








Factors associated with postoperative hypocalcemia following thyroidectomy in childhood

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Abstract

Background: Postoperative hypocalcemia is a frequent complication after thyroidectomy. Hypoparathyroidism may develop as transient (TtHP), with normalization within six months from surgery, or permanent (PtHP) if the patient requires replacement therapy. We analyzed factors associated with the development of postoperative hypoparathyroidism and in detail PtHP following thyroid surgery in a pediatric population.

Procedure: A retrospective multicenter study analyzing 326 patients was carried out. We recorded gender, age, tumor size, thyroiditis, extrathyroidal extension, lymph node dissection (central/lateral compartment, unilateral/bilateral), parathyroid autotransplantation, and histology. Additionally, calcium levels were acquired postoperatively.

Results: We analyzed pediatric patients ≤ 18 years who underwent thyroidectomy clustered into age groups (≤ 15 or > 15). Patients' mean follow-up was 5.8 years (1-11 years). Postoperative hypoparathyroidism occurred in 36 (11.0%): 20 cases (6.13%) developed PtHP. Postoperative hypoparathyroidism was more frequent in younger patients ($P = 0.014$), in larger tumors ($P < 0.001$), in case of extrathyroidal extension ($P = 0.037$), and in central compartment ($P = 0.020$) and bilateral lymph node dissection ($P = 0.030$). PtHP was more frequent in older patients ($P = 0.014$), in case of thyroiditis ($P < 0.001$), and extrathyroidal extension ($P < 0.001$). Concerning the first postoperative calcium level measurement, in the postoperative hypoparathyroidism group, we registered a 8.17 mg/dL value with 14% pre/postoperative decrease (Δ_{Ca}), whereas in PtHP patient group calcium level was 7.91 mg/dL with 16.7% Δ_{Ca} .

Conclusions: The risk of postoperative hypoparathyroidism is related to younger age, tumor size, central compartment and bilateral lymph node dissection, extrathyroidal extension, and decrease in postoperative calcium levels. The risk of PtHP is related to

Abbreviations: DSV, diffuse sclerosing variant of papillary thyroid carcinoma; FMTC, familial medullary thyroid cancer; FTC, follicular thyroid carcinoma; MC, medullary carcinoma; MEN, multiple endocrine neoplasia; PTC, papillary thyroid carcinoma; PtHP, permanent hypoparathyroidism; TT, total thyroidectomy; TtHP, transient hypoparathyroidism.

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older age, thyroiditis, extrathyroidal extension, and decrease in postoperative calcium levels.

KEYWORDS

cancer, children, hypocalcemia, hypoparathyroidism, thyroid, thyroidectomy

1 | INTRODUCTION

Along with the recurrent laryngeal nerve paralysis and bleeding, postoperative hypocalcemia is the major and most frequent complication that occurs after thyroid surgery.¹ Commonly, it arises following removal or insult to the parathyroid glands at neck surgery.²⁻⁶ Hypoparathyroidism is defined by a decrease in serum calcium levels and PTH: it may occur as a transient form (TtHP), with progressive normalization within six months from surgical treatment, or permanent (PtHP), whenever the patient continues to require replacement therapy.^{2,7-9} Numerous reports have attempted to correlate the incidence of post-surgical complications with the type of thyroid disease associated, positive family history of thyroid cancer, gender of the patient, type of operation, cervical lymph nodes involvement, extrathyroidal invasion, thyroiditis, surgical expertise, and surgical timing.^{6,10-20} Others have investigated the possible link between the development of hypocalcemia and some biochemical parameters, like preoperative vitamin D levels, postoperative PTH, and magnesium levels and pre- and postoperative serum calcium levels.²¹⁻³⁵ Calcium level lower than 1.9 mmol/L (7.61 mg/dL) after 24 h from thyroid surgery has been reported as predictive for the development of permanent hypocalcemia.² The risk factors identified by the scientific community are different and are currently a matter of debate. In the present study, the main endpoint was to analyze, in a pediatric population following thyroidectomy, rate and factors associated with the development of postoperative hypoparathyroidism, with particular regard to PtHP.

2 | METHODS

This retrospective multicenter study analyzes pediatric patients (≤ 18 years), undergoing thyroidectomy over a 11-year period (January 2009–December 2019) at five institutions (Division of Pediatric Surgery and Division of Endocrine Surgery at University of Pisa, Division of Pediatric Surgery at “Regina Margherita Hospital” in Turin, General Pediatric and Thoracic Surgery at Bambino Gesù Children’s Hospital-Research Institute in Rome, and Pediatric Surgery at Department of Woman and Child Health in Padua and the Department of Pediatrics at National Cancer Institute in Milan). We ensured that participating surgeons who were enrolled into this study were all high-volume surgeons (> 20 total thyroidectomy per year) who shared the same operative protocols.³⁶

