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Routine low-dose calcium supplementation after thyroidectomy does not reduce the rate of symptomatic hypocalcemia: a prospective randomized trial

Jun Woo Lee[1,2], Jong-Kyu Kim[1,2], Hyungju Kwon[1,2], Woosung Lim[1,2], Byung-In Moon[1,2], Nam Sun Paik[1,2]

[1]Department of Surgery, Ewha Womans University Medical Center, Seoul, Korea
[2]Breast and Thyroid Cancer Center, Ewha Womans University Cancer Hospital, Seoul, Korea

Purpose: Routine supplementation of high-dose calcium significantly decreased the risk of postoperative symptomatic hypocalcemia after thyroidectomy. However, there is an ongoing debate about whether the same results can be achieved with low-dose calcium supplementation.
Methods: Patients (n = 138) who underwent total thyroidectomy for thyroid cancer were 1:1 randomly assigned to receive oral supplements of 1,500 mg/day elemental calcium and 1,000 IU/day cholecalciferol for 2 weeks or no supplementation. Primary objective was to compare the incidence of symptomatic hypocalcemia for 3 days after total thyroidectomy. Secondary objective was to find the predictors for postoperative hypocalcemia in patients with thyroid cancer.
Results: Sixty-five patients in the calcium group and 69 patients in the control group were finally analyzed. The incidence of symptomatic hypocalcemia showed no difference between the calcium and control group (32.3% *vs.* 21.7%, P = 0.168). The total dosage of intravenous calcium (593.4 ± 267.1 mg *vs.* 731.6 ± 622.7 mg, P = 0.430) administered to patients with symptomatic hypocalcemia was also comparable between groups. In a multivariate analysis, parathyroid hormone level of 13 pg/mL at postoperative day 1 was only predictive for symptomatic hypocalcemia, and its incidence was 20.9 times (95% confidence interval, 6.8–64.5) higher in patients with parathyroid hormone <13 pg/mL. Other factors did not predict the development of hypocalcemia, including clinicopathological features and routine supplementation of low-dose calcium.
Conclusion: Routine low-dose calcium supplementation did not reduce the risk of postoperative hypocalcemia. Patients who may benefit from calcium supplementation should be carefully selected.
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Key Words: Calcium, Thyroidectomy, Hypocalcemia, Hypoparathyroidism, Thyroid neoplasms

INTRODUCTION

Thyroid cancer is now the most common cancer in Korea, and its incidence has increased over the past 20 years [1]. The age-standardized incidence rate per 100,000 men and women has increased from 2.1 and 10.4 in 1999 to 24.0 and 96.6 in 2013, respectively [1]. Because surgery is the mainstay of treatment for thyroid cancer, there is a growing interest in reducing postoperative complications [2]. Postoperative transient hypocalcemia is the most frequent complication after thyroidectomy, with a reported incidence of 1.6%–50% [3-5]. The causes of postoperative hypocalcemia include unintentional injury to the parathyroid glands, inexperience of the surgeon, retrosternal goiter, hyperthyroidism, and extent of neck dissection [6]. Postoperative hypocalcemia is associated with longer hospital stay, the need for extra blood tests, and

increased medical costs [7,8].

Several studies investigated preventive measures to reduce postoperative hypocalcemia, including postoperative supplementation of calcium, vitamin D, and/or thiazide diuretics [9]. Of these measures, routine calcium and vitamin D supplementation has been most widely used, especially in outpatient thyroidectomy patients [10]. However, whether routine calcium and vitamin D supplementation can decrease the risk of symptomatic hypocalcemia after thyroidectomy remains undetermined. Some studies reported that routine calcium and/or vitamin D supplementation was effective in preventing postoperative symptomatic and biochemical hypocalcemia [11-13], whereas other studies reported no benefits [14,15]. These inconsistent results were probably due to the different doses of supplemented calcium; a higher dose of elemental calcium supplement (2,000–3,000 mg/day) usually resulted in a reduced risk of hypocalcemia, whereas a lower dose (600 mg/day) showed no effect.

