

# Routine oral calcium and vitamin D supplements for prevention of hypocalcemia after total thyroidectomy

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## Abstract

**Background:** The purpose of this study was to evaluate the clinical usefulness of routine oral calcium and vitamin D supplements in the prevention of hypocalcemia after total thyroidectomy.

**Methods:** Ninety patients who underwent total thyroidectomy were randomly assigned to routinely receive or not receive a supplement containing oral calcium (3 g/d) and vitamin D (1 g/d) for 2 weeks. Hypocalcemic signs and symptoms, serum calcium, and parathyroid hormone (PTH) levels were monitored and compared between the 2 groups.

**Results:** The incidences of symptomatic and laboratory hypocalcemia were significantly lower in the oral calcium/vitamin D group than in the group not receiving the supplement: 3 of 45 patients (7%) versus 11 of 45 (24%) and 6 of 45 (13%) versus 16 of 45 (36%), respectively ( $P \leq .02$ ). The hypocalcemic symptoms were minimal in the supplement group but more severe in the group not receiving the supplement. Serum calcium levels decreased in both groups after surgery but recovered earlier in the supplement group. No hypercalcemia or PTH inhibition developed in the supplement group.

**Conclusion:** Routine administration of a supplement containing oral calcium and vitamin D is effective in reducing the incidence and severity of hypocalcemia after total thyroidectomy. © 2006 Excerpta Medica Inc. All rights reserved.

*Keywords:* Total thyroidectomy; Hypocalcemia; Calcium; Vitamin D; Prevention

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Postoperative hypocalcemia is observed in up to one third of total or completion thyroidectomy patients and is the most common complication [1,2]. Hypocalcemia after total thyroidectomy is usually transient, and the incidence of permanent hypoparathyroidism is 3% or less according to the experience of most of the surgical units studied [1,2]. Despite being self-limiting in most patients, symptomatic hypocalcemia is of particular concern because of a delay in its manifestation and the consequent need for prolonged patient hospitalization or readmission. Several authors have attempted to identify risk factors in the development of hypocalcemia. Declines in serum calcium [3,4] or intact parathyroid hormone (iPTH) levels [5,6] after surgery have been suggested as being reliable predictors of postoperative hypocalcemia. Although measurements of serum calcium or iPTH allow the identification of patients who have no risk of

hypocalcemia after total thyroidectomy, it is not always easy to predict which patients can be discharged early from the hospital or to identify those requiring close monitoring of serum calcium levels or those that should receive calcium and vitamin D supplements.

Routine oral calcium and vitamin D supplements have been proposed to prevent the development of symptomatic hypocalcemia and to increase the likelihood of early hospital discharge after bilateral surgical treatment of the thyroid gland or exploration of the parathyroid glands [7,8]. Because symptomatic hypocalcemia usually develops as late as 24 hours to several days after surgery, postoperative treatment with oral calcium and vitamin D may be a useful approach for avoiding the risk of postoperative hypocalcemic crisis. This may, in turn, reduce the cost associated with multiple blood samplings in monitoring the development of hypocalcemia as well as costs associated with prolonged hospitalization [7–9]. For these reasons, the present study evaluated the clinical usefulness of routine administration of

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oral calcium and vitamin D supplements for the prevention of hypocalcemia after total thyroidectomy.

### Patients and Methods

A prospective controlled study of patients undergoing total thyroidectomy was performed from January to December 2004. All of the patients had no history of prior thyroid or neck surgery. Patients requiring unilateral lobectomy or subtotal or completion thyroidectomy were excluded, and only patients undergoing total thyroidectomy were enrolled into the study. Modified radical neck dissection was performed in patients with papillary thyroid carcinoma and clinically positive neck nodes. The parathyroid glands were carefully preserved, and the devascularized parathyroid glands were transplanted into the sternocleidomastoid muscle. All patients had normal renal function at the time of surgery. Patient information regarding age, sex, pathology, operative procedure, number of parathyroid glands preserved or autotransplanted, the presence of hypocalcemic symptoms, and oral or intravenous supplementation of calcium or vitamin D were recorded. Institutional review board approval was obtained in this study.

Postoperatively, the patients were randomly assigned to routinely receive or not receive oral calcium and vitamin D supplements. Patients in the supplement group were administered oral calcium (Korea United Pharmaceutical Co, Seoul, Korea), 3 g/d taken at 3 times (1 g every 8 hours), and vitamin D (Ilsung Pharmaceutical Co., Seoul, Korea), 1 g/d taken twice (0.5 g every 12 hours). Treatment was started on the night of the operation and continued to postoperative day 14. Patients not receiving supplement were administered the therapy only when symptomatic hypocalcemia developed. Intravenous calcium gluconate was administered if significant hypocalcemia persisted despite oral supplementation.

