undergoing lymph node dissection in the study groups.

An increase in nodule size has been linked to developing HPP. Paek et al. reported that especially patients with a tumor size of 1.5 cm or greater developed HPP [14]. In our patient group, patients developing permanent HPP had a significantly greater mean excised tumor size than the other groups. Increasing tumor size complicates dissection plans and prevents the identification of the parathyroid glands. Therefore, increasing tumor size constitutes a risk factor for developing HPP.

In conclusion, female gender, low preoperative calcium level, the number of incidentally excised parathyroid glands, and nodule size were found as risk factors for developing postoperative HPP. Our patient population did not include patients who underwent parathyroid autotransplant and central neck dissection during surgery. The retrospective design of the study, and the small number of patients developing HPP cause difficulty in determining risk factors. Female gender, low preoperative calcium level, the number of incidentally excised parathyroid glands, and nodule size were considered risk factors for developing postoperative HPP; thus, it is recommended to follow such patients closely at the postoperative period.

Scientific Responsibility Statement
The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest
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