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Abstract

Risk factors of postoperative hypocalcemia after total thyroidectomy in pediatric patients with thyroid cancer

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Purpose: Hypocalcemia is the most common complication following thyroidectomy. We investigated the frequency and risk factors of hypocalcemia after total thyroidectomy in pediatric patients with thyroid cancer.

Methods: This retrospective study included 98 patients, diagnosed with thyroid cancer after total thyroidectomy <20 years of age during 1990—2018 and followed up more than 2 years at Seoul National University Hospital. Oral calcium and active vitamin D (1-hydroxycholecalciferol or 1,25-dihydroxycholecalciferol) were prescribed when postoperative calcium level was lower than 8.0 mg/dL and when a patient complained of hypocalcemic symptoms. Postoperative hypocalcemia was defined as requiring active vitamin

D supplementation to maintain blood calcium levels above 8.5 mg/dL following surgery.

Results: The study included 27 boys (27.6%) and 71 girls (72.4%). The mean age at diagnosis was 14.9 ± 3.7 years. Hypocalcemia occurred in 43 (43.9%) patients. Twenty-one (21.4%) patients discontinued active vitamin D less than 6 months, and 14 (14.3%) continued active vitamin D for more than 2 years. Tumor multifocality (Odds ratio (OR) 3.7 vs. single tumor, P=0.013) and preoperative calcium levels (OR 0.2, P=0.028) were independent predictors for developing hypocalcemia immediately after total thyroidectomy. In addition, age (OR 0.8, P=0.011) and preoperative calcium levels (OR 0.04, P=0.014) significantly decreased the risk for persistent hypocalcemia requiring active vitamin D for more than 2 years.

Conclusion: Hypocalcemia occurred in about two-fifth after total thyroidectomy in pediatric thyroid cancer. Among them, one-third of patients continued active vitamin D medication for more than 2 years, which was predicted by young age and low preoperative calcium levels.

Keywords : Hypocalcemia, Parathyroid hormone, Thyroid neoplasms, Thyroidectomy

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LIST OF ABBREVIATIONS

RAIT, radioactive iodine therapy

25OHD, 25−hydroxyvitamin D

iPTH, intact parathyroid hormone

ETE, extrathyroidal extention

PTG, parathyroid gland

CND, central neck dissection

LND, lateral node dissection

PGRIS, parathyroid gland remaining *in situ*

PTC, papillary thyroid cancer

FTC, follicular thyroid cancer

MTC, medullary thyroid cancer

HCC, Hürthle cell carcinoma

PDTC, poorly differentiated thyroid cancer

Introduction

Although thyroid malignancy is less common in pediatric population, the incidence rate of pediatric thyroid cancer has increased worldwide[1-3]. For children with differentiated thyroid cancer, total thyroidectomy is strongly recommended as initial surgical approach, and post-operative radioactive iodine therapy (RAIT) is indicated for intermediate or high risk patients[4]. Pediatric thyroid cancer presented at a more advanced stage at diagnosis with a higher recurrence rate[5], but showing a lower mortality rate compared to adulthood thyroid cancer[6].

Postoperative hypocalcemia due to hypoparathyroidism remains the most common complication after thyroid surgery. Most patients recovered within a few months, but some continued active vitamin D medications for persistent hypocalcemia[7]. Patients with persistent hypocalcemia had an increased risk of long-term morbidity in association with renal, cardiovascular diseases[7,8]. The prevalence of postoperative hypocalcemia after pediatric thyroid surgery varied from 0 to 36.4%[9-19] depending on the indication of surgery, extent of lymph node dissection or definition of hypocalcemia/hypoparathyroidism. Although several studies conducted with a large number of pediatric thyroid cancer patients in other countries revealed risk factors of hypocalcemia including central neck dissection (CND) or extent of surgery[9,11,17], no pediatric study has been conducted in Korea. Considering the high survival rate and long-life expectancy of pediatric thyroid cancer survivors, efforts to prevent risk factors for postoperative hypocalcemia are warranted.

In this study, we investigated the frequency and follow-up course of hypocalcemia after total thyroidectomy in pediatric patients with thyroid cancer. We analyzed risk factors for postoperative hypocalcemia requiring active vitamin D medication, and predictors for discontinuing medication within 2 years after thyroidectomy.

