

Factors associated with postoperative hypocalcemia following surgery for thyroid cancer in childhood

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June 1, 2021

Abstract

Background: Postoperative hypocalcemia is a frequent complication after thyroid surgery. Hypoparathyroidism may develop as transient (TtHP), with normalization within six months from surgery, or permanent (PtHP) if the patient requires replacement therapy. The present study analyzes rates and factors associated with the development of TtHP or PtHP following thyroid surgery in a pediatric population. **Procedure:** A retrospective multicenter study analyzing 363 patients was carried out. We recorded gender, age, tumor size, type of surgery, lymph node dissection, histology. Calcium levels were acquired daily for 72 hours after discharge. Subsequent sample collection was customized on the patient's hypocalcemia severity. **Results:** We analyzed 363 patients aged [?]18 years (mean age 14.2 years) who underwent thyroid surgery clustered into age groups ([?]15 or >15). Patients mean follow-up was 5.8 years (1-11yrs). At histology 310 (85%) were papillary carcinoma, 32 (9%) were follicular carcinoma, 6 (2%) presented diffuse sclerosing variant of papillary thyroid carcinoma whilst 15 (4%) had familial medullary carcinoma. TtHP developed in 36 (9.9%), PtHP in 20 (5.5%) cases. TtHP was more frequent in younger patients ($p=0.009$). Both PtHP and TtHP were increased in case of larger tumors ([?]2 cm) ($p=0.001$). All TtHP and PtHP were in TT group. PtHP rate was increased if lymph node dissection was carried out ($p<0.001$). **Conclusions:** The risk of hypoparathyroidism is related to younger age, tumor size, TT and lymph node dissection therefore surgeons should tailor surgery as much as possible to avert such complication.

Introduction

Along with the recurrent laryngeal nerve paralysis and bleeding, postoperative hypocalcemia is the major and most frequent complication that occurs after thyroid surgery¹. Commonly it arises following removal or insult to the parathyroid glands at neck surgery²⁻⁶. Hypoparathyroidism is defined by a decrease in serum PTH and calcium levels: 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^{7,8}. 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, surgical expertise and surgical timing^{6, 9-13}. The identification of fewer than two parathyroid glands during thyroidectomy is also associated with the devel-

opment of hypocalcemia¹⁴. Others have investigated the possible link between the development of transient hypocalcemia and low levels of preoperative vitamin D associated with low postoperative parathyroid hormone (PTH)¹⁵⁻²². Another biochemical parameter which has been correlated with transient hypocalcemia is the post-operative serum magnesium concentration, independently of the serum calcium levels²³⁻²⁶. The calcium level less than 1.88 mmol/l or lower after 24h from thyroid surgery has been reported as predictive for the development of permanent hypocalcemia²⁷⁻³². The risk factors identified by the scientific community are different, depending on TtHP or PtHP and are currently a matter of debate. In the present study the main end-point was to analyze, in a pediatric population following thyroid surgery, rate and factors associated with the development of TtHP or PtHP.

Methods

This retrospective multicenter study analyzes pediatric patients, operated over a 11 year period (January 2009 - December 2019) at several institutions (Division of Paediatric 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, Pediatric Surgery at Department of Woman and Child Health in Padua and the National Cancer Institute in Milan).

The variables taken into consideration are: gender, age, tumor size, type of surgery performed (total thyroidectomy - TT or hemithyroidectomy - HT), autotransplantation into the ipsilateral sternocleidomastoid muscle in case of incidental parathyroidectomy, lymph node dissection, histology (papillary carcinoma, diffuse sclerosing variant, follicular carcinoma, medullary carcinoma within genetic forms, such as MEN2A, MEN2B and FMTC). The age range at the operation was 4 - 18, with a mean age of 13.6 years. The exclusion criteria were: primitive hypoparathyroidism, 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. Post-operative hypocalcemia was defined as a serum calcium level of less than 8 mg/dl. The first measurement was made within 24 hours after the operation. A serum level check was repeated once a day in the three days following discharge. Postoperative parathyroid hormone (PTH) levels were determined in case of persistent low serum calcium levels³³⁻³⁴. In patients with serum calcium levels <8 mg/dl with or without associated symptoms, intravenous or oral calcium was administered. In case of persistent hypocalcemia, subsequent serum calcium samples were drawn, with a frequency ranging from one per week to one per month⁴. Calcium supplementation doses were adjusted during follow-up according to symptoms and serum calcium levels³⁵. TtHP was considered when patients received calcium supplementation and/or had a normalization in PTH levels within 6 months after surgical treatment. PtHP was defined as the need for calcium supplementation with or without active Vitamin D even 6 months after surgery⁷.

Statistical Analysis

The categorical data were summarized with the absolute and percentage frequency. To compare the percentages of hypoparathyroidism, both in terms of transient and permanent, the z-test for proportions was used, so as to allow observing whether the pathology is randomly distributed or preferentially between the two variables examined. The significance was set at 0.05 ($p < 0.05$). All analyzes were performed with SPSS technology v. 26.