Although calcium supplementation in higher doses significantly decreased postoperative hypocalcemia, higher doses can have adverse effects including nausea, reduced appetite, constipation, and risk of hypercalcemia [16]. Delbridge [17] indicated that 12% of patients receiving routine calcium supplements required readmission due to hypercalcemia. Additional laboratory assessments to prevent hypercalcemia can be burdensome and incur extra medical costs. High calcium doses or hypercalcemia may further suppress normal parathyroid hormone (PTH) secretion and prolong suppression of the parathyroid glands [14]. Stimulated by these observations, we investigated the use of low-dose calcium supplementation for preventing postoperative hypocalcemia.

We hypothesized that low-dose calcium (1,500 mg/day elemental calcium) would reduce the rate of symptomatic hypocalcemia in patients with thyroid cancer after total thyroidectomy. The present study investigated the effect of routine calcium supplementation and aimed to find the predictors for postoperative hypocalcemia in patients with thyroid cancer.

METHODS

Patient selection

Eligible patients had a diagnosis of papillary thyroid carcinoma and underwent bilateral total thyroidectomy. Patients with suspicious lymph node on ultrasound underwent therapeutic central lymph node (LN) dissection. Patients were 20 years of age or older were enrolled. Eligibility also included acceptable renal and hepatic function and adequate thyroid function. Patients underwent modified radical neck dissection or combined resection of adjacent organ including trachea were excluded. Patients were also excluded if parathyroid adenoma

was found during total thyroidectomy; history of neck surgery or radiation therapy; or prior use of calcium and/or vitamin D.

Study design

This study was a prospective randomized nonblinded controlled trial conducted in Korea (ClinicalTirals.gov identifier: NCT03484416). The protocol was approved by the Institutional Review Board of Ewha Womans University Mokdong Hospital (approval number: 2017-09-055), and written informed consent was obtained from each participant. Enrolled participants were randomly assigned in a 1:1 ratio to receive calcium and vitamin D (routine calcium group) or no supplementation (control group). Random assignment was performed after completion of bilateral total thyroidectomy, using a computer-generated permuted blocks (size 4).

Study end points

The primary endpoint of the study was to investigate the effect of routine calcium and vitamin D supplementation, as assessed by the incidence of symptomatic hypocalcemia for 3 days after total thyroidectomy. Symptomatic hypocalcemia was defined as an ionized calcium concentration below 4.6 mg/dL (normal range, 4.6–5.4 mg/dL) associated with hypocalcemic symptoms [18]. Hypocalcemic symptoms were defined as perioral numbness, tingling sense or paresthesia at extermities, or muscle cramp and assessed by single endocrine surgeon (HK). Secondary objective was to find the predictors for postoperative hypocalcemia in patients with thyroid cancer.

Procedures

Patients in the routine calcium group received oral supplements of 1,500 mg/day elemental calcium and 1,000 IU/day cholecalciferol for 2 weeks, beginning on the first postoperative day (POD) to the 14th POD, whereas patients in the control group received no supplementation. Serum concentrations of PTH and ionized calcium were measured 1 and 14 days postoperatively. If symptomatic hypocalcemia developed, patients in both groups received 2.0 g of intravenous calcium, followed by oral supplementation with 3,000–4,000 mg/day elemental calcium and 1,000–2,000 IU/day cholecalciferol up to the 14th POD. If hypocalcemic symptoms were persistent or worsening 2 hours after intravenous calcium administration, patients were administered another intravenous calcium supplementation.

All patients were followed at intervals of 2 weeks, 3 months, and then 6 months. Follow-up tests included clinical evaluation for hypocalcemia, and a thyroid function test. Hypocalcemia was considered permanent in patients who required calcium supplementation for longer than 6 months after thyroidectomy.

Statistical analysis

The benchmark data for power calculation was adapted from the meta-analysis by Alhefdhi et al. [19], which demonstrated that the incidence of postoperative hypocalcemia were 6.8% versus 25.9% for calcium and vitamin D versus no intervention. Assuming the risk of symptomatic hypocalcemia in the routine calcium group equal to 6.8% and in the control group equal to 25.9%, with a 2-tailed alpha of 5% and 80% power, 116 patients were required for 1:1 randomization without continuity correction. Considering 20% dropout rate, we planned to enroll 138 patients.