Materials and Methods

1. Subjects

The medical records of 111 patients who underwent total thyroidectomy for pediatric thyroid cancer (<20 years of age) at Seoul National University Children's Hospital between August 1990 and June 2018 were retrospectively reviewed. All patients underwent total thyroidectomy or completion thyroidectomy within 6 months followed by initial lobectomy or subtotal thyroidectomy. After excluding 13 patients who had taken calcium and/or vitamin D medication before surgery (n = 2) and those followed up less than 2 years (n = 11), 98 patients were finally included in this study (Fig. 1). The timing of last follow-up was defined as the last date of outpatient clinic visit without reoperation.

2. Clinicopathological presentation and surgical management

The management and follow-up strategies of thyroid cancer were described previously[5]. In brief, surgical approaches including total thyroidectomy, subtotal thyroidectomy, or lobectomy was conducted as initial treatment in accordance with prophylactic or therapeutic lymph node dissection. RAIT was recommended for patients with large tumor (>1cm), extrathyroidal extension (ETE), lymph node and/or lung metastasis. Clinical and treatment information including previous radiation history, type of operation (laparoscopic or open), type of node dissection, the number of autotransplanted parathyroid glands (PTGs) were obtained. Autotransplantation of PTGs into the sternocleidomastoid muscle was performed after frozen-section confirmation when the viability of PTG was questionable or when PTG was unintentionally removed or devascularized during surgery[4]. Type of neck dissection was defined by the 2009 American Thyroid Association consensus statement[20]. In detail, CND included resection of prelaryngeal and pretracheal nodes with at least one paratracheal lymph node, and lateral node dissection (LND) was defined as resection of cervical lymph node levels ll−V. Meanwhile, “plucking” or “berry−picking” method performed in the past that removed only clinically involved nodes rather than complete nodal group within the compartment[20] was classified as “other” node dissection group. Pathologic findings including tumor size, multifocality, ETE, TNM staging[21], the weight of thyroid specimen, and presence of PTGs in specimen were obtained. Since autotransplanted or inadvertently excised PTGs result in decreased amount of functioning parathyroid parenchyma after thyroidectomy, the importance of *in situ* preserved PTGs has been emphasized[22,23]. Thus, we used the concept of PGRIS (Parathyroid Gland Remaining *In Situ*)−score by substracting the number of autotransplanted PTGs during thyroidectomy and the number of PTGs identified in pathological specimen from 4, the total number of PTGs in normal thyroid anatomy [PGRIS−score = 4 − (PTGs autotransplanted + PTGs in the specimen)].

3. Biochemical assessment and evaluation of postoperative hypocalcemia

Perioperative data on calcium, phosphorus, 25-hydroxyvitamin D (25OHD), and intact parathyroid hormone (iPTH) levels were collected. Postoperative calcium levels were measured within 12 hours after thyroid surgery with monitoring of hypocalcemic symptoms such as tingling, numbness, and paresthesia. Oral calcium and active vitamin D (1-hydroxycholecalciferol or 1,25-dihydroxycholecalciferol) were prescribed when postoperative calcium level was lower than 8.0 mg/dL and when a patient complained of hypocalcemic symptoms. After discharge, patients were followed up at outpatient clinic with regular monitoring of serum calcium and/or iPTH levels. Active vitamin D was tapered off as permitted by clinical symptoms, serum calcium and/or iPTH levels. Postoperative hypocalcemia was defined as requiring active vitamin D supplementation to maintain blood calcium levels above 8.5 mg/dL following surgery. Total duration, dose and type of active vitamin D medications were investigated with follow-up course. Since all the patients who took active vitamin D at 2 years after surgery maintained the medication until the date of last follow-up, patients were classified into hypocalcemia (no), hypocalcemia (yes,

<2yr) and hypocalcemia (yes, ≥2yr) groups according to whether patients took active vitamin D medication (no or yes) and the duration of medication (less or more than 2 years).

4. Statistical analysis

All statistical analyses were performed using the IBM Statistical Package for the Social Sciences (SPSS) version 25.0 software (IBM SPSS Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation or median [25^{th}–75^{th} percentiles]. The Shapiro-Wilk test was used to assess the normality. Analysis of variance (ANOVA) or Kruskal-Wallis test was used to compare the differences in the means of continuous variables between the three groups with parametric and non-parametric data, respectively. The difference within two subsets was analyzed using the Bonferroni method with *P*-values set at 0.025. The chi-squared test for trend analysis was used to compare the proportion of three groups. Logistic regression analysis was performed to find risk factors for postoperative hypocalcemia. The multivariate-adjusted model was constructed with the variables found to be significant ($P<0.1$) in univariate analysis. Statistical significance was defined as a $P<0.05$ (twotailed).

