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Original Article

Preoperative prophylactic active vitamin D to streamline total thyroidectomy

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Abstract

Background: Hypocalcaemia is a common complication after total thyroidectomy (TT). Treatment consists of calcium and active vitamin D supplementation. Low levels of vitamin D before surgery have been shown to be a risk factor for postoperative hypocalcaemia, yet studies examining routine preoperative vitamin D supplementation have shown conflicting results. This retrospective cohort study aims to investigate the potential benefit of preoperative active vitamin D supplementation on hypocalcaemia and its symptoms after TT.

Methods: This study included patients undergoing TT at Uppsala University Hospital from January 2013 to December 2020, resulting in a total of 401 patients after exclusion. Routine preoperative alfacalcidol treatment was initiated for all TT patients in January 2017 resulting in two groups for comparison: one group (pre-January 2017) that was prescribed preoperative alfacalcidol and one that was not. Propensity score matching was used to reduce bias. The primary outcome was early postoperative hypocalcaemia (serum calcium, S-Ca less than 2.10 mmol/l); secondary outcomes were symptoms of hypocalcaemia and length of stay.

Results: After propensity score matching, there were 108 patients in each group. There were 2 cases with postoperative day one S-Ca less than 2.10 in the treated group and 10 cases in the non-treated group ($P < 0.001$). No patients in the treated group had a S-Ca below 2.00 mmol/l. Preoperative alfacalcidol was associated with higher mean serum calcium level day one (2.33 *versus* 2.27, $P = 0.022$), and reduced duration of hospital stay ($P < 0.001$). There was also a trend toward fewer symptoms of hypocalcaemia (18.9 per cent *versus* 30.5 per cent, $P = 0.099$).

Conclusions: Prophylactic preoperative alfacalcidol was associated with reduced biochemical hypocalcaemia and duration of hospital stay following TT. Also, with this protocol, it is suggested that routine day 1 postoperative S-Ca measurement is not required.

Introduction

Total thyroidectomy (TT), complete removal of the thyroid gland, is performed for various indications, such as benign thyroid disease and malignancies[1,2]. Complications of TT include hypocalcaemia, vocal cord paralysis, haematoma, and infection. The overall risk of complication is significantly higher after TT compared with unilateral thyroidectomy[1].

Postoperative hypocalcaemia is a commonly occurring complication of TT and one cause of delayed discharge[3,4]. It occurs as a result of low parathyroid hormone (PTH), which in turn is caused by removal of, or damage to, the parathyroid glands or their vascularization during surgery[4,5]. The incidence of the complication varies greatly across studies, as demonstrated in several review articles, a difference that can be partially attributed to the lack of clear definitions of postoperative hypocalcaemia and hypoparathyroidism[4–9]. A review article by Lorente-Poch and colleagues in 2014 proposed the following definitions: postoperative hypocalcaemia (serum calcium (S-Ca) less than 2 mmol/l within 24 h after TT), and protracted hypoparathyroidism (intact PTH concentration less than 13 pg/ml and/or need for calcium replacement at 4-6 weeks after surgery). Another study by Sitges-Serra and colleagues showed that as many as 50.2 per cent of patients had a S-Ca below 2 mmol/l 24 h after surgery, and a study from Mexico reported a rate of 32.8 per cent. A large UK study by Chadwick and colleagues found that 23.6 per cent of patients had a S-Ca level below 2.10 mmol/l at day 1 after surgery[10].

Treatment of hypoparathyroidism after surgery consists of oral calcium, in the form of calcium carbonate or calcium citrate, combined with the active metabolite of vitamin D. Severe hypocalcaemia, which can lead to seizures and spasms, is treated with intravenous calcium[11]. Other symptoms of hypocalcaemia include paraesthesia, cramps, laryngospasm, numbness, and weakness[11,12]. The goal of calcium therapy is to maintain S-Ca in the lower normal ranges[13]. Treatment with recombinant PTH is under investigation and seems to be both safe and effective; however, some concerns remain, including long term safety as well as cost[4].

To avoid postoperative hypocalcaemia altogether, preoperative treatment with calcium and active vitamin D is theoretically of interest. A study by Maxwell and colleagues found that preoperative calcium and calcitriol reduced the duration of hospital stay as well as total cost[14]. A randomized trial by Donahue and colleagues, however, could not show any statistically significant difference in duration of hospital stay, or hypocalcaemia with preoperative calcium and calcitriol supplementation[15]. These studies with a total of 65 and 82 patients respectively show conflicting results and highlight the need for larger studies to explore the potential benefit of active

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vitamin D treatment before surgery. The aim of this study was to examine the use of prophylactic preoperative active vitamin D (alfacalcidol) to prevent hypocalcaemia after TT.

