The Effect of Pre-Thyroidectomy Calcitriol Prophylaxis on Post-Thyroidectomy Hypocalcaemia in Children

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Abstract

Introduction: Transient or persistent hypoparathyroidism is one of the most well-known complications of total thyroidectomy and may lead to symptomatic hypocalcaemia. In children, treatment of post-thyroidectomy hypocalcaemia usually consists of postoperative calcium and/or vitamin D supplementation. In 2013, we implemented prophylactic pre-thyroidectomy calcitriol supplementation for all children undergoing total thyroidectomy at the Amsterdam UMC. The objective of this study was to evaluate the efficacy of this prophylactic calcitriol supplementation in preventing post-thyroidectomy hypocalcaemia in children.

Methods: In a retrospective case study, we included all children (age <18 years), who underwent a total or completion thyroidectomy in the Amsterdam UMC, between 2000 and 2020. Patients were divided into two groups, patients with preoperative calcitriol supplementation and those without (controls). Hypocalcaemia was defined as total serum calcium concentration of <2.0 mmol/L. The primary outcome measure was the occurrence of hypocalcaemia in the first 72 h after surgery. Secondary outcome measures were occurrence of symptomatic hypocalcaemia, need for medical intervention within the first 72 h after surgery, and length of hospitalization.

Results: A total of 51 patients were included; 26 with calcitriol prophylaxis and 25 controls. There was no significant difference in occurrence of hypocalcaemia (17/26 prophylaxis group; 18/25 control group). Median postoperative calcium concentrations in the first 72 h were significantly higher in the group with prophylaxis at 30–35 h (2.26 vs. 2.01 mmol/L) and 36–41 h (2.17 vs. 1.92 mmol/L). Occurrence of symptomatic hypocalcaemia, need for medical intervention, and length of hospitalization were not significantly different between the groups.

Conclusion: Calcitriol prophylaxis resulted in somewhat higher postoperative calcium concentrations but did not reduce the occurrence of hypocalcaemia or affect clinical outcome measures such as occurrence of symptomatic hypocalcaemia and length of postoperative hospitalization.
Introduction

Hypoparathyroidism is a well-known complication of thyroid surgery [1]. Transient hypoparathyroidism results from compromised vascular supply of the parathyroid glands during thyroidectomy, while injury or inadvertent removal of the parathyroid glands may cause permanent hypoparathyroidism [1].

The incidence of hypoparathyroidism after thyroidectomy is reported to be around 25% with higher incidences reported in children [2]. In a systematic review including 15 studies, representing 1,552 pediatric thyroidectomy patients, the pooled incidence of transient hypocalcaemia was 35.5% and persistent hypocalcaemia 4.2% [3]. Since hypoparathyroidism may lead to symptomatic hypocalcaemia with neurological complaints (muscle spasms, paresthesia) and cardiac arrhythmia, close postsurgical monitoring of serum calcium concentrations is warranted. This often leads to prolonged hospitalization and therefore, treatment strategies aiming at reducing the occurrence of hypocalcaemia have the potential to not only reduce morbidity but also hospitalization and the associated health care costs.

In adults, both pre- and post-thyroidectomy calcium and/or vitamin D supplementation are used to prevent post-thyroidectomy hypocalcaemia [4, 5]. In children, the most common practice consists of postoperative treatment. In a recent systematic review of 15 studies on hypocalcaemia prevention after thyroidectomy in children, only three studies reported the use of preoperative calcium/vitamin D supplementation [3, 6–8].

At the Amsterdam UMC, standard practice after thyroidectomy is to closely monitor calcium concentrations during the first 72 h postoperatively and treat with calcium and calcitriol in case of hypocalcaemia (total serum calcium <2.0 mmol/L). In 2013, additional prophylactic pre-thyroidectomy calcitriol supplementation was implemented, starting 3 days preoperatively, and continued for 5 days after surgery, after which it is gradually decreased and stopped 2 weeks after surgery.

The objective of this study was to evaluate the efficacy of prophylactic preoperative calcitriol supplementation in preventing post-thyroidectomy hypocalcaemia in children. We performed a retrospective cohort study comparing post-thyroidectomy serum calcium concentrations of children with prophylactic calcitriol treatment (cohort 2013–2020) to those of children without prophylactic calcitriol treatment (cohort 2000–2012). The primary outcome measure was the occurrence of hypocalcaemia, defined as total serum calcium concentration of <2.0 mmol/L, in the first 72 h after surgery. Secondary outcome measures included the occurrence of symtomatic hypocalcaemia, need for medical intervention for hypocalcaemia within the first 72 h after surgery, and length of hospitalization.