Results

1. Baseline characteristics

Demographic, clinical, and operative characteristics of 98 patients (27 boys and 71 girls) are described in Table 1. The mean age at diagnosis of thyroid cancer was 14.9 ± 3.7 years. The number of childhood cancer survivors who had received radiation therapy was 11 (11.2%). After surgery, 67 (69.1%) received RAIT for remnant ablation. For the initial treatment, 80 (81.6%) underwent total thyroidectomy, and the remaining 18 (18.4%) received completion thyroidectomy after subtotal thyroidectomy or lobectomy. Sixty-nine (70.4%) underwent CND with or without LND. Eighty-two (83.7%) received open thyroidectomy, while others received laparoscopic or robotic surgery (n=16, 16.3%). The pathological diagnoses were 80 papillary thyroid cancers (PTCs, 81.6%), 11 follicular thyroid cancers (FTCs, 11.2%), 4 medullary thyroid cancers (MTCs, 4.1%), 2 poorly differentiated thyroid cancer (PDTCs, 2.0%), and one Hürthle cell carcinoma (HCC, 1.0%). The size of the tumor was 2.1 ± 1.3 cm, and the weight of the thyroid specimen was 21.6 ± 12.8 gram. The rates of bilaterality, multifocality, lymph node metastasis, and lung metastasis were 24.7%, 34.7%, 69.3%, and 10.2%, respectively. Microscopic and gross ETE presented in 52.1% and 9.4%. PTGs were autotransplanted in 18 (18.4%) during operation, and incidental parathyroidectomy was reported in 46 (51.7%) – a single PTG in 35 patients (39.3%), two or more PTGs in 11 patients (12.4%). The number (%) of patients with 1–2, 3, and 4 of PGRIS−score was 21 (23.6%), 31 (34.8%), and 37 (41.6%), respectively. The mean concentration of calcium (9.4 ± 0.3 mg/dL, reference range 8.8−10.5 mg/dL), phosphorus (4.4 ± 0.7 mg/dL, reference range 3.3−5.7 mg/dL) and iPTH (39.3 ± 18.0 pg/mL, reference range 15−65 pg/mL) before the operation were within normal range. Low serum level of 25OHD was detected (14.7 ± 6.4 ng/mL, reference range 30−100 ng/mL), although it was only measured in 9 patients.

2. Postoperative hypocalcemia and follow−up course

Forty−three (43.9%) patients were diagnosed with postoperative hypocalcemia requiring active vitamin D medication after surgery (Fig. 2A). During the median follow−up of 9.1 years (range 2.1−23.0 years), 29 patients discontinued active vitamin D medication; less than 6 months (n = 21), 6−12 months (n = 3), 12−18 months (n = 3), and 18−24 months (n = 2) (Fig. 2B). Remaining 14 patients continued active vitamin D for more than 24 months after surgery.

3. Comparison according to the duration of active vitamin D medication

Preoperative calcium level was significantly lower in hypocalcemia (yes, ≥2yr) group compared to hypocalcemia (no) group (9.2 ± 0.3 mg/dL vs. 9.5 ± 0.3 mg/dL, $P<0.025$; Table 2). There were no significant differences in age at diagnosis, sex, pathologic diagnosis, neck dissection modality, multifocality, lymph node and lung metastasis, ETE and PGRIS-score among the three groups (Table 2).

4. Risk factors for postoperative hypocalcemia

Table 3 included the results of univariate and multivariate analysis for risk of overall hypocalcemia (yes) and hypocalcemia (yes, ≥2yr) compared to hypocalcemia (no), respectively. In multivariate-adjusted models including possible risk factors identified in univariate analysis, multifocality (odds ratio [OR] 3.7, 95% confidence interval [CI] 1.3-10.5, $P=0.013$) and preoperative calcium levels (OR 0.2, 95% CI 0.1-0.8, $P=0.028$) were independent predictors for developing hypocalcemia (yes). For hypocalcemia (yes, ≥2yr), age (OR=0.8, 95% CI 0.6–0.9, *P*=0.011) and preoperative calcium levels (OR=0.04, 95% CI 0.003–0.5, *P*=0.014) were identified as significant predictors. No risk factors were identified in univariate analysis for hypocalcemia (yes, <2yr) compared to hypocalcemia (no) and hypocalcemia (yes, ≥2yr).