Statistical tests were performed using IBM SPSS Statistics ver. 22.0 (IBM Co., Armonk, NY, USA). Continuous variables were compared using Student t-tests and Mann-Whitney U-tests, and categorical variables were compared using chi-square tests. Bivariate logistic regression model was used to evaluate the relationship between PTH level and the development of hypocalcemia. Recursive partitioning and regression trees (RPART) classification algorithm in R 3.4.0 (R Development Core Team, Vienna, Austria) was used to identify the optimal cutoff value for PTH level. Two-sided P-values ≤0.05 were considered statistically significant.

RESULTS

From March 2016 to May 2017, 142 patients with thyroid cancer underwent total thyroidectomy in our institution (Fig. 1). Three patients refused the study and 1 patient with concomitant parathyroid adenoma were excluded. The remaining 138 patients were randomly 1:1 assigned after total thyroidectomy, whether to receive or not to receive routine calcium supplementation. After randomization, 4 patients in the calcium group with incomplete perioperative data (n = 2), consent withdrawal (n = 1), or lost to follow-up (n = 1) were further excluded from analysis. Sixty-five patients in the calcium group and 69 patients in the control group were included for the final analysis.

Effect of low-dose calcium and vitamin D supplementation

The clinicopathologic characteristics of the 134 included patients are shown in Table 1. The calcium group and control group were well-matched for sex, age, the number of inadvertently resected or autotransplanted parathyroid glands, and American Joint Committee on Cancer TNM stage. The incidence of symptomatic hypocalcemia was higher in the calcium group than in the control group (32.3% vs. 21.7%, P = 0.168), although the difference was not statistically significant. On POD 1, serum concentrations of ionized calcium (4.2 ± 0.4 mg/dL vs. 4.3 ± 0.3 mg/dL, P = 0.100) and PTH (20.2 ± 11.6 pg/mL vs. 21.6 ± 13.1 pg/mL, P = 0.524) were comparable in the calcium and control groups. The increase in PTH level from POD 1 to 14 was also similar in both groups (6.8 ± 10.3 pg/mL vs. 8.6 ± 14.2 pg/mL, P = 0.410). The risk of permanent hypocalcemia was comparable between the groups (0.0% vs. 1.4%, P = 0.330).

Twenty-one patients (32.3%) in the calcium group and 15 (21.7%) in the control group experienced symptomatic hypocalcemia. The total dosage of intravenous calcium (593.4 ± 267.1 mg vs. 731.6 ± 622.7 mg, P = 0.430) needed in patients with symptomatic hypocalcemia were comparable between the 2 groups. The majority of patients experienced symptomatic hypocalcemia within 24 hours (71.4% vs. 66.7%, P = 0.760) in both groups. Only 1 patient in the control group developed hypocalcemic symptom after 48 hours. No patients experienced hypercalcemia in either group.

Predictors for postoperative hypocalcemia

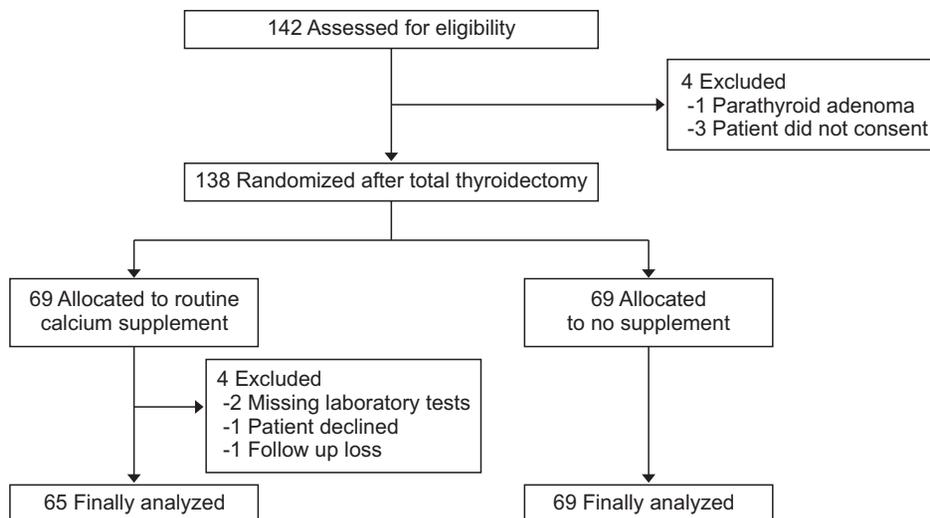Using the RPART classification algorithm, POD 1 PTH level

Fig. 1. Consolidated standards of reporting clinical trials flow chart.