The variables taken into consideration are gender, age, tumor size, presence of thyroiditis, extrathyroidal extension, central and lateral

compartment lymph node dissection, unilateral or bilateral lymph node dissection, parathyroid autotransplantation into the ipsilateral sternocleidomastoid muscle in case of incidental parathyroidectomy, histology (papillary carcinoma, diffuse sclerosing variant, follicular carcinoma, medullary carcinoma within genetic forms, such as multiple endocrine neoplasia 2A [MEN 2A], MEN 2B, and familial medullary thyroid cancer [FMTC]), pre- and postoperative serum calcium level (mg/dL), and preoperative/postoperative serum calcium level decrease (Δ_{Ca}). We clustered patients into two age groups (children and adolescents): ≤ 15 years or > 15 years according to previous studies.³⁷

The exclusion criteria were primitive hyperparathyroidism, a known condition of low levels of vitamin D, low calcium level measured preoperatively, previous parathyroidectomy due to hyperparathyroidism or patients who received supplementary calcium treatment due to other causes. Follow-up after surgery consisted of measuring serum calcium levels by blood sampling. The first measurement was made within 24 hours after the operation (postoperative day 1, POD1).¹⁸ A serum level check was repeated once a day in the following 72 hours. In patients with low serum calcium levels with or without associated symptoms, intravenous or oral calcium was administered. Subsequent serum calcium samples were drawn, with a frequency ranging from one per week to one per month.⁴ Calcium supplementation doses were adjusted during follow-up according to symptoms, serum calcium, and PTH levels.³⁸ TtHP was considered when patients received calcium supplementation and had a normalization of these parameters within six months after surgical treatment. PtHP was defined as the need for calcium supplementation, with or without active vitamin D, protracting for more than six months after surgery.⁷⁻⁹

2.1 | Statistical analysis

The categorical data were summarized with the absolute and percentage frequency. To analyze categorical variables, chi-squared test or Fisher exact test (when appropriate) were used. To analyze continuous variables *t* test for independent samples (two-tailed) was performed. The significance was set at 0.05 and all analyzes were carried out with SPSS technology v. 27.

3 | RESULTS

We analyzed 326 patients aged ≤ 18 years (mean age, 14.8 years) who underwent thyroidectomy due to thyroid carcinoma: 190 males (58%) and females 136 (42%). We clustered patients into age groups:

TABLE 1 Statistics: frequency (%) of categorical variables and mean (SD) of continuous variables associated with postoperative hypoparathyroidism including patients who will be affected by temporary (TtHP) or permanent hypoparathyroidism (PtHP)

Variable		Postoperative hypoparathyroidism		P value
		No	Yes	
Sex	Males	172/190 (90.5%)	18/190 (9.5%)	0.374
	Females	118/136 (86.8%)	18/136 (13.2%)	
Age	≤15 years	159/187 (85.0%)	28/187 (15.0%)	0.014
	>15 years	131/139 (94.2%)	8/139 (5.8%)	
Dimension	< 2 cm	179/190 (94.2%)	11/190 (5.8%)	<0.001
	≥2 cm	111/136 (81.6%)	25/136 (18.4%)	
Thyroiditis	Yes	106/119 (89.1%)	13/119 (10.9%)	0.895
	No	184/207 (88.9%)	23/207 (11.1%)	
Extrathyroidal extension	Yes	112/133 (84.2%)	21/133 (15.8%)	0.037
	No	178/193 (92.2%)	15/193 (7.8%)	
Central compartment lymph node dissection	Yes	99/119 (83.2%)	20/119 (16.8%)	0.020
	No	191/207 (92.3%)	16/207 (7.7%)	
Lateral compartment lymph node dissection	Yes	118/138 (85.3%)	20/138 (14.7%)	0.175
	No	172/188 (91.5%)	16/188 (8.5%)	
Unilateral/bilateral lymph node dissection	Unilateral	102/120 (85.0%)	18/120 (15.0%)	0.030
	Bilateral	42/60 (70.0%)	18/60 (30.0%)	
Parathyroid autotransplantation	Yes	13/16 (81.3%)	3/16 (18.8%)	0.549
	No	277/310 (89.4%)	33/310 (10.6%)	
Histology	PTC	251/280 (89.6%)	29/280 (10.4%)	0.910
	DSV	5/6 (83.3%)	1/6 (16.7%)	
	FTC	22/25 (88.0%)	3/25 (12.0%)	
	MC	12/15 (80.0%)	3/15 (20.0%)	
Preoperative serum calcium level (mg/dl)		9.6 (0.33)	9.46 (0.44)	0.054
Postoperative serum calcium level (mg/dl)		8.85 (0.42)	8.17 (0.56)	<0.001
Δ_{Ca} (%)		8.0 (4.0)	14.0 (6.0)	<0.001
TOTAL		290/326 (89.0%)	36/326 (11.0%)	

Abbreviations: DSV: diffuse sclerosing variant of papillary thyroid carcinoma; FTC: follicular thyroid carcinoma; MC: medullary carcinoma; PTC: papillary thyroid carcinoma; Δ_{Ca} : pre-/postoperative calcium levels decrease.