Methods

For this single center retrospective cohort study, patients were included from a local database containing the names of all pediatric patients (<18 years at the time of surgery) who underwent a total or completion hemithyroidectomy (= second hemithyroidectomy) between 2000 and 2020. Thyroid surgery was always performed by a dedicated team consisting of a pediatric surgeon with special interest in endocrine surgery and an endocrine surgeon performing more than 50 thyroidectomies per year. Intraoperatively, parathyroid glands were identified visually and preserved. In some cases, tissue was removed for frozen section to confirm the presence of parathyroid tissue, after which parathyroid reimplantation was performed. Autofluorescence for parathyroid identification was not used. In patients with thyroid cancer, central lymph node dissection was performed prophylactically before 2015. From 2015 onward, it is only performed in case of suspicious lymph nodes upon inspection.

Patients were divided into two cohorts: patients without prophylactic preoperative calcitriol treatment and patients with prophylactic preoperative calcitriol treatment. Prophylactic calcitriol treatment was implemented in 2013 according to the following protocol: 0.5 μg calcitriol twice daily, 3 days before surgery until 5 days post-surgery; 0.5 μg calcitriol once a day, 6–10 days post-surgery; and 0.5 μg calcitriol on alternate days 11–15 days post-surgery. Calcium concentrations were closely monitored during the first 72 h postoperatively (every 6 h during the first 48 h followed by every 12 h), and in case of hypocalcaemia (total serum calcium <2.0 mmol/L), treatment was started. Before 2013, this meant starting calcium and calcitriol, and from 2013 onward, additional calcium supplementation was started and calcitriol continued or increased. In the absence of hypocalcaemia, calcitriol was stopped at the 16th day after surgery. Calcium supplementation in the first 48 h after surgery usually consists of intravenous supplementation. When prolonged treatment is suspected, intravenous supplementation is replaced by oral supplementation.

All included patients were treated in the Emma Children’s Hospital, Amsterdam University Medical Centers, a tertiary care hospital for pediatric endocrine disorders including surgical treatment. Details on patient characteristics, thyroid disease, surgery details, and postoperative treatment were collected from medical charts. Laboratory results were collected from an electronic laboratory database. Besides calcium concentration in the first 72 h after surgery, data on the occurrence of transient and persistent hypoparathyroidism were also collected. Hypocalcaemia resolving during hospital stay was classified as “rapidly resolved hypocalcaemia.” Hypocalcaemia resolving within 6 months after surgery was regarded as transient, and hypocalcaemia persisting after 6 months was classified as permanent hypocalcaemia.

Indication for surgery was classified based on the results of post-surgery pathology and was divided into three groups: (1) prophylactic (for MEN2A/2B syndrome), (2) benign (multinodular...
goiter, autoimmune thyroid disease), or (3) malignancy (thyroid cancer). Patients with MEN2A/B syndrome and only positive tumor markers and/or C-cell hyperplasia upon pathological examination were classified as prophylactic indication.

The primary outcome was occurrence of hypocalcaemia in the first 72 h after surgery. Hypocalcaemia was defined as a total calcium concentration <2.0 mmol/L, and severe hypocalcaemia as total calcium concentration <1.8 mmol/L. Because serum calcium concentrations were not always measured at the exact same time points for every patient, these measurements were divided into 6-h time frames for the first 48 h and 12-h time frames between 48 and 71 h after surgery. If instead of total calcium only ionized calcium was measured, the total serum calcium concentration was calculated using the ionized calcium and a recent patient’s albumin concentration. Albumin was measured using the bromcresol green method on subsequent analytical platforms (Hitachi 747, Modular, Cobas 8000) from Roche Diagnostics. Total calcium concentration was calculated using the formula CaTot = ([0.006 × Alb] − 0.079 + Ca²⁺)/0.813 [9]. We used sets of ionized and total calcium of patients who had both measurements performed at our clinical chemistry laboratory, to test the usefulness of this formula for our patient group. Overall, the measured and calculated total calcium results were very comparable.

Secondary outcome measures were occurrence of symptomatic hypocalcaemia, need for medical intervention within the first 72 h after surgery, and length of hospitalization. Symptomatic hypocalcaemia was defined as the occurrence of paresthesia, tetany, convulsions, or heart rate disorders.