Table 1. Clinicopathological features of the routine calcium and control groups

Characteristic	Calcium supplement group (n = 65)	Control group (n = 69)	P-value
Female sex	54 (83.1)	63 (91.3)	0.153
Age (yr)	49.1 ± 10.9	51.2 ± 12.8	0.314
Combined central LN dissection	50 (76.9)	44 (63.8)	0.096
Inadvertent PTG excision			0.625
0 PTG	58 (89.2)	60 (87.0)	
1 PTG	5 (7.7)	8 (11.6)	
2 PTGs	2 (3.1)	1 (1.4)	
PTG autotransplantation	2 (3.1)	2 (2.9)	0.952
Tumor characteristics			
Tumor size (cm)	1.3 ± 1.1	1.1 ± 0.6	0.401
Minimal extrathyroidal extension	42 (64.6)	41 (59.4)	0.536
LN metastasis	25 (38.5)	28 (40.6)	0.802
AJCC 7th classification			0.094
T1N0	6 (9.2)	15 (21.7)	
T1N1a	7 (10.8)	10 (14.5)	
T1Nx	8 (12.3)	3 (4.3)	
T2N1a	1 (1.5)	0 (0)	
T3N0	17 (26.2)	20 (29.0)	
T3N1a	17 (26.2)	18 (26.1)	
T3Nx	9 (13.8)	3 (4.3)	
Laboratory findings			
Preoperative vitamin D (pg/mL)	30.2 ± 10.1	29.7 ± 10.3	0.580
Preoperative PTH (pg/mL)	20.2 ± 11.6	21.6 ± 13.1	0.524
POD 1 PTH (pg/mL)	20.2 ± 11.6	21.6 ± 13.1	0.524
POD 1 ionized calcium (mg/dL)	4.2 ± 0.4	4.3 ± 0.3	0.100
POD 14 PTH (pg/mL)	27.0 ± 12.5	31.6 ± 13.0	0.039
POD 14 ionized calcium (mg/dL)	4.8 ± 0.4	4.8 ± 0.4	0.461
Increase in PTH from POD 1 to 14 (pg/mL)	6.8 ± 10.3	8.6 ± 14.2	0.093
Symptomatic hypocalcemia	21 (32.3)	15 (21.7)	0.168
IV calcium dosage (mg)	593.4 ± 267.1	731.6 ± 622.7	0.430
Occurred within 24 hr	15/21 (71.4)	10/15 (66.7)	0.760
Permanent hypocalcemia	0 (0)	1 (1.4)	0.330

Values are presented as number (%) or mean ± standard deviation.
LN, lymph node; PTG, parathyroid gland; AJCC, American Joint Committee on Cancer; POD, postoperative day; PTH, parathyroid hormone; IV, intravenous.

of 13 pg/mL was determined as the cutoff value for developing symptomatic hypocalcemia [20]. Forty-one patients (30.6%) showed POD 1 PTH < 13 pg/mL, whereas POD 1 PTH level was greater than or equal to 13 in 93 patients (Table 2). Except for age (55.0 ± 10.3 years *vs.* 48.0 ± 12.0 years, P = 0.002) and menopause status (68.6% *vs.* 43.9%, P = 0.015), the clinicopathologic features were comparable between the low and high PTH groups. The low PTH group showed higher risk of symptomatic hypocalcemia than the high PTH group (61.0% *vs.* 11.8%, P < 0.001). All patients in the high PTH group experienced symptomatic hypocalcemia within 24 hours of surgery, whereas 44.0% of patients in low PTH group developed symptom after 24 hours (P = 0.008).