Methods

This cohort study comprised patients who underwent TT between 1 January 2013 and 31 December 2020 at Uppsala University Hospital. All patients undergoing TT during this time interval were assessed for eligibility. Patients aged under 18 years, or with concurrent surgery for parathyroid disease, previous thyroid surgery, or other major surgery were excluded.

Preoperative alfacalcidol treatment was introduced as routine practice at Uppsala University Hospital on 1 January 2017 and two groups were formed based on surgery date, before or after 1 January 2017. As such, one group (all operated on between 1 January 2017 and 31 December 2020) were prescribed preoperative alfacalcidol 1 µg twice daily for three consecutive days leading up to the day of surgery, whereas the other group (all operated on before 1 Jan 2017) did not receive any preoperative active vitamin D supplementation. As it was not recorded whether any patients after 1 January 2017 chose not to take the prescribed preoperative alfacalcidol treatment, the outcome was analysed on an intention-to-treat basis.

Data regarding patients, diagnosis, surgery, inpatient care, and follow-up were prospectively gathered as part of the clinical routine. The data were collected and saved in a standardized way on paper forms or in Uppsala University Hospital's electronic records for both clinical use and with the purpose of subsequent registration of the data in SQRTPA (Scandinavian Quality Registry for Thyroid, Parathyroid and Adrenal Surgery) where 100 per cent of the patients in this study are included. The following parameters were registered: age, sex, indication for surgery, type of surgery, pre- and postoperative serum calcium levels, pre- and postoperative PTH levels, operating time (skin to skin), thyroid specimen weight, number of parathyroid glands identified and whether parathyroid reimplantation was performed or not, postoperative symptoms of hypocalcaemia, postoperative surgical site infection, rebleeding, recurrent laryngeal nerve (RLN) paralysis, and duration of hospital stay. The clinical routine during the whole study interval was that before surgery, all patients received both written and oral information about postoperative symptomatic hypocalcaemia and were told to call on the nurses if any of the following symptoms appeared: cramps, tingling, numbness, or twitching in hands, feet, and/or face. The nurses prospectively recorded the symptoms in the electronic charts and informed the responsible clinician.

The routine post-surgery follow-up after discharge included laryngoscopy, serum thyroid stimulating hormone (TSH), S-Ca, serum albumin, and a visit or telephone follow-up in the outpatient clinic at 4–6 weeks after surgery. Those with continuing use of calcium or active vitamin D after the 4–6-week check-up were followed until discontinuation of medication or for at least 6 months. Permanent hypoparathyroidism was defined as patients using calcium or active vitamin D medication at more than 6 months after surgery. Permanent