### Statistical Analysis

χ² test, Fisher’s Exact test, and Fisher-Freeman-Halton tests were used for comparison of patient characteristics, surgery characteristics, hypocalcaemia, and treatment outcomes. Since age, serum calcium concentration, PGRIS (parathyroid glands remaining in situ) score, length of hospitalization, and duration of follow-up were all distributed abnormally, the Mann-Whitney U test was used to analyze these variables. A p value <0.05 was considered statistically significant. Statistical analyses were performed in SPSS, version 26.

### Results

Fifty-one patients were included. Twenty-six patients received preoperative calcitriol treatment and 25 did not. Baseline characteristics are given in Table 1. Significant differences between cases and controls were only found in sex (0% males vs. 48% males, p < 0.001) and median length of follow-up (2 years [0–6] vs. 4 years [0–18], p < 0.001). There were no significant differences in indication for surgery, extent of surgery, parathyroid gland status, and surgical complications like infection and recurrent laryngeal nerve (RLN) injury (Table 1).

Hypocalcaemia within the first 72 h after surgery was seen in 17 of the 26 calcitriol treated patients (65.4%) and in 18 of the 25 controls (72%) (p = 0.764). Although there were fewer cases of severe hypocalcaemia in the calcitriol group (10 [38.5%] vs. 13 [52%]), this was not

| Table 1. Baseline and surgery characteristics of 51 pediatric thyroidectomy cases |
|-----------------------------------|----------------|----------------|----------------|
|                                    | Calcitriol group (n = 26) | Controls (n = 25) | p value |
| Median age at surgery in years (range) | 14 (3–17) | 13 (1–17) | 0.828 |
| Gender female                       | 26 | 13 | <0.05 |
| Median length of follow-up in years (range) | 2 (0–6) | 4 (0–18) | <0.05 |
| Completion thyroidectomy            | 2 | 2 | 1.000 |
| Indication for surgery              | 0.276 |
| Prophylactic                        | 2 | 6 |
| Benign disease                      | 13 | 9 |
| Graves’ disease                     | 10 | 3 | 0.079 |
| Malignant disease                   | 11 | 10 |
| Extent of surgery                   | 0.564 |
| No lymph node dissection            | 18 | 18 |
| Central lymph node dissection       | 4 | 3 |
| Central + lateral lymph node dissection | 4 | 2 |
| Node picking                        | 0 | 2 |
| Parathyroid status                  | 0.781 |
| Parathyroid gland in pathology report | 11 | 12 |
| Parathyroid autotransplant          | 7 | 4 | 0.499 |
| Median PGRIS score (range)          | 3 (0–4) | 3 (2–4) | 0.360 |

RLN, recurrent laryngeal nerve; PGRIS, parathyroid glands remaining in situ.
There was no significant difference in symptomatic hypocalcaemia (6 calcitriol group vs. 5 controls, \( p = 1.000 \)) or in the duration of hypocalcaemia (rapidly resolved/transient/persistent; \( p = 0.426 \)). There were no differences in need for treatment <72 h, and while fewer children with calcitriol prophylaxis required a form of intravenous treatment (10 [66.7%] vs. 14 [77.8%]), this was not statistically significant (\( p = 0.697 \)). Two patients in each arm were not treated with calcium supplementation (Table 2). These cases of hypocalcaemia resolved spontaneously within 6–18 h after surgery.

Since Graves’ disease and central lymph node dissection are considered high-risk factors for developing post-thyroidectomy hypocalcaemia we performed a subanalysis for these groups. The patient groups were too small for individual analysis but when comparing these 26 high-risk surgeries (13 Graves’ disease; 13 central lymph node dissection) with the other 25 (lower risk) surgeries, hypocalcaemia was more common in the high-risk group although not statistically significant (21/26 vs. 14/25, \( p = 0.075 \)).

In a subgroup-analysis of all patients with transient hypoparathyroidism, we compared patients with calcitriol prophylaxis (\( n = 8 \)) to those without prophylaxis (\( n = 5 \)) and found no significant differences for any of the outcome measures. A similar subgroup-analysis of all patients with persistent hypoparathyroidism, also did not show significant differences between patients with calcitriol prophylaxis (\( n = 5 \)) and those without (\( n = 5 \)).

Median length of hospitalization was similar in both groups (3 days). Two outliers were excluded from the control group because of prolonged hospital stay due to another elective surgery during hospital admission in one case and a Port-a-Cath infection in a second case.