Univariate and multivariate analyses indicated that POD 1 PTH level was the only predictive marker of symptomatic hypocalcemia in all patients (Table 3). The incidence of the symptomatic hypocalcemia was 20.9 times (95% confidence interval [CI], 6.8–64.5, P < 0.001) higher in the low PTH group. The development of postoperative symptomatic hypocalcemia was not correlated with clinicopathologic features, combined central neck dissection, number of sacrificed parathyroid glands, or routine supplementation of low-dose calcium. Subgroup analysis in female patients also indicated that POD 1 PTH was the only predictive marker and menopause showed no association with symptomatic hypocalcemia (odds ratio, 2.7; 95% CI, 0.4–16.7, P = 0.281).

DISCUSSION

Routine supplementation with low-dose calcium (1,500

Table 2. Clinicopathological features of the low and high PTH groups

Characteristic	Low PTH group (n = 41)	High PTH group (n = 93)	P-value
Age (yr)	55.0 ± 10.3	48.0 ± 12.0	0.002
Female sex	35 (85.4)	82 (88.2)	0.653
Menopause in female	24/35 (68.6)	36/82 (43.9)	0.015
Combined central LN dissection	30 (73.2)	64 (68.8)	0.612
Inadvertent PTG excision			0.427
1 PTG	5 (12.2)	8 (8.6)	
2 PTGs	0 (0)	3 (3.2)	
PTG autotransplantation	2 (4.9)	2 (2.2)	0.393
Pathologic features			
Tumor size (cm)	1.3 ± 1.4	1.1 ± 0.6	0.289
Minimal extrathyroidal extension	26 (63.4)	57 (61.3)	0.815
LN metastasis	19 (46.3)	34 (36.6)	0.286
AJCC 7th classification			0.663
T1N0	6 (14.6)	15 (16.1)	
T1N1a	5 (12.2)	12 (12.9)	
T1Nx	3 (7.3)	8 (8.6)	
T2N1a	0 (0)	1 (1.1)	
T3N0	8 (19.5)	29 (31.2)	
T3N1a	14 (34.1)	21 (22.6)	
T3Nx	5 (12.2)	7 (7.5)	
Postoperative findings			
Symptomatic hypocalcemia	25 (61.0)	11 (11.8)	<0.001
Occurred within 24 hr	14/25 (56.0)	11/11 (100)	0.008
IV calcium dosage (mg)	691.9 ± 505.2	558.0 ± 275.9	0.417
Permanent hypocalcemia	1 (2.4)	0 (0)	0.131

Values are presented as mean ± standard deviation or number (%).
PTH, parathyroid hormone; LN, lymph node; PTG, parathyroid gland; AJCC, American Joint Committee on Cancer; IV, intravenous.

Table 3. Predictive factors for transient hypoparathyroidism in univariate and multivariate analyses

Covariates	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
Clinical features				
Age at surgery	1.003 (0.971–1.035)	0.875	0.963 (0.922–1.007)	0.095
Male sex	0.545 (0.147–2.022)	0.365	0.190 (0.033–1.076)	0.061
Surgical characteristics				
Combined CLND	0.800 (0.352–1.816)	0.594	0.667 (0.194–2.294)	0.520
T stage	Reference (T1)		Reference (T1)	
T stage (T2)	<0.001 (0.000–infinite)	>0.999	1.225 (0.000–infinite)	>0.999
T stage (T3)	1.044 (0.471–2.312)	0.915	0.995 (0.370–2.679)	0.992
N1a stage	1.319 (0.608–2.860)	0.483	1.478 (0.509–4.292)	0.472
Sacrificed parathyroid glands	Reference (none)		Reference (none)	
1 Gland sacrificed	1.194 (0.344–4.151)	0.780	1.095 (0.231–5.194)	0.909
2 Glands sacrificed	<0.001 (0.000–infinite)	0.999	<0.001 (0.000–infinite)	0.999
Parathyroid autotransplantation	2.824 (0.383–20.834)	0.309	3.508 (0.241–51.032)	0.358
POD 1 PTH <13 pg/mL	11.648 (4.789–28.327)	<0.001	20.649 (6.622–64.388)	<0.001
Routine calcium supplementation	1.718 (0.793–3.722)	0.170	2.453 (0.839–7.173)	0.101