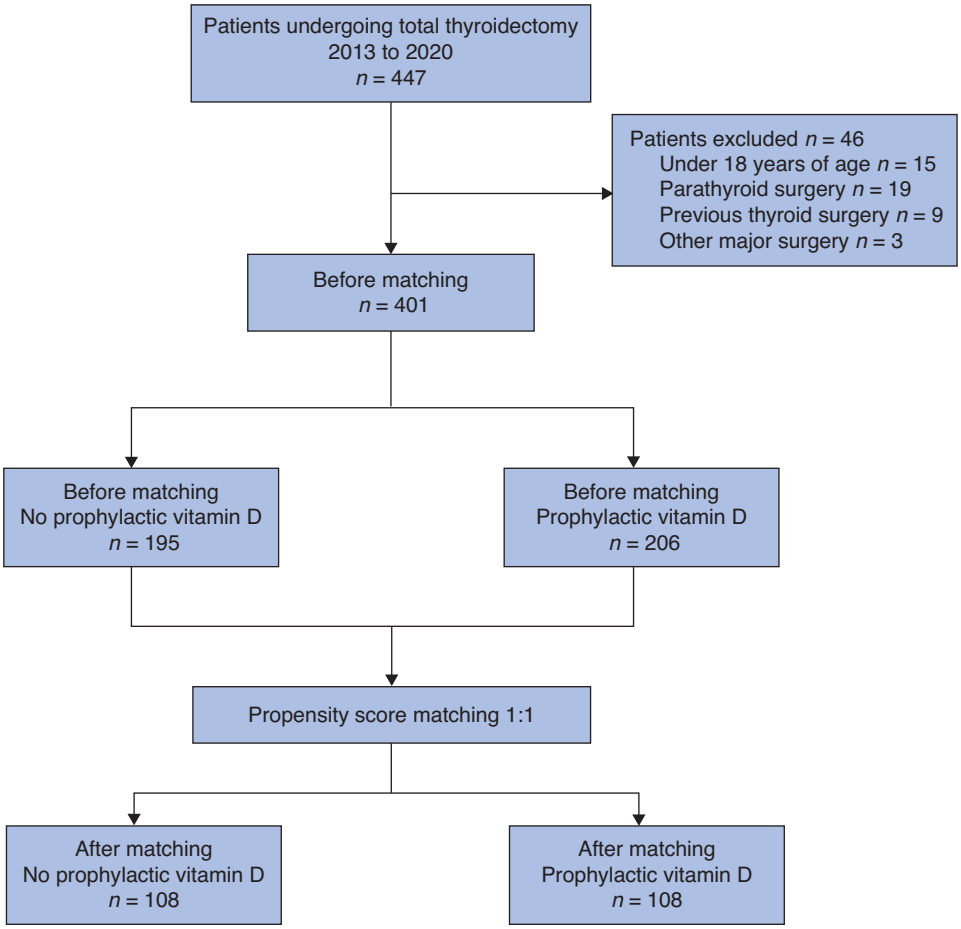

Fig. 1 Study population diagram

Table 1 Baseline characteristics of the entire study population

Patient variables	Total $n = 401$
Age at surgery, years, mean(s.d.)	49.0(17.1)
Sex	
Male	79 (19.7)
Female	322 (80.3)
Serum calcium before surgery, mmol/l*, mean(s.d.)	2.33(0.14)
No data, n	8
Indication for surgery	
Compression symptoms	85 (21.2)
Excluding malignancy	20 (5.0)
Malignancy	83 (20.7)
Thyrotoxicosis	211 (52.6)
Other	2 (0.5)
Type of operation	
TT only	318 (79.3)
TT with sternotomy	5 (1.2)
TT with central LND	35 (8.7)
TT with central and lateral LND	43 (10.7)
Number of parathyroid glands identified	
0	18 (4.5)
1	35 (8.7)
2	95 (23.7)
3	136 (33.9)
4	117 (29.2)
Parathyroid autotransplantation	
Yes	82 (20.4)
No	319 (79.6)
Operating time, min, mean(s.d.)	103.5(42.4)
No data, n	1
Thyroid weight, g, median (i.q.r.)	96.3 (20.0–103.0)
No data, n	174
Thyroid weight, g	
<25	76 (19.0)
25–75	77 (19.2)
>75	74 (18.5)
No data, n	174 (43.4)
Reoperation for bleeding	
Yes	8 (2.0)
No	393 (98.0)
Surgical site infection	
Yes	24 (6.0)
No	373 (93.0)
No data, n	4 (1.0)

Values are n (%) unless otherwise stated. *Reference range 2.15–2.50 mmol/l. TT, total thyroidectomy; LND, lymph node dissection; i.q.r., interquartile range.

RLN palsy was defined as those not objectively (by laryngoscopy) recovering from a temporary paresis within 6 months.

The primary outcome was early postoperative biochemical hypocalcaemia, defined in this study as S-Ca below 2.10 mmol/l on postoperative day 1 in similarity with Chadwick and colleagues[10]. Secondary outcomes included any difference in S-Ca between groups on postoperative day 1, symptoms of hypocalcaemia after surgery, and duration of hospital stay. Total S-Ca levels at day 1 and at follow-up were corrected for albumin. The formula used was corrected calcium = total calcium + 0.02 × (40 – albumin), where calcium is stated in mmol/l and albumin in g/l. This is a widely used formula, originally stated in the British Medical Journal in 1977[16]. Variables based on corrected calcium using this formula are marked in the tables below.

After surgery, a 1-h PTH was routinely measured and those with a PTH within the normal range (1.6–6.9 pmol/l) discontinued all supplementation directly. Patients with a PTH lower than 1.6 pmol/l were treated with oral calcium supplementation as needed. In those with a 1-h PTH lower than 1.0 pmol/l, alfacalcidol treatment (2 µg daily) was continued at least 1 week after surgery in conjunction with a fixed dose of oral calcium (1 g four times daily). If the patient was discharged with a fixed dose of calcium and/or active vitamin D due to a low 1-h PTH, S-Ca was routinely checked within 1–2 weeks.

Statistical analysis

Statistical analysis was performed with SPSS® version 27 (IBM, Armonk, New York, USA). A propensity score match was used to reduce bias when comparing the cohorts[17]. The propensity score was calculated based on the following characteristics: age, sex, S-Ca before surgery, indication for surgery, type of operation, number of parathyroid glands identified, parathyroid autotransplantation, operating time, and thyroid weight, resulting in a score between 0 and 1. A calliper/tolerance of 0.05 was used to match the groups in a 1:1 ratio using a nearest neighbour greedy matching algorithm. Standardized mean difference (SMD), also known as Cohen's *d*, was calculated to indicate differences between the compared groups. A SMD of 0 indicates that there is no difference between the groups[18].

Data were analysed and summarized in tables. To visualize differences between the groups, statistical tests for unmatched and matched groups were used as appropriate, specified in the respective tables. For unmatched data, a Student's *t* test, Mann–Whitney *U* test, chi-squared test, and Fisher's exact test were used. For matched data, Paired-samples *t* test, Wilcoxon sign test and McNemar–Bowker test were used, and cases where one or both patients in the pair had missing data were not included in the analysis. Significance was defined as $P < 0.050$ for all statistical tests.