Table 1. Baseline demographic, clinical and operative characteristics of the study population

	Total (n = 98)
Patient characteristics	
Male, n (%)	27 (27.6)
Age at diagnosis, yr	14.9 ± 3.7
Follow−up duration, yr	9.1 [2.1−23.0]
Previous history of radiation therapy, n (%)	11 (11.2)
Radioactive iodine ablation, n (%)	67 (69.1)
Operative and pathologic findings	
Total thyroidectomy: Completion thyroidectomy, n (%)	80: 18 (81.6: 18.4)
Node dissection (none: CND: LND: CND+LND: other), n (%)	16: 29: 7: 40: 6 (16.3: 29.6: 7.1: 40.8: 6.1)
Operation type (open: laparoscopic or robotic), n (%)	82: 16 (83.7: 16.3)
Histology (PTC: FTC: MTC: PDTC: HCC), n (%)	80: 11: 4: 2: 1 (81.6: 11.2: 4.1: 2.0: 1.0)
Tumor size, cm	2.1 ± 1.3
Thyroid specimen weight, gram	21.6 ± 12.8
Location (unilateral: bilateral), n (%)	73: 24 (75.3: 24.7)
Multifocal tumor, n (%)	34 (34.7)
Lymph node metastasis, n (%)	61 (69.3)
Lung metastasis, n (%)	10 (10.2)
Extrathyroidal extension (no: microscopic: gross), n (%)	37: 50: 9 (38.5: 52.1: 9.4)
Number of autotransplanted parathyroid glands (0:1:≥2)	80: 17: 1 (81.6: 17.4: 1.0)
Presence of parathyroid glands in specimen (0:1:≥2)	43: 35: 11 (48.3: 39.3: 12.4)

Parathyroid glands remaining *in situ* (PGRIS)−score (1−2:3:4)	21: 31: 37 (23.6: 34.8: 41.6)
Preoperative laboratory findings	
Preoperative serum calcium, mg/dL (8.8−10.5)	9.4 ± 0.3
Preoperative serum phosphorus, mg/dL (3.3−5.7)	4.4 ± 0.7
Preoperative serum 25−hydroxyvitamin D, ng/mL (30−100)	14.7 ± 6.4
Preoperative serum intact parathyroid hormone, pg/mL (15−65)	39.3 ± 18.0

Data are expressed as mean ± standard deviation, median [25^{th}−75^{th} percentiles] or number (%).

CND, central neck dissection; LND, lateral neck dissection; PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma; MTC, medullary thyroid carcinoma; PDTC, poorly differentiated thyroid carcinoma; HCC, Hürthle cell carcinoma; PGRIS, Parathyroid glands remaining in situ

Missing values (number) for radioactive iodine ablation (n=1), thyroid specimen weight (n=14), location (n=1), lymph node metastasis (n=10), extrathyroidal extension (n=2), presence of parathyroid glands in specimen (n=9), PGRIS−score (n=9), preoperative serum calcium (n=15), phosphorus (n=34), 25−hydroxyvitamin D (n=89) and intact parathyroid hormone (n=61)

Table 2. Comparison of clinical, pathological characteristics and laboratory findings among patients with or without hypocalcemia

	hypocalcemia (no)	hypocalcemia (yes, <2yr)	hypocalcemia (yes, ≥2yr)	*P*−value*
Number of patients, n (%)	55 (56.1)	29 (29.6)	14 (14.3)	
Age at diagnosis, yr	15.3 ± 3.7	15.0 ± 3.7	13.4 ± 3.7	0.161
Male, n (%)	19 (70.4)	6 (22.2)	2 (7.4)	0.078
Papillary thyroid carcinoma, n (%)	42 (52.5)	24 (30.0)	14 (17.5)	0.051
Central neck dissection, n (%)	39 (56.5)	20 (29.0)	10 (14.5)	0.968
Multifocal tumor, n (%)	15 (44.1)	12 (35.3)	7 (20.6)	0.071
Lymph node metastasis, n (%)	33 (54.1)	18 (29.5)	10 (16.4)	0.692
Lung metastasis, n (%)	6 (60.0)	1 (10.0)	3 (30.0)	0.589
Gross extrathyroidal extension, n (%)	4 (44.4)	2 (22.2)	3 (33.3)	0.190
Radioactive iodine therapy, n (%)	40 (74.1)	18 (62.1)	9 (64.3)	0.309
PGRIS−score, n (%)				0.317
1 or 2	11 (52.4)	6 (28.6)	4 (19.0)	
3	16 (51.6)	10 (32.3)	5 (16.1)	
4	22 (59.5)	12 (32.4)	3 (8.1)	
Preoperative serum calcium, mg/dL	9.5 ± 0.3†	9.4 ± 0.4	9.2 ± 0.3†	0.049