Serum ionized and total calcium and iPTH levels were checked the morning of the operation and at 1 and 24 hours after total thyroidectomy. Serum ionized calcium levels were measured twice a day and total calcium levels daily until hospital discharge. The reference ranges of ionized calcium and total calcium were 1.2 to 1.38 mmol/L and 8.5 to 10.5 mg/dL, respectively. The following blood work was also obtained preoperatively and postoperatively: albumin, urea, creatinine, magnesium, phosphate, and electrolytes. Serum calcium levels were corrected for measured abnormal serum albumin levels [10]. Serum iPTH levels were measured by using a standard ELSA-PTH immunoradiometric assay (Cis Bio International, Cedex, France) at 1 hour and 1 and 3 days after surgery. The normal range of iPTH, according to the assay manufacturer, is 8 to 76 pg/mL. The detection limit of the assay is 0.7 pg/mL, and the intraassay and interassay coefficients of variation are below 7% at PTH concentrations of 6 to 95 pg/mL. All patients were clinically evaluated for signs and symptoms of hypocalcemia. Postoperative hypocalcemia was defined as either symptomatic or laboratory. Hypocalcemic symptoms and signs, from perioral tingling and numbness to carpopedal spasms and tetany, were registered in detail. Laboratory hypocalcemia was defined as serum ionized calcium levels of <1.0 mmol/L or total calcium concentrations of <8.0

Table 1  
Characteristics of patients with/without routine oral calcium and vitamin D supplements

Variable	No supplement	Supplement	P value*
No. of patients	45	45	NS
Age†	46 ± 2	48 ± 2	NS
Sex (M/F)	9/36	8/37	NS
Thyroid disease (n)			NS
Malignancy	37	38	
Benign	8	7	
Operation (n)			NS
Total thyroidectomy alone	35	36	
Total thyroidectomy + MRND	10	9	
No. of parathyroid glands preserved‡	3.5 ± 0.1	3.4 ± 0.1	NS
Parathyroid autotransplantation (n)	9	10	NS
Temporary hypocalcemia (n)			
Symptomatic	11	3	.020
Laboratory‡	16	6	.014
Intravenous calcium	5	0	.022
Permanent hypocalcemia	2	1	NS

MRND = modified radical neck dissection; NS = not significant; M = male; F = female.

\* A *P* value < .05 was considered as significance.

† Mean ± standard error of the mean.

‡ Defined as serum ionized calcium levels of < 1.0 mmol/L or total calcium levels of < 8.0 mg/dL.

mg/dL, even if recorded only in a single measurement, either during the hospital stay or at any time after discharge from the hospital [11].

This study protocol required hospitalization of all patients for a minimum of 3 days after surgery in order to perform the required blood tests. All patients were followed at 1 week and at 1, 3, and 6 months after surgery, at which times serum ionized calcium, total calcium, and iPTH levels were measured.

The *t* test was used when comparing continuous variables between different groups; the paired *t* test was used for comparison of paired samples; and the chi-square test was used for categorical data analysis, with SPSS 11.0 for Windows (SPSS Inc, Chicago, IL). Data from each group were expressed as mean ± standard error of the mean. *P* < .05 was regarded as statically significant.

### Results

Ninety patients underwent total thyroidectomy over the study period. The ratio of males to females was 17 of 73, and patient age ranged from 21 to 77 years, with a mean age of 47 years. Each group included 45 patients; the clinical characteristics of the 2 groups are summarized in Table 1. There were no differences in age and sex between the 2 groups (with and without routine oral calcium and vitamin D supplements). The thyroid diseases of the patients included well-differentiated thyroid carcinoma in 75 patients, multinodular goiter in 10, and diffuse toxic goiter in 5. The operative procedures were total thyroidectomy alone in 71 patients and combined with modified radical neck dissection in 19 patients with metastatic papillary thyroid carcinomas. The mean number of preserved parathyroid glands was 3.4,

Table 2

Comparison of serum test values (mean  $\pm$  standard error of the mean) after total thyroidectomy between groups with and without oral calcium and vitamin D supplements