Ethical considerations

The study was approved by the Swedish Ethical Review Authority on 24 February 2021, diary no. 2021-00402. After consultation with the Swedish Medical Products Agency (S-MPA) diary no. 4.1.2-2021-035034, S-MPA approval was deemed void due to the epidemiological nature of the study.

Results

A total of 447 patients were identified. Patients under 18 years of age at surgery (n = 15), concurrent surgery for parathyroid disease ($n = 19$), previous thyroid surgery ($n = 9$) and concurrent other major surgery ($n = 3$) were excluded (*Fig. 1*). The latter consisted of one case of adrenal gland surgery, one case of arterial surgery in the neck region, and one case of thrombectomy and vein surgery in the neck region.

After exclusion, 401 patients remained. Mean age at surgery was 49.0 years and 80.3 per cent were female. Mean total S-Ca before surgery was 2.33 (reference range 2.15–2.50). The most common indication for surgery was thyrotoxicosis, consisting of 52.6 per cent of the cohort. Type of operation was divided into four groups as illustrated in *Table 1*. Among the five that had a sternotomy, none underwent lymph node dissection (LND). Eighty-two cases of parathyroid autotransplantation were identified. Some 108 (26.9 per cent) patients received antibiotics before surgery.

Mean(s.d.) PTH 1 h after surgery was 2.3(1.9) pmol/l and mean(s.d.) S-Ca 1 day after surgery was 2.30(0.14) mmol/l. Furthermore, 21 patients developed S-Ca levels less than 2.1 mmol/l 1 day after surgery and out of these, 5 patients had S-Ca less than 2.0 mmol/l (5.2 per cent and 1.2 per cent

Table 2 Baseline data in groups before and after propensity score matching

Patient variables	Before matching				After matching		
	Preoperative vitamin D *n* = 206	No preoperative vitamin D *n* = 195	*P*	SMD	Preoperative vitamin D *n* = 108	No preoperative vitamin D *n* = 108	SMD
Age at surgery, years, mean(s.d.)	51.2(17.8)	46.5(15.9)	0.006*	27.9	49.0(17.7)	43.6(16.0)	31.8
Sex							
Male	48 (23.3)	31 (15.9)	0.062†	18.7	20 (18.5)	20 (18.5)	0
Female	158 (76.7)	164 (84.1)			88 (81.5)	88 (81.5)	
Serum calcium before surgery, mmol/l¶, mean(s.d.)	2.34(0.15)	2.31(0.13)	0.035*	21.4	2.34(0.18)	2.33 (0.15)	5.9
No data, n	*n* = 2	*n* = 6					
Indication for surgery							
Compression symptoms	47 (22.8)	38 (19.5)	0.405§	8.1	22 (20.4)	21 (19.4)	2.5
Excluding malignancy	11 (5.3)	9 (4.6)		3.2	2 (1.9)	4 (3.7)	−10.9
Malignancy	48 (23.3)	35 (17.9)		13.4	22 (20.4)	17 (15.7)	12.2
Thyrotoxicosis	99 (48.1)	112 (57.4)		−18.7	62 (57.4)	66 (61.1)	−7.5
Other	1 (0.5)	1 (0.5)		0	0 (0)	0 (0)	0
Type of operation							
TT only	164 (79.6)	154 (79.0)	0.989§	1.5	85 (78.7)	90 (83.3)	−11.7
TT with sternotomy	2 (1.0)	3 (1.5)		−4.5	2 (1.9)	2 (1.9)	0
TT with central LND	18 (8.7)	17 (8.7)		0	10 (9.3)	7 (6.5)	10.4
TT with central and lateral LND	22 (10.7)	21 (10.8)		−0.3	11 (10.2)	9 (8.3)	6.6
Number of parathyroid glands identified							
0	14 (6.8)	4 (2.1)	0.003†	22.9	2 (1.9)	3 (2.8)	−5.9
1	24 (11.7)	11 (5.6)		21.8	8 (7.4)	7 (6.5)	3.5
2	52 (25.2)	43 (22.1)		7.3	33 (30.6)	31 (28.7)	4.1
3	70 (34.0)	66 (33.8)		0.4	35 (32.4)	39 (36.1)	−7.8
4	46 (22.3)	71 (36.4)		−31.3	30 (27.8)	28 (25.9)	4.2
Parathyroid autotransplantation							
Yes	38 (18.4)	44 (22.6)	0.307†	−10.4	19 (17.6)	20 (18.5)	−2.3
No	168 (81.6)	151 (77.4)			89 (82.4)	88 (81.5)	
Operating time, min, mean(s.d.)							
No data, n	92.7(37.9) *n* = 0	115.0(43.9) *n* = 1	<0.001*	−54.3	101.6(40.3)	98.9(31.4)	7.2
Thyroid weight, g							
<25	37 (18.0)	39 (20.0)	<0.001†	−5.1	26 (24.1)	21 (19.4)	11.4
25–75	47 (22.8)	30 (15.4)		18.9	22 (20.4)	21 (19.4)	2.5
>75	52 (25.2)	22 (11.3)		36.5	15 (13.9)	17 (15.7)	−5.1
No data, n	70 (34.0)	104 (53.3)		−39.7	45 (41.7)	49 (45.4)	−7.5