CI, confidence interval; CLND, central lymph node dissection; POD, postoperative day; PTH, parathyroid hormone.

mg/day) after thyroidectomy did not reduce the rate of symptomatic hypocalcemia or the need for intravenous calcium in the present study. We also found that POD 1 PTH level < 13 pg/mL could be a predictive factor for the development of postoperative hypocalcemia. Routine supplementation of low-dose calcium is currently used in many centers, whereas few published reports investigated the efficacy of this low-dose calcium supplementation. To my best knowledge, only Choe et al. [21] reported the efficacy of low-dose calcium and suggested that routine supplementation of low-dose calcium (1,200 mg/day) did not prevent severe symptomatic hypocalcemia requiring intravenous calcium gluconate. Although prophylactic calcium supplementation was cost-effective, not labor-intensive, and expeditious, the optimal dosing is needed for further validation [22].

As low-dose calcium supplementation showed no preventive effect for postoperative hypocalcemia, issues were raised of the patients who could be safely discharged earlier without medication and for whom calcium supplement would be helpful. Over 60% of patients whose PTH level <13 pg/mL suffered from hypocalcemic symptoms, and 44.0% of symptomatic patients developed symptom after 24 hours. On the contrary, although 11.8% of patients with POD 1 PTH level over 13-pg/mL experienced symptomatic hypocalcemia, such patients developed symptom within 24 hours in all cases. Our results indicated that close monitoring of calcium level and appropriate calcium supplementation was beneficial for patients with PTH level <13 pg/mL. Early discharge can be considered safe for the asymptomatic patients during the first 24 hours, whose PTH level ≥13 pg/mL.

In the present study, we demonstrated that POD 1 PTH level <13 pg/mL was associated with the development of symptomatic hypocalcemia. The cutoff value of 13 pg/mL was determined by RPART classification algorithm in R. The statistical base of RPART is described elsewhere [20]. RPART algorithm helped us to calculate the cutoff value, which maximized the statistical separation between the groups [23]. Previous studies reported that postoperative PTH could be the most powerful predictor of hypocalcemia, with a different cutoff value from 9.6 to 23 pg/mL [24-26]. Most of these studies suggested the cut-off value of 10–15 pg/mL, which was consistent with our results. We demonstrated that POD 1 PTH level of 13 pg/mL was predictive for symptomatic hypocalcemia, and its incidence was about 20 times higher in patients with PTH <13 pg/mL.

We found that postoperative low PTH level < 13 pg/mL was associated with age and menopause status. Menopause may impair intestinal calcium absorption, which increases the risk of postoperative hypocaclcemia [27,28]. However, as older age might be associated with menopause in women, we investigated the association using multivariate logistic regression model. After adjusting confounders, menopause showed no association with postoperative symptomatic hypocalcemia. Other researchers also indicated that the incidence of transient hypoparathyroidism and PTH levels were comparable between pre-menopausal and postmenopausal women [29]. Khosla et al. [27] further demonstrated that serum PTH level was not associated with menopausual status. Therefore, menopause might have no effect on the PTH level after surgery.

This study had some limitations. First, most of the previous studies used ionized calcium level less than 4.0 mg/dL to define hypocalcemia (1.00 mmol/L). In the present study, we used the American Association of Clinical Endocrinologists and American College of Endocrinology definition of symptomatic hypocalcemia, which requires an ionized calcium concentration below 4.6 mg/dL (1.15 mmol/L) associated with hypocalcemic symptoms [18]. This higher calcium concentration cutoff level resulted in a comparatively high proportion of patients with symptomatic hypocalcemia, and thus direct comparison of our study results with others may not be relevant. Second, the results of our study may be affected by the higher percentage of patients who performed combined central LN dissection and parathyroid autotransplantation in the routine calcium group, although there were no statistical differences. Further validation studies in larger populations are warranted.

In conclusion, routine low-dose calcium and vitamin D supplements after total thyroidectomy did not reduce the risk of postoperative hypocalcemia. Patients who may benefit from calcium and/or vitamin D supplementation should be carefully selected.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGEMENTS

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