Data are expressed as mean ± standard deviations, or number (%), PGRIS, Parathyroid glands remaining *in situ*

*P value between the three groups

† P <0.025 vs. hypocalcemia (no), using Bonferroni method

Table 3. Univariate and multivariate logistic regression analysis to identify the factors that independently predict postoperative hypocalcemia

	Overall hypocalcemia (yes) vs. hypocalcemia (no)				hypocalcemia (yes, ≥2yr) vs. hypocalcemia (no)			
Variables	Univariate OR (95% CI)	*P*-value	Multivariate OR (95% CI)	*P*-value	Univariate OR (95% CI)	*P*-value	Multivariate OR (95% CI)	*P*-value
Age at diagnosis, yr	0.9 (0.8-1.0)	0.252			0.9 (0.8-1.0)	0.095	0.8 (0.6-0.9)	0.011
Female (vs. male)	2.3 (0.9-6.0)	0.084	2.1 (0.7-6.2)	0.161	3.2 (0.6-15.6)	0.157		
Multifocal tumor (vs. single)	2.1 (0.9-4.9)	0.083	3.7 (1.3-10.5)	0.013	2.7 (0.8-8.9)	0.110		
CND (vs. no CND)	0.9 (0.4-2.3)	0.902			1.4 (0.4-5.4)	0.583		
Gross ETE (vs. no or micro ETE)	1.7 (0.4-6.7)	0.457			3.4 (0.7-17.5)	0.141		
RAIT (vs. no)	0.6 (0.2-1.4)	0.234			0.6 (0.2-2.2)	0.469		
PGRIS-score (vs. 1or 2)	Reference				Reference			
3	1.0 (0.3-3.1)	0.957			1.2 (0.2-5.8)	0.870		
4	0.8 (0.3-2.2)	0.601			0.4 (0.1-2.3)	0.294		
Preoperative serum calcium, mg/dL	0.3 (0.1-1.0)	0.059	0.2 (0.1-0.8)	0.028	0.1 (0.0-0.6)	0.020	0.04 (0.003-0.5)	0.014

OR, odds ratio; CI, confidence interval; CND, central neck dissection; ETE, extrathyroidal extension; RAIT, radioactive iodine therapy; PGRIS, Parathyroid glands remaining *in situ*

Fig. 1.