Values are number (per cent) unless otherwise indicated. TT, total thyroidectomy; LND, lymph node dissection. *Student's *t* test, two-tailed. †Chi-squared test. §Fisher's exact test. ¶Reference range 2.15–2.50 mmol/l.

respectively). Mean (i.q.r.) duration of hospital stay was 1 (1–2) day after surgery. At follow-up, mean(s.d.) S-Ca was 2.38(0.14) mmol/l. Out of the total 401 patients, 85 patients reported hypocalcaemic symptoms at follow-up (21.2 per cent).

After surgery, 24 patients had a surgical site infection (6.0 per cent) and eight (2.0 per cent) underwent reoperation for bleeding. A total of 29 patients (3.6 per cent of nerves at risk) had postoperative RLN palsy. Of these, six had RLN palsy before surgery and three underwent intentional resection of the RLN. Some 12 of these 29 patients recovered function of the RLN and for 3 patients there was no follow-up. Thus, excluding the intentional resections, eight patients suffered a permanent RLN palsy by the study definition (2.0 per cent of nerves at risk).

At the time of discharge, 35.9 per cent (144 patients), had fixed calcium and/or alfacalcidol medication. After 6 months, 27 patients, accounting for 6.7 per cent, remained on calcium and/or alfacalcidol treatment for postoperative hypoparathyroidism.

Treatment groups

Of a total of 401 patients, 206 were operated on after 1 January 2017 and had routinely been prescribed preoperative alfacalcidol supplementation, whereas the 195 that were operated on between 1 Jan 2013 and 31 Dec 2016 had not.

Baseline data before propensity score matching

The two groups were, before matching, found to be significantly different in mean age at surgery (51.2 *versus* 46.5, $P = 0.006$) and total S-Ca before surgery (2.34 mmol/l *versus* 2.31 mmol/l, $P = 0.035$). There was also a significant difference in number of parathyroid glands identified, mean operating time (skin to skin), and thyroid specimen weight (*Table 2*) Additionally, there was a significant difference between the groups regarding preoperative antibiotics; 37.4 per cent of patients in the preoperative alfacalcidol treatment group received antibiotics compared with 15.9 per cent in the non-alfacalcidol group ($P < 0.001$).

Postoperative outcome between groups before matching

Postoperative data between the two groups were compared. PTH 1 h after surgery was found to be lower in the group that received preoperative alfacalcidol, at 2.0 pmol/l, compared with 2.6 pmol/l in the group that did not receive alfacalcidol ($P = 0.002$) (*Table 3*). However, the total albumin-corrected S-Ca was found to be significantly higher in the treatment group (2.33 *versus* 2.27, $P < 0.001$). Regarding symptoms for hypocalcaemia at any point after surgery, fewer patients in the preoperative