When plotting all calcium measurement in the first 72 h post-surgery, calcium levels did seem to be higher with calcitriol prophylaxis than without, as shown in Figure 1. Median postoperative calcium concentrations were higher in the group with prophylaxis at all time-intervals, except 18–23 h. This difference in mean calcium concentrations was significant at the intervals 30–35 h (2.26 vs. 2.01 mmol/L; \( p = 0.041 \)) and 36–41 h (2.17 vs. 1.92 mmol/L; \( p = 0.003 \)). Since Figure 1 also includes patients who received calcium treatment for hypocalcaemia, we made an additional survival plot (Kaplan-Meier curve) illustrating the proportion of patients in both groups without hypocalcaemia in hours after surgery (Fig. 2). The difference was not significant (log rank \( p = 0.455 \)).

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**Table 2. Hypocalcaemia outcome <72 h post-surgery**

|                         | Calcitriol group (n = 26) | Controls (n = 25) | \( p \) value |
|-------------------------|---------------------------|------------------|--------------|
| Hypocalcaemia (total Ca < 2.0 mmol/L) | 17                        | 18               | 0.764        |
| Severe hypocalcaemia (total Ca < 1.8 mmol/L) | 10                        | 13               | 0.331        |
| Symptomatic hypocalcaemia | 6                         | 5                | 1.000        |
| Treatment administered  | 15                        | 16               | 1.000        |
| Intravenous calcium supplementation | 10                        | 14               | 0.697        |
| Rapidly resolved hypocalcaemia | 4                         | 4                | 1.000        |
| Transient hypocalcaemia | 8                         | 5                | 0.305        |
| Persistent hypocalcaemia | 5                         | 9                | 0.305        |
| Median length of hospitalization in days (range) | 3 (2–8)                  | 3 (2–10)        | 0.356        |

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**Fig. 1.** Median total calcium concentrations (mmol/L) in the first 72 h after thyroidectomy in 26 patients with calcitriol prophylaxis (red) and 25 patients without prophylaxis (blue). Bars display 95% confidence intervals, \* indicates significant result (\( p < 0.05 \)).
Discussion

We evaluated the effect of a local prophylactic calcitriol treatment strategy to prevent post-thyroidectomy hypocalcaemia in children. While serum calcium levels in the first 72 h were significantly higher in the calcitriol group compared to controls without pre- or postoperative calcitriol treatment (Fig. 1), there was no significant reduction in the occurrence of symptomatic hypocalcaemia, need for treatment or in length of hospitalization.

Hypoparathyroidism induced hypocalcaemia is the most common complication after thyroidectomy in children and adults. Hypoparathyroidism continuing beyond 6 months after surgery is usually defined as permanent hypoparathyroidism. However, it has been proposed that instead of permanent the term persistent should be used since late recovery of parathyroid function after 6 months is common. In a study including 71 adult and 23 pediatric thyroidectomy patients with persistent hypoparathyroidism at 6 months, late recovery after a median follow-up of 20 months was observed in 11 children (47.8%) and 34 adults (47.9%), indicating that almost half of patients with persistent hypoparathyroidism showed late parathyroid recovery. Treatment strategies aiming at reducing the occurrence of post-thyroidectomy hypocalcaemia have the potential to not only reduce morbidity but also hospitalization and associated health care costs.

Radakrishnan et al. [3] systematically reviewed studies on hypocalcaemia prevention and management practices in pediatric thyroidectomy patients. In the 15 included studies, treatment strategies were very variable with most studies reporting postoperative calcium and/or vitamin D supplementation. Of the three studies mentioning the use of preoperative calcium and/or vitamin D supplementation, two of these studies used calcitriol [7, 8]. In a retrospective study of 91 pediatric thyroidectomy patients including 41 patients with calcitriol (0.1–0.5 μg daily) and calcium carbonate pretreatment (750–1,500 mg three to four times daily), Yu et al. [7] reported no significant difference in the occurrence of hypocalcaemia. Breuer et al. [8] used a very similar preoperative calcitriol treatment strategy as ours in a subset of patients in a study on outcome after thyroidectomy in children with Graves’ disease. Calcitriol treatment in 20 patients reduced the need for postoperative calcium infusion from 50% to 16% and the duration of intravenous calcium infusion was shortened by more than 50% [8]. Since these children were operated for benign thyroid disease, comparison with our cohort is difficult.