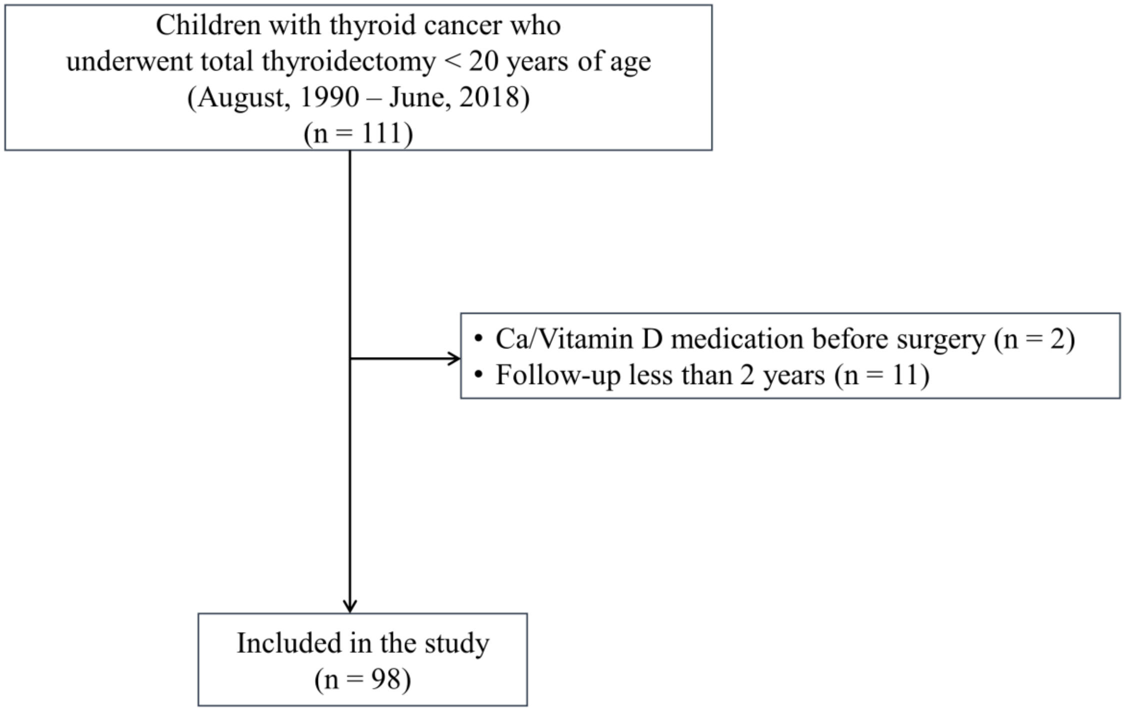

Figure 1. Flow chart of the study participants.

Fig. 2.

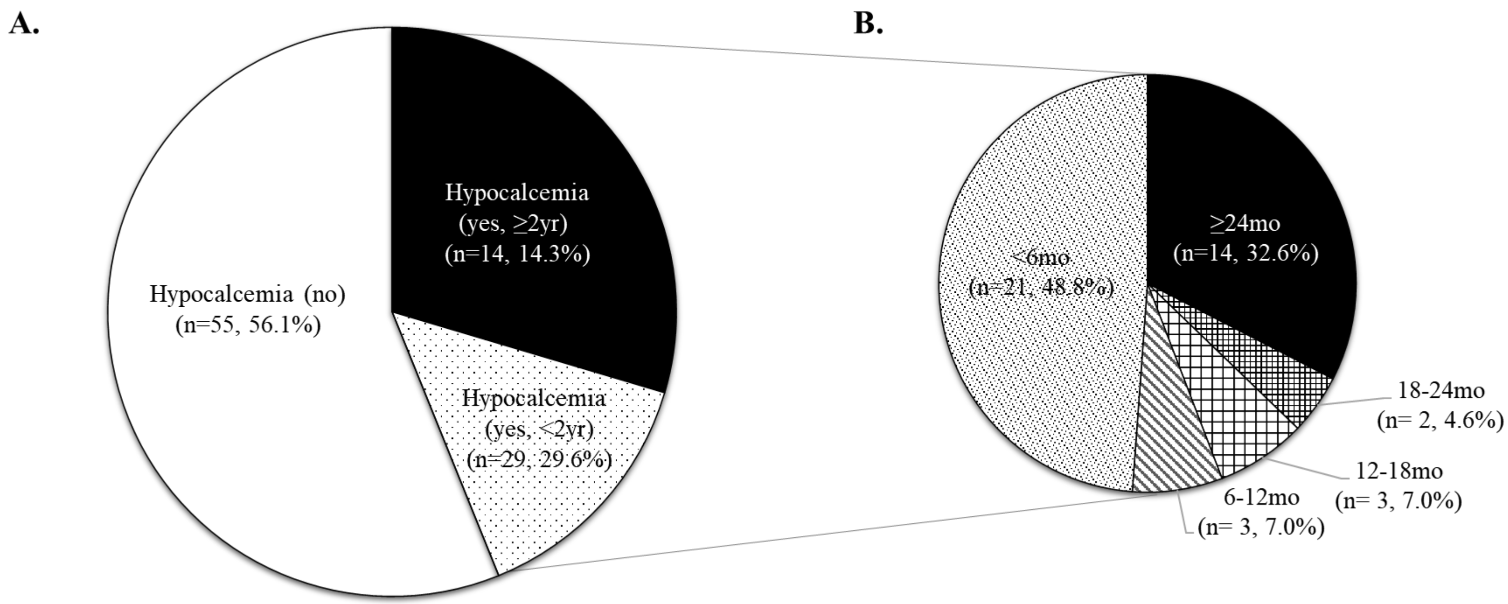

Figure 2. (A) Prevalence of postoperative hypocalcemia in pediatric patients with thyroid cancer. (B) Duration of active vitamin D therapy in postoperative hypocalcemia patients.