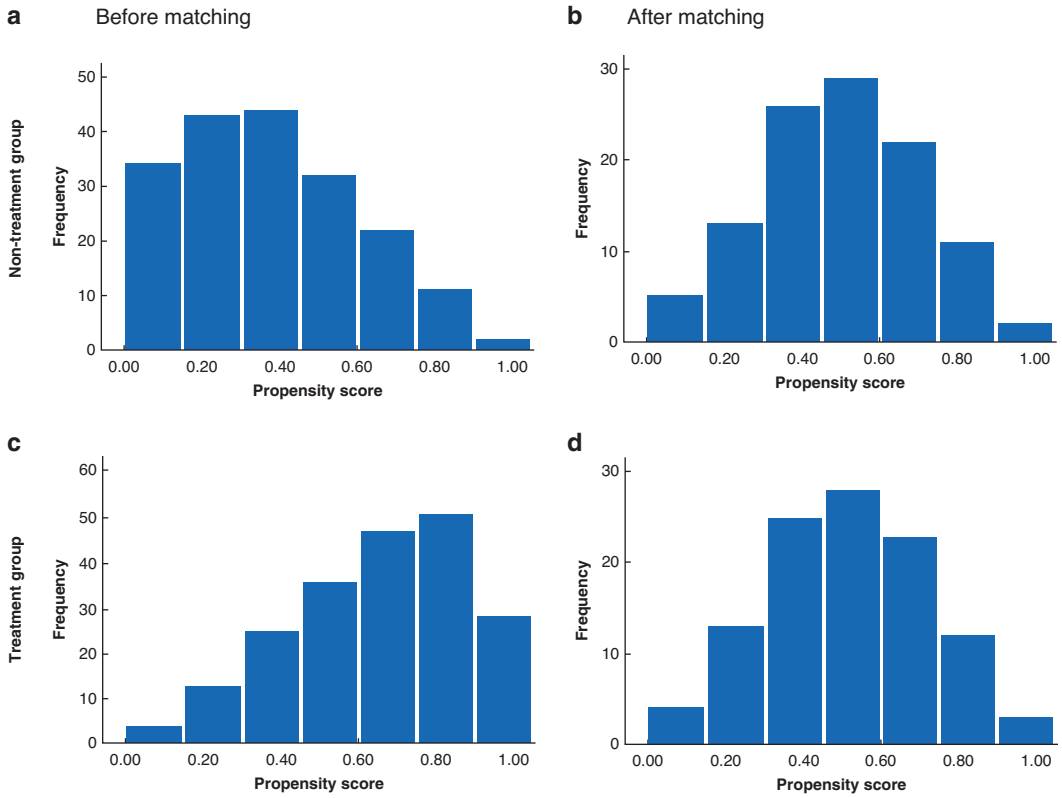

Fig. 2 Propensity scores before and after matching
a Before matching, non-treatment group. **b** After matching, non-treatment group. **c** Before matching, treatment group. **d** After matching, treatment group.

Table 3 Results before and after propensity score matching

Patient variables	Before matching			After matching		
	Preoperative vitamin D $n=206$	No preoperative vitamin D $n=195$	P	Preoperative vitamin D $n=108$	No preoperative vitamin D $n=108$	P
PTH 1 h after surgery, pmol/l‡‡, mean(s.d.)	2.0(1.4)	2.6(2.3)	0.002*	1.8(1.2)	2.5(2.2)	0.011**
PTH 1 h after surgery, pmol/l‡‡						
<1.6	94 (46.8)	79 (41.4)	0.283†	51 (51.0)	45 (45.0)	0.480¶
≥1.6	107 (53.2)	112 (58.6)		49 (49.0)	55 (55.0)	
Serum calcium day 1 after surgery, mmol/l††, mean(s.d.)	2.33(0.14)	2.27(0.14)	<0.001*	2.32(0.15)	2.27(0.15)	0.022**
Serum calcium day 1 after surgery, mmol/l††						
<2.00	0 (0.0)	5 (2.6)	0.061‡	0 (0.0)	4 (3.8)	0.083¶
≥2.00	188(100)	184 (97.4)		97 (100.0)	102 (96.2)	
Serum calcium day 1 after surgery, mmol/l††						
<2.10	5 (2.6)	16 (8.2)	0.023[c]	2 (2.1)	10 (9.4)	<0.001¶
≥2.10	183 (88.8)	173 (88.7)		95 (97.9)	96 (90.6)	
Duration of hospital stay, days, median (i.q.r.)	1 (1–1)	1 (1–2)	<0.001§	1 (1–1)	1 (1–2)	<0.001#
Serum calcium at 4–6-week follow-up, mmol/l, mean(s.d.)	2.38(0.13)	2.38(0.16)	0.950*	2.37(0.13)	2.37(0.12)	0.514**
Symptoms of hypocalcaemia from surgery to follow-up						
Yes	34 (17.8)	51 (27.7)	0.022†	18 (18.9)	29 (30.5)	0.099¶
No	157 (82.2)	133 (72.3)		77 (81.1)	66 (69.5)	
Permanent hypoparathyroidism						
Yes	12 (6.2)	15 (8.2)	0.450†	6	6	1¶
No	183 (93.8)	169 (91.8)		92	92	
Reoperation for bleeding						
Yes	3 (1.5)	5 (2.6)	0.428‡	2 (1.9)	3 (2.8)	1¶
No	203 (98.5)	190 (97.4)		106 (98.1)	105 (97.2)	
Surgical site infection						
Yes	15 (7.3)	9 (4.7)	0.303†	6	4	0.754¶
No	190 (92.7)	183 (95.3)		100	102	

Values are number (per cent) unless otherwise stated. Missing data not analysed. *Student's *t* test, two-tailed. †Chi-squared test. ‡Fishers exact test. §Mann–Whitney *U* test. ¶McNemar–Bowker test, two-sided. #Wilcoxon signed rank test. **Paired samples *t* test. ††Reference range 2.15–2.50 mmol/l. ‡‡Reference range 1.6–6.9 pmol/l. PTH, parathyroid hormone; i.q.r., interquartile range.

treated group experienced such symptoms (17.8 per cent *versus* 27.7 per cent, $P = 0.022$) (*Table 3*). Out of all patients ($n = 85$) reporting symptoms of hypocalcaemia, 33.3 per cent (17 of 51) in the non-treated group and 11.8 per cent (4 of 34) in the treated group had a S-Ca level below 2.15 mmol/l on postoperative day 1 or at follow-up. Two patients were readmitted due to hypocalcaemia in the non-treated group, whereas there were no readmissions within 30 days in the pre-treatment group. The duration of hospital of stay was shorter in the treated group (total days in hospital 30 days after surgery $n = 262$), with median (i.q.r.) being 1 (1–1) day. In the non-treated group, the total number of days in hospital 30 days after surgery was 419, median (i.q.r.) also 1 (1–2; $P < 0.001$ between groups) day.