Results

We analyzed 363 patients aged [?]18 years (mean age 14.2 years) who underwent surgery due to thyroid carcinoma: 210 males (58%), females 153 (42%). We clustered patients into age groups: [?] 15 years or > 15 years. In the first subgroup we included 207 cases (57%) while 156 (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 210 (57%) cases the tumor was < 2 cm, while in 153 (42%) it was [?] 2 cm. Three hundred twenty six patients (90%) underwent total thyroidectomy, 37 (10%) a hemithyroidectomy. Lymph node dissection was carried out in 175 (48%) patients. In 16 cases (4%), due to incidental parathyroidectomy, we performed an

autotransplantation into the ipsilateral sternocleidomastoid muscle. At histological examination 310 (85%) were papillary carcinoma in the classical variant, 32 (9%) were follicular carcinoma, 6 (2%) presented diffuse sclerosing variant of papillary thyroid carcinoma whilst 15 (4%) had medullary carcinoma: 6 MEN 2A (2%), 4 MEN 2B (1%), 5 FMTC (1%). TtHP developed in 36 (10%), PtHP in 20 (6%) cases. No significant differences between TtHP and PtHP groups were reported with regard to gender ($p=0.408$ for TtHP and $p=0.974$ for PtHP) and parathyroid autotransplantation ($p=0.437$ for TtHP and $p=0.673$ for PtHP). TtHP was more frequent in subjects with age ≥ 15 years ($p=0.009$). Both PtHP and TtHP were increased in case of larger tumors (≥ 2 cm) ($p=0.001$). Concerning surgical approach, all the patients who presented TtHP and PtHP belonged to the TT group. PtHP rate was increased in patients who underwent lymph node dissection ($p<0.001$). No significant histologic differences for TtHP and PtHP were reported. Table 1 and 2 report the statistical analysis performed on all the parameters we investigated in our cohort of patients.

Discussion

Hypocalcemia is one of the most frequent complications of thyroid surgery, due to decreasing PTH levels following surgery associated with intraoperative ischemia and/or reduction in volume of parathyroid glands or incidental parathyroidectomy³⁶. To date, few studies focused on hypocalcemia following thyroid surgery in children and adolescents, analyzing the possible predictive factors of this complication^{5, 36-42}. In reported case-series TtHP incidence ranges from 13.6% to 34%⁴³⁻⁴⁴ following total thyroidectomy in pediatric age. Nordenström et al.⁴⁵ report that out of 274 patients, below 18 years of age undergoing thyroidectomy, 7.3% developed PtHP, while Klein Hesselink et al.³⁰, analyzed 105 patients aged ≥ 18 years operated for differentiated thyroid cancer and reported that 23.8% of patients developed PtHP. Our data demonstrated that both TtHP and PtHP incidences are in line with current literature^{30,43-46}. Scholtz et al.⁴⁷ mention the existence of a female prevalence for postoperative hypoparathyroidism, linked to greater susceptibility to thyroid diseases. On the contrary, in our study, gender was not a determining factor in predicting the risk of developing these complications. De Groot JW et al.⁴⁸, confirmed by Kluijfhout WP⁴⁹ et al. and Moley JF 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 during surgery or due to the greater fragility of the anatomical structures. The data we analyzed are in agreement with what was discussed above: patients with age ≥ 15 years have a significantly greater risk of developing TtHP; with regard to PtHP, data do not suggest any age-based difference. Younger children have a greater ability to recover from TtHP; in fact, in our series, two thirds of patients affected by postoperative hypocalcemia completely recovered. Patients between 16 and 18 years of age are less likely to recover, since all patients with TtHP developed PtHP. In our study, tumor size is associated with postoperative hypocalcemia: TtHP is more frequent in tumors ≥ 2 cm and size seems to be even more relevant for PtHP. TT behaves as a positive predictive factor for hypocalcemia with regards to low volume surgeons, as shown by Hauch et al.⁵¹ confirmed by Sosa⁹. In our series, this complication occurred only in patients who underwent TT, we report no hypocalcemia related to HT; however Newman et al.⁵² reported 9 cases (11%) of hypoparathyroidism out of 82 patients analyzed aged ≥ 21 years, who underwent lobectomy. In the present study, lymph node dissection seems to assume a fundamental role for PtHP; the reasons behind this might reside in the wider resection performed or the prolonged duration of surgery, which is in line with current literature⁵³. With reference to the histotype as a predictor for the development of hypocalcemia in children, Scholz et al.⁴⁷ identify PTC to be the most common, but in our experience this data does not reach significance. During surgery it is crucial to carry out a meticulous dissection aimed at preserving parathyroid glands and keeping their vascularization intact; a fundamental factor for post-operative normocalcemia is the preservation of at least three parathyroid glands in situ after surgery⁵⁴. In order to prevent postoperative hypoparathyroidism, in case of inadvertent parathyroidectomy, parathyroid autotransplantation may be performed^{55,56}, even though its effective utility has been questioned⁵⁷. We did not report any significant difference for what concerns parathyroids autotransplantation in TtHP and PtHP groups.

Conclusions

From the data obtained from our work, we found an association of TtHP with the age at which the patients

underwent surgery and the size of the tumor, while the size of the tumor and the lymph node dissection are associated with the development of PtHP. Moreover, no patients who have undergone HT presented with TtHP or PtHP. This might suggest that children, operated for thyroid cancer, should be treated with the least invasive surgical approach possible, in order to reduce the risk of development of hypoparathyroidism.

Conflict of interest

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

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