Discussion

Among pediatric patients with thyroid cancer in a large tertiary center in Korea, postoperative hypocalcemia occurred in 43.9% after total thyroidectomy. Among them, proportion of patients continued active vitamin D medication more than 2 years was 32.6% (14.3% of total). Tumor multifocality and preoperative calcium levels were predictive for postoperative hypocalcemia, and young age at diagnosis and low preoperative calcium levels were risk factors for persistent hypocalcemia requiring active vitamin D more than 2 years.

The frequency of overall postoperative hypocalcemia (43.9%) in this study was higher than that observed in previously published reports. The frequencies of transient and persistent hypocalcemia in pediatric thyroid cancer patients were reported to be 7.4~33.1% and 0~23.8% in previous studies[8−18]. The incidence rate differs depending on the indication or extent of surgery, lymph node dissection modalities, area of study conduction and follow−up duration[9−19,22,24], as well as variable definitions of postoperative hypocalcemia/hypoparathyroidism using different time points (6 months after operation[11,12,15,24], 1 year after operation[22] or at last follow−up[9]), biochemical values (serum calcium[15], ionized calcium[25]or PTH levels[9,10]) or treatment requirements (active vitamin D and/or calcium[11,12,16,22,24] supplementation postoperatively). The lack of agreement on the definition of postsurgical hypocalcemia/hypoparathyroidism and the criteria for active vitamin D treatment makes it difficult to compare the incidence rates across studies.

In this study, tumor multifocality was identified as a risk factor for overall hypocalcemia. The risk for postoperative hypocalcemia increased when PTGs are removed inadvertently, or devascularized by ligation of blood supply during surgery. Considering the association between multifocal tumor and advanced stage at diagnosis[26,27], the more extensive surgery adversely affected blood supply of the PTGs during surgery[5,26,28], leading to increased risk for postoperative hypocalcemia. One study[17] including a large number of pediatric thyroid cancer patients in Belarus also demonstrated tumor multifocality as a significant risk factor for postoperative hypocalcemia, in association with tumor extension and the degree of surgical aggressiveness. Previous studies also identified other attributable factors for extensive surgery, such as lymph node or lung metastasis, gross ETE as significant risk factors[4,9,10] contributing postoperative hypocalcemia, although not demonstrated in our study.

Preoperative calcium level was common risk factor for developing hypocalcemia immediately after surgery, and persistent hypocalcemia requiring active vitamin D for more than 2 years. This may indicate that baseline function of PTGs in hypocalcemia (yes) group was lower than that in patients with hypocalcemia (no) group. In addition to blood calcium level[25,29], preoperative vitamin D deficiency[30-32] also has been identified as a risk factor for hypocalcemia after thyroid surgery. Although we cannot evaluate the relationship between preoperative calcium levels and vitamin D deficiency in all patients, 8 of 9 patients who received 25OHD measurements were vitamin D deficient in this study. Considering the importance of sufficient calcium and 25OHD levels preoperatively in previous studies[25,29-32], and high prevalence of vitamin D deficiency in Korean adolescents[33], it is recommended to measure both calcium and 25OHD levels before thyroidectomy and to make an effort to maintain sufficient serum calcium concentration.

Risk of persistent hypocalcemia requiring active vitamin D for more than 2 years increased when age at diagnosis was younger. Young age is not only known as a significant risk factor predicting poor prognosis in pediatric thyroid cancer[34], but also a predictor for the high incidence of endocrine-specific complications such as recurrent laryngeal nerve injury and hypoPTH[9,35,36]. The reasons for the higher incidence of postoperative hypocalcemia in children include anatomical difficulty with narrow surgical field of view, emphasizing the need for more delicate operation by a skillful surgeon[37].

The extent of lymph node dissection and PGRIS−score did not predict the occurrence of postoperative hypocalcemia in this study. It remains controversial whether the lymph node dissection modality affects the occurrence of postoperative hypocalcemia. Several studies[9,11,12] have reported that CND increases the risk of both transient and persistent hypocalcemia. However, other studies showed no clear correlation[10,37] since the risk for sacrificing PTGs were compensated by extra−careful operation of experienced surgeons to save PTGs. Higher PGRIS−score, indicating that more PTGs were preserved *in situ*, was identified as the preventive factor for postoperative hypocalcemia in both adult[22] and pediatric[38] studies previously. However, our study included only pediatric thyroid cancer, contrary to previous studies including both benign and thyroid malignancy[22,38]. More aggressive exploration to investigate possible nodal metastasis during cancer surgery may adversely affect blood supply compared to benign thyroid disease[39], although PTGs are saved *in situ*. This may explain why a high

PGRIS-score were not a preventive factor for postoperative hypocalcemia in this study.