≤ 15 years or > 15 years. In the first subgroup, we included 187 cases (57%), whereas 139 (43%) were older. All the patients underwent a mean follow-up of 5.8 years (range, 1-11 years). We grouped the patients according to the tumor size: in 190 (58%) cases, the tumor was < 2 cm, whereas in 136 (42%) it was ≥ 2 cm. Thyroiditis was present in 119 (36%) patients, whereas extrathyroidal extension was present in 133 (40.9%) patients. Central compartment lymph node dissection was carried out in 119 (36.5%) patients, while lateral compartment lymph node dissection was performed in 138 (42.3%). Unilateral lymph node dissection was carried out in 120 (37%) patients, while bilateral lymph node dissection, comprising both central and

lateral compartment, was performed in 60 (18%). In 16 cases (5%), due to incidental parathyroidectomy, we performed an autotransplantation into the ipsilateral sternocleidomastoid muscle. At histological examination, 280 (86%) patients were papillary carcinoma in the classical variant, 6 (2%) presented diffuse sclerosing variant of papillary thyroid carcinoma, 25 (8%) were follicular carcinoma, while 15 (4%) had medullary carcinoma: 6 MEN 2A (2%), 4 MEN 2B (1%), and 5 FMTC (1%).

Postoperative hypoparathyroidism occurred in 36 (11.0%): among them, 16 cases (45%) developed TtHP and 20 (55%) PtHP, respectively, 4.91% and 6.13% of all patients examined.

TABLE 2 Statistics: Frequency (%) of categorical variables and mean (SD) of continuous variables associated with permanent postoperative hypoparathyroidism (PtHP)

Variable		Permanent hypoparathyroidism (PtHP)		P value
		No	Yes	
Sex	Males	6/18 (33.3%)	12/18 (66.7%)	0.314
	Females	10/18 (55.6%)	8/18 (44.4%)	
Age	≤15 years	16/28 (57.1%)	12/28 (42.9%)	0.014
	>15 years	0/8 (0%)	8/8 (100%)	
Dimension	< 2 cm	4/11 (36.4%)	7/11 (63.6%)	0.777
	≥2 cm	12/25 (48.0%)	13/25 (52.0%)	
Thyroiditis	Yes	11/13 (84.6%)	2/13 (15.4%)	<0.001
	No	5/23 (21.7%)	18/23 (78.3%)	
Extrathyroidal extension	Yes	16/21 (76.2%)	5/21 (23.8%)	<0.001
	No	0/15 (0%)	15/15 (100%)	
Central compartment lymph node dissection	Yes	8/20 (40.0%)	12/20 (60.0%)	0.793
	No	8/16 (50.0%)	8/16 (50.0%)	
Lateral compartment lymph node dissection	Yes	10/20 (50.0%)	10/20 (50.0%)	0.680
	No	6/16 (37.5%)	10/16 (62.5%)	
Unilateral/bilateral lymph node dissection	Unilateral	13/31 (41.9%)	18/31 (58.1%)	0.788
	Bilateral	3/5 (60.0%)	2/5 (40.0%)	
Parathyroid autotransplantation	Yes	2/3 (66.7%)	1/3 (33.3%)	0.840
	No	14/33 (42.4%)	19/33 (57.6%)	
Histology	PTC	15/29 (51.7%)	14/29 (48.3%)	0.355
	DSV	0/1 (0%)	1/1 (100%)	
	FTC	1/3 (33.3%)	2/3 (66.7%)	
	MC	0/3 (0%)	3/3 (100%)	
Preoperative serum calcium level (mg/dL)		9.51 (0.51)	9.59 (0.37)	0.574
Postoperative serum calcium level (mg/dL)		8.44 (0.44)	7.91 (0.43)	<0.001
ΔCa (%)		11.9 (4.1)	16.7 (5.1)	0.004
Total		16/36 (44.4%)	20/36 (55.6%)	

Abbreviations: DSV: diffuse sclerosing variant of papillary thyroid carcinoma; FTC: follicular thyroid carcinoma; MC: medullary carcinoma; PTC: papillary thyroid carcinoma; ΔCa: pre/postoperative calcium levels decrease.

Postoperative hypoparathyroidism was more frequent in patients ≤15 years ($P = 0.014$), in case of larger tumors (≥ 2 cm) ($P = 0.001$), extrathyroidal extension ($P = 0.037$), central compartment lymph node dissection ($P = 0.020$), and bilateral lymph node dissection ($P = 0.030$).