Variable	No supplement	Supplement	P value*
Total calcium (mg/dL)			
PO day 1	8.3 $\pm$ 0.1	8.4 $\pm$ 0.1	NS
PO day 2	8.0 $\pm$ 0.1	8.5 $\pm$ 0.1	.045
PO day 3	7.9 $\pm$ 0.1	8.6 $\pm$ 0.1	.002
PO day 7	8.4 $\pm$ 0.1	9.0 $\pm$ 0.1	.003
PO month 1	8.9 $\pm$ 0.2	9.2 $\pm$ 0.2	NS
Intact PTH (pg/mL)			
PO hour 1	30.1 $\pm$ 2.7	27.6 $\pm$ 2.1	NS
PO day 1	25.8 $\pm$ 2.3	23.8 $\pm$ 3.9	NS
PO day 3	23.6 $\pm$ 3.9	22.5 $\pm$ 4.8	NS
PO day 7	24.8 $\pm$ 2.9	20.5 $\pm$ 2.5	NS
PO month 1	31.6 $\pm$ 4.8	33.4 $\pm$ 4.5	NS

PO = postoperative; PTH = parathyroid hormone; NS = not significant.

\* *t* test, *P* value < .05.

and the parathyroids were autotransplanted in 19 patients (21%). The pathology, operative procedure, and parathyroid gland status were comparable between patients of the 2 groups.

Symptomatic hypocalcemia developed in 14 patients (16%), in 11 of 45 in the group not receiving supplement (24%) and in 3 of 45 in the supplement group (7%) ( $P = .02$ ). Laboratory hypocalcemia developed in 22 patients (24%), 16 of 45 in the group not receiving supplement (36%) and 6 of 45 in the supplement group (13%) ( $P = .014$ ). The incidence of hypocalcemia was significantly lower in the supplement group than in the no-supplement group ( $P \leq .02$ ). Hypocalcemic symptoms were minimal in the supplement group but more severe in the no-supplement group, including carpopedal spasms in 3 patients. Intravenous calcium was administered to 5 patients in the no-supplement group but not to any patients in the supplement group ( $P = .022$ ). Permanent hypocalcemia developed in 3 patients (3%).

Serum calcium and iPTH levels decreased by 3 days after thyroidectomy and nearly completely recovered approximately 3 months after surgery in both groups. Total calcium values measured at postoperative days 2, 3, and 7 were lower in the group not receiving supplement than in the supplement group ( $P < .05$ ) (Table 2 and Fig. 1). However, there was no statistical difference in the preoperative and postoperative iPTH levels of the 2 groups. The decrease in patient serum calcium and iPTH levels during the early days after surgery was less, and the levels recovered earlier in the supplement group than in the no-supplement group (Fig. 1). Hypercalcemia or other side effects did not develop in any of the patients receiving routine oral supplements.

## Comments

The present study shows that routine oral calcium and vitamin D supplements significantly reduce the incidence of hypocalcemia after total thyroidectomy ( $P \leq .02$ ). Postoperative treatment prevented a significant decrease of serum calcium levels as well as the subsequent development of

major hypocalcemic symptoms after total thyroidectomy. In the supplement group, the symptoms were minimal and patients did not experience hypocalcemic crisis. By contrast, hypocalcemic symptoms were more severe in the group that did not receive supplement. In this group, 3 patients suffered from carpopedal spasms and 5 patients required intravenous calcium administration after their persistent significant hypocalcemia failed to respond to subsequent administration of oral calcium and vitamin D supplements. Therefore, our data suggest that routine oral calcium and vitamin D supplements can significantly reduce the incidence and severity of hypocalcemia after total thyroidectomy, although they do not completely eliminate the occurrence of postoperative hypocalcemia.

Two studies have evaluated the efficacy of routine calcium supplements for the prevention of hypocalcemia after thyroidectomy [7,8]. Moore [7] reported that only 4 of 124 patients who received daily treatment of calcium (5 g) after bilateral thyroid resection developed hypocalcemia, and 1 required administration of intravenous calcium. Based on empirical observations, the prophylactic use of oral calcium to reduce the risk of hypocalcemic crisis and increase the likelihood of early hospital discharge was recommended. Bellantone et al [8] reported in a prospective control study that only 3 of 26 patients (11%) receiving oral calcium supplement (3 g/d) had symptoms related to hypocalcemia after total thyroidectomy, whereas 11 of 27 patients (40%) not receiving calcium supplement had symptoms. These studies suggest that postthyroidectomy hypocalcemia can be considerably prevented by the routine administration of calcium supplements.