Baseline data after propensity score matching

After propensity score matching 1:1, with a 0.05 tolerance, 108 patients were in each group. The goal of the matching was to reduce bias in baseline variables to better compare outcomes. The SMD values between the groups before and after matching are indicated in *Table 2* and the variation in propensity scores between the groups before and after matching are shown in *Fig. 2*, both in general indicating more homogenous groups after the match.

Postoperative outcome between groups after propensity score matching

Finally, outcome data after matching was analysed in paired samples (*Table 3*). There were 2 cases with postoperative day 1 S-Ca less than 2.10 in the treated group and 10 cases in the non-treated group ($P < 0.001$). Mean S-Ca day 1 after surgery was also significantly lower in the group that did not receive preoperative alfacalcidol (2.32 *versus* 2.27, $P = 0.022$). There were no patients with a S-Ca below 2.00 mmol/l in the treated group and four in the non-treated group; however, this did not achieve statistical significance. Regarding symptoms of hypocalcaemia at any point after surgery, there was a trend towards fewer cases that experienced symptoms in the alfacalcidol-treated group although this did not reach statistical significance ($P = 0.099$; *Table 3*). Moreover, there were fewer total postoperative in-hospital days in the treated matched group ($n = 142$) than in the non-treated group ($n = 215$), median (i.q.r.) being 1 (1–1) day in the treated, and 1 (1–2) day in the non-treated group ($P < 0.001$). Thus, in total 73 hospital bed days were saved in the treated group, making the rate 67.6 hospital bed days saved per 100 TTs.

Discussion

This study attempted to examine the effect of preoperative prophylactic active vitamin D on biochemical hypocalcaemia following TT. In the pre-treated group, fewer patients had a S-Ca below 2.10 mmol/l and mean S-Ca on postoperative day 1 was higher. There was also a trend towards fewer reported symptoms of hypocalcaemia in the pre-treated group. As previously discussed, studies examining the effect of preoperative vitamin D have shown conflicting results. Maxwell and colleagues showed some benefits after treatment with calcium (1000–1500 mg three times daily) and calcitriol (0.25–0.5 µg twice daily)[14]. Donahue and colleagues found no significant advantages of 1500 mg calcium and 0.25 µg calcitriol before surgery[15]. However, the latter study by Donahue and colleagues was, according to their own assessment, underpowered. Some differences in the pre-treatment protocols are also noted. For example, preoperative calcium was not used in the present study. However, alfacalcidol was prescribed instead of calcitriol as in the above-mentioned studies and a higher dose was used (2 µg daily). Although similar in time of onset at 1–3 days, alfacalcidol has a longer half-life and this may have impacted the outcome[13]. Maxwell and colleagues reported a much higher number of patients with a calcium level below 8.0 mg/dl (equals 2.0 mmol/l) at 24 h, 31 per cent for the non-treated group and 15 per cent in the treated group[14]. The present findings were substantially lower at 2.6 per cent and 0 per cent respectively. Another study on hypocalcaemia based on the UK Registry of Endocrine and Thyroid Surgeons found that 23.6 per cent of patients have a S-Ca below 2.10 mmol/l on day 1[10]. As shown in *Table 3*, there were 8.2 and 2.4 per cent of patients in this study, in the non-treated and treated groups respectively, with serum calcium levels below 2.10 mmol/l after correction for albumin. This is notably lower than the findings in the aforementioned study, in both groups, and may be explained by differences in postoperative supplementation routine or possibly in different rates of parathyroid preservation. In the clinical routine in this study, postoperative calcium supplementation and/or active vitamin D was prescribed after surgery, provided that the level of PTH was low at 1 h after surgery, perhaps resulting in higher calcium levels on day 1 than previous studies. Furthermore, postoperative S-Ca levels were corrected for albumin. As a result, patients with false biochemical hypocalcaemia, on account of hypoalbuminaemia, were not included in the numbers.

There was a significant difference in duration of hospital stay, with a longer stay in the group that did not receive preoperative supplementation (*Table 3*). In total, 67.6 fewer hospital bed days per 100 TTs were used during the latter time interval with alfacalcidol treatment; however, seeing as the groups did not undergo surgery simultaneously, but instead before or after 1 January 2017, it is possible that this difference may be explained by intangible changes in practice over time. Of note, there were no registered readmissions within 30 days of surgery after pre-treatment with alfacalcidol and this may thus contribute to the streamlining of patient care after TT. Even though there is a trend towards ambulatory or 23-h surgery in some centres, most TTs are still performed as inpatient procedures, as shown by Maniakas and colleagues in their study from 2017 investigating practices among thyroid surgeons in 52 different countries[16]. Biochemical hypocalcaemia, or apprehension of subsequent symptomatic hypocalcaemia, is a possible cause of protracted stay after TT and, as such, the protocol adopted in this study may facilitate 23-h thyroidectomy for a larger proportion of patients.