In our study, RAIT had no impact on the incidence of postoperative hypocalcemia in pediatric thyroid cancer patients. Theoretically, the beta-rays released by RAIT may have effect on parathyroid function[40]. However, it is still unclear whether RAIT affects the function of PTGs postoperatively in thyroid cancer patients. Some studies reported that serum calcium levels decreased after RAIT, whereas other studies suggested that RAIT did not affect the parathyroid function[40]. About 70% of the subjects received postoperative RAIT in our study, but the dose and the number of RAIT varied from patient to patient. To investigate the effect of RAIT on postoperative hypocalcemia, more stratified analysis should be needed.

This study was limited by its cross-sectional, retrospective design and small sample size. Second, few data on preoperative 25OHD concentration was additional limitation. Third, postoperative iPTH level which is known to be a useful predictor for postoperative hypocalcemia[41] was not prospectively followed in all patients.

In conclusion, postoperative hypocalcemia occurred in about two-fifth of patients after total thyroidectomy in pediatric thyroid cancer, with one-third of them (one-seventh of total) required medication more than 2 years. Patients with young age, multifocal tumor and low preoperative calcium levels should be monitored intensively for the occurrence of hypocalcemia after thyroidectomy. Efforts to prevent hypocalcemia and ensure adequate calcium concentration before surgery are warranted.

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국문초록

소아 갑상선암 환자에서 갑상선 전절제술 후 발생한 저칼슘혈증의 위험요인

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목적: 저칼슘혈증은 갑상선절제술 후 발생할 수 있는 가장 흔한 합병증이다. 이 논문에서는 소아 갑상선암 환자에서 갑상선 전절제술 후 저칼슘혈증의 발생 빈도와 위험인자를 확인하고자 하였다.

방법: 본 연구에서는 1990년부터 2018년 사이 서울대병원에서 20세 미만에 갑상선 전절제술을 시행하고 갑상선암으로 진단된 뒤 2년 이상 추적관찰한 98명의 환자에 대하여 후향적으로 조사하였다. 수술 후 칼슘 농도가 8.0 mg/dL 미만이고 저칼슘혈증 증상이 있는 경우 경구 칼슘과 활성 비타민 D (1-하이드록시콜레칼시페롤 또는 1,25-디하이드록시콜레칼시페롤) 제제를 투약하였다. 수술 후 저칼슘혈증은 칼슘 농도를 8.5 mg/dL 이상으로 유지하기 위하여 활성 비타민 D 투약이 지속적으로 필요한 경우로 정의하였다.

결과: 연구에는 남자 27명 (27.6%)과 여자 71명 (72.4%)이 포함되었다. 진단 당시 평균 연령은 14.9 ± 3.7세였다. 저칼슘혈증은

43명 (43.9%)의 환자에서 발생하였다. 21명 (2.4%)의 환자는 6개월 이내에 활성 비타민 D를 중단하였고, 14명 (14.3%)은 2년 이상 활성 비타민 D 복용을 지속하였다. 다발성 종양 (odds ratio [OR] = 3.7 vs. 단일종양, *P*=0.013)과 수술 전 칼슘 수치 (OR 0.2, *P*=0.028) 는 갑상선 전절제술 직후 저칼슘혈증 발병을 예측할 수 있는 인자로 확인되었다. 또한, 연령 (OR 0.8, *P*=0.011)과 수술 전 칼슘수치 (OR 0.04, *P*=0.014)가 2년 이상 활성 비타민 D 복용을 필요로 하는 지속적인 저칼슘혈증의 위험을 유의하게 예측하는 인자로 확인되었다.

결론: 소아 갑상선암에서 갑상선 전절제술 후 약 2/5에서 저칼슘혈증이 발생하였다. 그 중 1/3이 2년 이상 활성 비타민 D 투약을 지속하였으며, 진단시 연령이 어릴수록 그리고 수술 전 칼슘 수치가 낮을수록 2년 이상 투약을 필요로 하는 저칼슘혈증이 발생할 가능성이 높다.

주요어: 저칼슘혈증, 부갑상선 호르몬, 갑상선 종양, 갑상선절제술

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