Serum calcium levels decrease in most patients early after total thyroidectomy and are secondary to the impairment of parathyroid function in most cases [12]. Several days after surgery, serum calcium levels begin to recover in parallel with the increase of iPTH levels. Nonetheless, postoperative calcium supplements administered prophylactically may contribute to preventing the initial drop in serum calcium concentrations. Our study revealed that the decrease in serum calcium was less and that calcium levels

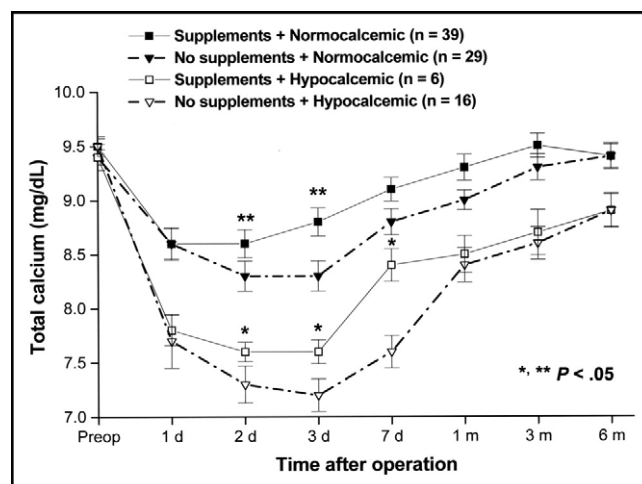


Fig. 1. Changes in serum total calcium levels before and after total thyroidectomy.

recovered earlier in patients receiving supplement than in patients not receiving supplement. Consequently, routine calcium supplements seem to prevent the occurrence of major hypocalcemic symptoms.

In a prior study [8], regimens of oral calcium alone and of a calcium and vitamin D combination were effective. However, the study also revealed that the addition of vitamin D to oral calcium supplements was associated with significantly higher serum calcium concentrations on postoperative days 2 and 3 and with a lower incidence of hypocalcemia. Although it has been reported that vitamin D administration inhibits iPTH secretion by normally functioning parathyroid glands [13], prior studies and our own results showed that iPTH secretion was not affected by vitamin D administration in postthyroidectomy patients. Therefore, the early use of vitamin D in addition to calcium supplements can be recommended for patients undergoing total thyroidectomy. The dosages and durations of calcium and vitamin D administration are also of concern. In a previous study [7] in which patients were given oral calcium on an empirical basis, an elderly patient supplemented with calcium 5 g/d for 2 weeks became lethargic and hypercalcemic. In another prospective controlled study [8], the daily administration of oral calcium (3 g) and vitamin D (1 g) for 7 days after surgery did not lead to complications. In the present study, oral calcium (3 g) and vitamin D (1 g) were administered daily to patients for 2 weeks after total thyroidectomy. Hypercalcemia or other side effects were not observed. Given that serum calcium decreased after surgery and then recovered during the postoperative period of more than 1 month in this study, a treatment duration of 2 weeks is proposed.

The prevention of significant symptomatic hypocalcemia will allow early discharge of postthyroidectomy patients from the hospital. In turn, early discharge eliminates the necessity of multiple blood samplings for close monitoring of serum calcium or iPTH levels. Our medical health care system is national and supported by the government. Most patients pay for only a small part of medical costs and thus prefer to remain in the hospital for as long as possible until all postoperative problems are eliminated. Despite the advantages for patients, multiple blood samplings and prolonged hospitalization increase the total cost of the country's medical health care system. In our country, the 1-time mean costs of the following blood tests are total calcium, \$1.5; ionized calcium, \$5.5; and iPTH, \$20. In contrast, the total price of calcium and vitamin D supplements is only about \$1.5 per day. Thus, if thyroidectomy patients are discharged from the hospital on the day of the procedure or the day after, the total medical costs per patient can be reduced by more than \$300 to 500 compared with the costs of patients remaining in the hospital for more than 3 days

after surgery. The avoidance of multiple blood samplings and prolonged hospitalization is a major cost saving and may be even greater in developed countries.

In conclusion, our data suggest that routine oral calcium and vitamin D supplements are effective in reducing the incidence and severity of hypocalcemia after total thyroidectomy. Only a minority of patients receiving the supplements presented with minimal symptoms related to hypocalcemia, and higher levels of serum calcium during the first few days after total thyroidectomy were measured in patients receiving the supplement. We therefore advocate routine oral calcium and vitamin D supplements in the prevention of postoperative hypocalcemia and for increasing the likelihood of a safe and early discharge from the hospital. This will ultimately lead to improved patient satisfaction and significant cost savings. However, this should be investigated by another, carefully designed study that includes a comparison between patients receiving routine oral supplements and being discharged early and those not given supplements and having a standard hospital stay.

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