Regarding those patients complaining of symptoms of hypocalcaemia, only 33.3 per cent of patients in the non-treated group and only 11.8 per cent of patients in the treated group had a measured S-Ca level below 2.15 at day 1 or at follow-up. Although these numbers suggest relatively few of the patients reporting symptoms had biochemical hypocalcaemia, some patients experienced symptoms before day 1 after surgery, or between hospital discharge and follow-up. This suggests that patients with symptoms arising from actual low S-Ca may be quite low; however, these patients may also have had normal spot S-Ca levels due to ongoing calcium and active vitamin D supplementation, and that the calcium level may fluctuate during the day in such circumstances. Either way, this makes

analysing symptoms of hypocalcaemia in this cohort rather difficult. Moreover, the cohort may have been underpowered to detect a smaller but still clinically relevant difference regarding symptomatic hypocalcaemia.

Many of the patients in this study probably had no use for the pre-treatment, as they had normal PTH after surgery and no biochemical hypocalcaemia would have ensued, and therefore it was important to analyse any adverse reactions as well as the cost of pre-treatment of all patients undergoing TT. No adverse reaction was seen nor was any hypercalcaemia measured in any of the pre-treated patients. Moreover, the cost of alfacalcidol in Sweden is 0.10 Euro per pill, making the cost for pre-treatment at 0.60 Euro per patient. In relation to the cost in Sweden of one saved hospital bed day (700–800 Euro/24 h) or one S-Ca blood test (2.6 Euro), this is indeed negligible. After the completion of this study, prophylactic vitamin D treatment has remained as the clinical routine.

Permanent hypoparathyroidism is often defined as the need for treatment with calcium or vitamin D 12 months after surgery. Previous Swedish studies have shown rates from 5.0 to 12.5 per cent depending on definition, both excluding malignancies[17,18]. Although examining the rates of permanent hypoparathyroidism was not the main goal of this study, numbers indicate a rate of 6.7 per cent after 6 months, which is in line with previous findings.

This study has a number of strengths. First, a relatively large number of patients was included. Also, thanks to the electronic patient record system in the study hospital, it was possible to identify all TTs undertaken during the study interval and to assess for eligibility. Compared with previous studies on preoperative vitamin D supplementation, this study included more patients, before as well as after matching. The two previous studies on vitamin D discussed had 65 and 82 patients, compared with the present study of 216 patients after matching[14,15]. Finally, with use of propensity score matching, it was possible to compare non-treated and treated groups in a way that reduced bias[19,20]. The tolerance of 0.05 was found to be a reasonable trade-off between the number of patients remaining after matching and the maximum baseline difference between patients. Graphs on propensity score frequencies after matching and SMD regarding baseline characteristics were reasonably similar.

There were some limitations. Given that the compared groups underwent surgery during different time periods, some outcome data, such as duration of hospital stay, can be difficult to assess. Therefore, further studies, preferably in the form of a randomized clinical trial, are needed to confirm that pre-treatment vitamin D leads to a reduced duration of stay. The results of this study can provide a solid foundation for the design of a power calculation. Also, some follow-up data were lacking, due to referrals of patients back to their home clinics at other hospitals. It was also difficult to a firmly draw conclusions on prophylactic alfacalcidol and postoperative hypocalcaemia when defined as a serum calcium below 2.00 mmol/l, according to Lorente-Poch and colleagues, given the small number of patients with such low levels[8].

In this cohort study based on prospectively collected data, the benefit of preoperative alfacalcidol supplementation before TT was examined with propensity score matching. One microgram of alfacalcidol twice daily for 3 days before surgery was significantly associated with a reduced proportion of patients experiencing hypocalcaemia, defined as a calcium level below 2.10 mmol/l. Also, mean S-Ca level on day 1 was higher and there was a trend towards fewer symptoms of hypocalcaemia in the pre-treated group. Preoperative alfacalcidol supplementation may be beneficial in reducing biochemical hypocalcaemia following TT; it is safe, the cost is negligible, and it may reduce duration of hospital stay. As no patients had a S-Ca below 2.00 mmol/l on postoperative day 1 with this protocol, and no patients were readmitted to the hospital, it is also suggested that routine day 1 postoperative calcium measurement is not required.

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Data availability

The data that support the findings of this study are available on request from the corresponding author (M.A.). The data are not publicly available due to ethical regulations and restrictions (such as information that could compromise the privacy of research participants).

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