Also in adults, hypocalcaemia preventive treatment practices are very variable including both pre- and postoperative treatment protocols [5]. Shonka et al. [10] recently reported the results of a phase II randomized study of preoperative calcitriol treatment in adults. In this study, 23 patients with calcitriol treatment (1 μg twice daily for 7 days prior to surgery) were compared to 24 patients receiving placebo. All patients received the same postoperative treatment consisting of 1 g calcium carbonate thrice a day and 0.5 μg calcitriol twice a day. The authors concluded that preoperative supplementation had no impact on postoperative hypocalcaemia. Similarly Donahue et al. [11] performed a randomized trial comparing 38 patients with oral calcitriol 0.25 μg twice a day and 1,500 mg calcium carbonate thrice daily 5 days preoperatively to 44 controls. The control group started the same medication postoperatively. No significant differences were found in postoperative calcium levels, need for intervention, or length of hospitalization. These findings did not support routine preoperative supplementation with calcitriol and calcium.

Khatiwada and Harris [12] performed a systematic review on trials using preoperative calcium and vitamin D supplementation in adults. Three of the nine studies included calcitriol treatment. Protocols were variable and seven out of nine included trials reported significantly reduced rates of postoperative hypocalcaemia (absolute risk reduction for hypocalcaemia 13–59%, absolute risk reduction for symptomatic hypocalcaemia 11–40%). The authors concluded that preoperative treatment should be considered [12]. These conflicting results are probably

Fig. 2. Survival plot showing proportion of patients without hypocalcaemia in hours after thyroidectomy; 26 patients with calcitriol prophylaxis (red), 25 patients without calcitriol prophylaxis (blue), log rank \( p = 0.455 \).
due to the use of variable treatment protocols in variable patient populations, making comparison of studies difficult.

The strength of this study lies in the use of a standardized treatment protocol at a single center in children operated by a small group of dedicated thyroid surgeons. However, the number of patients in our study is relatively small and may significant differences may become apparent in a larger cohort. It is possible that prophylactic treatment may be most effective in certain subgroups of patients, for example in patients with preexisting vitamin D deficiency. Our study is further limited by its retrospective character. The occurrence of symptomatic hypocalcaemia was not systematically assessed and reported, and also, data on parathyroid status were not uniformly reported. In addition, comparing an older and newer patient cohort has its limitations. Newer surgical techniques may have influenced surgical outcome.

There was a relatively high percentage of persistent hypocalcaemia in our study, in both the older and newer cohort (5/26 in the calcitriol group; 9/25 in the controls). In all cases, except one, this occurred in children receiving surgery for thyroid malignancy including extensive neck lymph node dissection. In various studies, lymph node dissection has been shown to be an independent risk factor for permanent hypoparathyroidism [13].

Preoperatively started calcitriol treatment will reduce intraoperative PTH concentrations. This may be considered a disadvantage as intraoperative PTH measurement may be helpful in identifying parathyroid glands and may also predict the occurrence of post-thyroidectomy severe hypocalcaemia [14, 15].

Even if prophylactic treatment would prevent hypocalcaemia in the immediate postoperative period it will not influence the occurrence of persistent parathyroid damage. Since persistent hypothyroidism requires lifelong treatment and affects quality of life, various new treatment strategies are being explored, like the use of synthetic PTH and parathyroid allotransplantation [1, 16, 17].

In conclusion, calcitriol prophylaxis started 3 days prior to thyroidectomy resulted in higher postoperative calcium concentrations in the first 72 h after surgery but did not reduce the occurrence of hypocalcaemia and did not affect clinical outcome measures such as occurrence of symptomatic hypocalcaemia and length of postoperative hospitalization. A larger, prospectively set up study including pretreatment vitamin D and calcium measurements is needed to further evaluate the efficacy of this prophylactic treatment strategy.

**Statement of Ethics**

This study protocol was reviewed and granted an exemption from requiring ethics approval by the Medical Ethics Review Committee of the Academic Medical Center, Amsterdam (reference number W20_548#20.609). Formal approval of patients/parents was not obtained and all data were anonymized.

**Conflict of Interest Statement**

The authors have no conflicts of interest to declare.

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**Author Contributions**

Lisanne M. Vendrig performed data collection and analysis and drafted the first version of the manuscript. Christiaan F. Mooij was involved in interpretation of results, discussed previous versions of the manuscript, and agreed to the submission of the final version. Joep P.M. Derikx was involved in interpretation of results, discussed previous versions of the manuscript, and agreed to the submission of the final version. Johannes C. Fischer was involved in interpretation of results, discussed previous versions of the manuscript and agreed to the submission of the final version. A.S. Paul van Trotsenburg was involved in interpretation of results, discussed previous versions of the manuscript, and agreed to the submission of the final version. Nitash Zwaveling-Soonawala performed data collection and analysis, supervised the project, discussed previous versions of the manuscript, and agreed to the submission of the final version.

**Data Availability Statement**

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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