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Perioperative determinants of transient hypocalcemia after pediatric total thyroidectomy☆

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ABSTRACT

Purpose: We seek to identify risk factors associated with hypocalcemia after pediatric total thyroidectomy.
Methods: We retrospectively reviewed patients younger than 21 years undergoing total thyroidectomy between January 2002 and January 2016. We defined hypocalcemia as any serum calcium <8 mg/dl or ionized calcium <1.0 mmol/L. Perioperative risk factors were identified through multivariate logistic regression.
Results: Ninety-one children underwent total thyroidectomy. The average age was 13.7 ± 4.4 years, and 77% were female. Transient hypocalcemia was diagnosed in 34% (n = 31) of patients. There was one case of permanent hypoparathyroidism. Predictors of transient hypocalcemia included age (OR 0.87, 95% CI 0.8–0.97, p = 0.01), lymphadenectomy (OR 6.6, 95% CI 1.7–31.6, p = 0.01), and hyperthyroidism (OR 13.3, 95% CI 1.3–1849, p = 0.03). Patients with malignancy undergoing central (OR 7.1, 95% CI 1.5–33.4, p = 0.01) or central plus lateral lymphadenectomy (OR 6.33, 95% CI 1.0–40.1, p = 0.05) had significantly increased risk for transient hypocalcemia. Malignancy, MEN2A/B, goiter, preoperative calcium supplementation, incidental parathyroid removal, and postoperative PTH <15 pg/ml were not associated with transient hypocalcemia.
Conclusions: Younger age, hyperthyroidism, and concomitant lymphadenectomy during total thyroidectomy increase risk of developing transient hypocalcemia. Malignant cases with central or central plus lateral lymphadenectomy are also at increased risk. Aggressive perioperative management of hypocalcemia should be initiated in patients with these risk factors.
Level of evidence: 2b

Thyroid disease requiring surgery in children is uncommon. Both benign and malignant etiologies may warrant surgical intervention. Graves' disease is the most common benign cause of hyperthyroidism in children while well-differentiated thyroid cancer such as papillary carcinoma is the most common endocrine malignancy in children [1]. Owing to a lack of pediatric evidence-based data, treatment for pediatric thyroid disease is often based on adult guidelines [2]. Morbidity, particularly postoperative hypocalcemia, is higher in children compared to adults undergoing total thyroidectomy [2–4]. Hypocalcemia is the most common endocrine-specific complication following thyroidectomy in adults and children. Rates of this complication vary widely from 1.6% to 50% [5,6]. While hypocalcemia is transient in the majority of cases, rarely permanent hypoparathyroidism can result and is typically seen in less than 2% of cases when performed at experienced surgical centers [6]. Hypocalcemia is thought to occur owing to trauma to the parathyroid glands during thyroidectomy, either by devascularization or by accidental removal [7].

Few studies have examined the determinants of postoperative transient hypocalcemia in children. This study identifies independent predictors of postoperative transient hypocalcemia following total thyroidectomy in children.

1. Material and methods

1.1. Patient population

All children younger than 21 years who underwent total thyroidectomy by a pediatric surgeon at a tertiary pediatric hospital were included in this study. The study time period was from January 2002 to January 2016. Patients were excluded from the study if they underwent previous thyroid resection, lobectomy, or completion thyroidectomy.

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Additionally, patients who lacked documented postoperative calcium levels were not included in the analysis.

1.2. Study design and clinical variables

This study was approved by the Institutional Review Board (H-37491). We performed a retrospective review of medical records. Patient demographic data collected included gender and age at the time of surgery. Preoperative diagnosis and indication for surgery were determined. Patients who received preoperative calcium supplementation were also documented. Operative notes were reviewed for extent of lymph node dissection and pathology reports were reviewed to determine pathologic diagnosis as well as the presence of any parathyroid tissue. Postoperative parathyroid hormone (PTH) and calcium levels were analyzed. For patients with multiple calcium levels obtained, the lowest level of the day was used. Patients who developed symptoms such as perioral numbness or tingling, cramps, convulsion and tetany (documented Chvostek's sign or Trousseau's sign) were categorized as symptomatic. We also collected data on IV calcium supplementation and duration of postoperative oral calcium supplementation.

Postoperative hypocalcemia was defined as calcium <8.0 mg/dl or ionized calcium <1.0 mmol/L. Any patient with calcium <8.0 mg/dL requiring calcium supplementation for more than 1 year and PTH <15 pg/ml without evidence of parathyroid recovery at time of last follow-up were categorized as having permanent hypocalcemia.

1.3. Statistical analysis

Mann–Whitney U test was used to analyze all continuous variables, while the chi-square test was used for categorical variables. Variables with a p-value <0.05 were considered significant. Any significant variables in the univariate analyses were included in a multivariate logistic regression with a Firth correction method applied to minimize biases.