PtHP was more frequent in patients > 15 years ($P = 0.014$), presence of thyroiditis ($P < 0.001$), and extrathyroidal extension ($P < 0.001$).

Concerning the first postoperative calcium level measurement (POD1), in the hypoparathyroidism group we registered a 8.17 mg/dL value (mean ± SD, 8.17 ± 0.56 mg/dL, $P < 0.001$) with 14% pre/postoperative decrease (Δ_{Ca}) (mean ± SD, 14.0 ± 6.0%, $P < 0.001$), whereas in PtHP patient group calcium level was 7.91 mg/dL (mean ± SD, 7.91 ± 0.43 mg/dL, $P < 0.001$) with 16.7 ΔCa (mean ± SD, 16.7 ± 5.1%, $P = 0.004$) (Tables 1 and 2).

4 | DISCUSSION

Hypocalcemia is one of the most frequent complications of thyroid surgery, associated with intraoperative ischemia and/or reduction in volume of parathyroid glands or incidental parathyroidectomy.^{38,39} To date, few studies have focused on hypocalcemia and the possible predictive factors of this complication following thyroid surgery in children and adolescents.^{40–43} In reported case series, TtHP incidence ranges from 13.6% to 34%^{44,45} following total thyroidectomy in pediatric age. Nordenström et al.⁴⁶ report that out of 274 patients, below 18 years of age undergoing thyroidectomy, 7.3% developed PtHP, whereas Klein Hesselink et al.⁹ analyzed 105 patients aged ≤18 years operated for differentiated thyroid cancer and reported that

23.8% of patients developed PtHP. Scholtz et al.⁴⁷ mention the existence of a female prevalence for postoperative hypoparathyroidism, likely associated with a greater susceptibility to thyroid diseases. Conversely, in our study, gender was not a determining factor in predicting the risk of developing these complications. De Groot et al.,⁴⁸ Kluijfhout et al.,⁴⁹ and Moley et al.⁵⁰ showed that the smaller the age of the patients, the greater is the probability of developing postoperative hypoparathyroidism, due to the difficulty in identifying parathyroid glands at surgery or due to the greater fragility of the anatomical structures. The data we analyzed are in line with said studies: patients with age ≤ 15 years have a significantly greater risk of developing postoperative hypoparathyroidism. Nevertheless, these children have a greater ability to regain parathyroid function; in fact, in our series, two thirds of patients affected by postoperative hypocalcemia completely recovered. Conversely, in our study, patients who suffered from postoperative hypoparathyroidism above 15 years of age all developed PtHP. In addition, our study demonstrates that tumor size is associated with postoperative hypocalcemia: conversely, this variable is not relevant for the development of PtHP. Interestingly enough and consistent with previous reports,²⁰ we found an association of both postoperative hypoparathyroidism and PtHP with extrathyroidal extension, whereas thyroiditis was associated only with PtHP.

Thyroidectomy behaves as a positive predictive factor for postoperative hypoparathyroidism with regard to low-volume surgeons (less than 20 cases/year), as shown by Hauch et al.⁵¹ and confirmed by Sosa et al.¹⁰ In the present study, we do not report any significant difference in terms of incidence of postoperative hypoparathyroidism among our high-volume surgical centers.

In our series, lymph node dissection plays a fundamental role for hypoparathyroidism; the reasons behind this might reside in the wider resection performed or the prolonged duration of surgery, which is in line with current literature.⁵²

With reference to the histotype as a predictor for the development of hypoparathyroidism in children, Scholz et al.⁴⁷ identify PTC to be the most common, but in our experience these data do not reach significance. At surgery, it is crucial to carry out a meticulous dissection aimed both at preserving at least three parathyroid glands and keeping their vascularization intact.⁵³ In order to prevent postoperative hypoparathyroidism, in case of inadvertent parathyroidectomy, parathyroid autotransplantation may be performed, even though its effective utility has been questioned.⁵⁴⁻⁵⁶ We did not report any statistically significant difference for what concerns parathyroids autotransplantation in our two groups.

In our cohort, postoperative calcium levels below 8.17 mg/dL and a ΔC_a above 14% were predictive of postoperative hypoparathyroidism and postoperative calcium levels below 7.91 mg/dL and a ΔC_a above 16.7% were predictive of PtHP.

One limitation of this study is that statistical analysis does not provide a multivariate analysis, for which we should expand the current database. Future prospective multicenter studies should address this limitation.

5 | CONCLUSIONS

The risk of postoperative hypoparathyroidism is related to younger age, tumor size, lymph node dissection, extrathyroidal extension, and postoperative calcium levels. The risk of PtHP is related to older age, thyroiditis, extrathyroidal extension, and postoperative calcium levels.

CONFLICTS OF INTEREST

All the authors confirm they have no conflicts of interest or competing interests to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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