2. Results

Ninety-one children met inclusion criteria for this study and were included in the analysis. Our cohort included 11 patients who were between the ages of 18 and 21 years old. As they were operated on by a pediatric surgeon and managed by a pediatric multidisciplinary team at our institution, we included these patients in our analysis. Primary surgeon for all cases was a pediatric surgeon. Two patients had a pediatric ENT surgeon and pediatric surgeon as co-primary surgeons on the case. Mean age of patients was 13.7 ± 4.4 years. Seventy-seven percent of patients were female Table 1.

Forty-seven (52%) patients underwent total thyroidectomy for concern for malignancy, the most common preoperative diagnosis. Twenty-nine (32%) patients underwent total thyroidectomy owing to refractory hyperthyroidism (underlying diagnosis was Graves' disease in 24 patients, Hashimoto's thyroiditis in 1 patient, McCune–Albright syndrome in 1 patient, and 3 patients with isolated refractory hyperthyroidism). MEN 2A/2B prophylaxis was the primary indication for 6 patients. Seven patients had an enlarging multinodular goiter requiring surgical intervention (underlying diagnosis was Hashimoto's thyroiditis in 2 patients, McCune–Albright syndrome in 1 patient, and multinodular goiter in 4 patients). The two patients categorized in the benign nodule group included a patient with PTEN hamartoma tumor syndrome with benign nodule on biopsy and a patient with cystic lesion that was benign on FNA biopsy. Neck ultrasound was the most common diagnostic imaging modality used prior to surgery. Seventy-two (79%) patients underwent preoperative ultrasound. More than half of our patients (59%) had a preoperative biopsy, with the majority performed using a fine needle aspiration technique. Biopsy results were 63% malignant or suspicious for malignancy (Bethesda Categories V and VI), 19% benign (Bethesda Category II), 15% indeterminate (Bethesda Categories III and IV) and 4% nondiagnostic (Bethesda Category I). The two patients with nondiagnostic biopsies underwent a subsequent biopsy with findings of malignancy (Bethesda Category VI) and indeterminate findings (follicular neoplasm, Bethesda category IV), respectively.

Forty-five percent (n = 41) of patients received preoperative calcium supplementation for 1 week prior to surgery. This regimen included oral calcium carbonate (750 mg–1500 mg three to four times a day to provide 30 mg/kg/day elemental calcium) and oral calcitriol (0.1–0.5 μg daily).

Thirty-one (34%) patients had concomitant lymph node dissection performed at the time of their total thyroidectomy. Central compartment dissection was performed in 17 (55%) patients while 5 (16%) patients underwent lateral (left or right) neck dissection. One patient had bilateral neck dissection at the time of their surgery and there were 8 (26%) patients who had a combined lateral and central lymph node dissection.

Pathologic diagnosis included 52 (57%) malignancies. The most common malignancy was papillary thyroid cancer in 43 patients. Six patients had medullary carcinoma, 2 patients had follicular carcinoma, and 1 patient had a teratoma. Of the benign pathologies, the primary pathologic diagnoses were Graves' disease (22 patients), Hashimoto's disease (3 patients), follicular adenoma (4 patients), adenomatous nodule (2 patients), isolated hyperplasia (4 patients), multinodular goiter (3 patients), and dyshormonogenetic thyroid (1 patient). In 22 cases (24%), inadvertent removal of a parathyroid gland was identified in the pathologic specimen. Additionally, 21 patients were found to have lymph node metastases (Table 2). Of these, 19 patients had formal lymphadenectomy, while in 2 patients metastases were found in the Delphian node. One patient with benign pathology underwent limited neck dissection owing to preoperative concern for possible malignancy. Preoperative biopsy showed follicular neoplasms in multiple sites. In patients with malignancy, thyroidectomy with lymphadenectomy resulted in a significantly higher rate of transient hypocalcemia compared to those undergoing total thyroidectomy without lymphadenectomy (50% versus 14%, p = 0.006). Forty-two percent of patients found to have malignant thyroid disease did not have lymphadenectomy performed.

Table 1
Demographic and clinical characteristics of pediatric patients undergoing total thyroidectomy.

Variable		Total patients (n = 91)
Gender	Female	70 (77%)
	Male	21 (23%)
Age (mean)		13.7 ± 4.4 years
Diagnosis	Malignancy	47 (52%)
	Graves'	24 (26%)
	Hashimoto's thyroiditis	3 (3%)
	MEN 2A/2B	6 (7%)
	McCune Albright Syndrome	2 (2%)
	PTEN hamartoma syndrome	1 (1%)
	Enlarging goiter/mass	5 (5%)
	Refractory hyperthyroidism	3 (3%)
Ultrasound		72 (79%)
Biopsy		54 (59%)
Lymphadenectomy		31 (34%)

Table 2
Comparison of postoperative hypocalcemia by pathology and extent of surgery.

Variable	No hypocalcemia (n = 60)	Hypocalcemia (n = 31)	p-value
Malignant	**34**	**18**	**0.006**
No Lymphadenectomy	19	3	
LN +	1	1	
LN −	18	2	
Lymphadenectomy	15	15	
LN +	9	10	
LN −	6	5	
Benign	**26**	**13**	1.0
No Lymphadenectomy	25	13	
Lymphadenectomy	1	0	