Comparison Between Perioperative Treatment with Calcium and with Calcium and Vitamin D in Prevention of Post Thyroidectomy Hypocalcemia

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Abstract Even though thyroid surgery is quite safe, mechanical damage, devascularization or inadvertent removal of the parathyroid glands are possible. Though postoperative mortality is extremely low, post thyroidectomy hypocalcemia is one of the most common and potentially life-threatening complication following thyroid surgery. The clinical manifestation varies from minimal twitching to life threatening tetany and can prolong the hospital stay. The purpose of this study is to evaluate the clinical usefulness of routine oral calcium with Vitamin D supplements in reducing the incidence and severity of hypocalcemia after total thyroidectomy. This safe and cost effective therapy may prevent the threatening complications like tetany and reduce the hospital stay.

Keywords Hypocalcemia · Calcium · Vitamin D · Total thyroidectomy

Introduction

Hypocalcemia is an important and common complication following thyroid surgery with reports varying from 0.5 to 50%. Various causes for postoperative hypocalcemia have been suggested including haemodilution or increased

urinary calcium excretion secondary to surgical stress, calcitonin release secondary to thyroid gland manipulation, hungry bone syndrome (reversal of toxic thyroid osteodystrophy) and interference with the functioning of the parathyroid glands either through direct injury, removal or devascularisation [1]. Although the development of post-operative hypocalcemia is likely to be multifactorial in nature, thyroid lobectomy alone is hardly ever associated with this complication, which is most common following total thyroidectomy where there is a greater risk of parathyroid injury. In the post-operative period, inadequate production of PTH may lead to hypocalcemia. Hypoparathyroidism, and the resulting hypocalcemia, may be transient or permanent [2].

Hypocalcemia varies from an asymptomatic biochemical abnormality to a life-threatening disorder-Tetany, depending on the duration, severity, and rapidity of development. In the setting of acute hypocalcemia, rapid treatment may be necessary. 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. In hypocalcemia after total thyroidectomy, it is not always easy to predict which patient will be requiring close monitoring of serum calcium levels or those that should receive calcium with vitamin D supplements [1].

In the previous studies it has been observed that routine administration of a supplement containing oral calcium in the postoperative period is effective in reducing the incidence and severity of hypocalcemia after total thyroidectomy [3, 5–7]. Calcium supplementation as 1 L/d of a high-calcium mineral water has been found to enhance blood calcium levels and to increase the likelihood of early hospital discharge in thyroidectomized patients [4]. Although calcium supplementation reduces the incidence

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of post thyroidectomy hypocalcemia, its incidence is still high especially after total thyroidectomy, where both parathyroid glands are at risk. Vitamin D is the 25, hydroxy cholecalciferol which is activated to 1,25,dihydroxycholecalciferol in the kidney. vitamin D increases the intestinal absorption of calcium and plays an important part in the regulation of serum calcium level. Because symptomatic hypocalcemia usually develops as late as 24 h to 15 days after surgery, perioperative treatment with oral calcium with vitamin D supplement may be a useful approach for avoiding the risk of postoperative hypocalcemic crisis [7]. The present study evaluated the clinical usefulness of oral calcium with vitamin D for the prevention of post thyroidectomy hypocalcemia. We compared the post thyroidectomy hypocalcemia in two groups. One group received oral calcium (2 gm/day) daily; and second group received oral calcium (2 gm/day) daily with vitamin D (60,000 IU thrice a week) for 1 week prior to surgery and continued for 2 weeks after surgery.

The prevention of distressing symptoms of hypocalcemia improves patient's quality of life and prevents life threatening complication like tetany. It allows safe and early discharge of post thyroidectomy patients from the hospital. In turn, early discharge eliminates the necessity of multiple blood samplings for close monitoring of serum calcium levels.

Materials and Methods

A prospective controlled study of patients undergoing total thyroidectomy was performed from January 2007 to December 2009. A total of 48 patients who underwent total thyroidectomy formed the basis of this study. Institutional review board approval was obtained.

Patients had no history of prior thyroid or neck surgery. Patients requiring unilateral lobectomy were excluded, and only patients undergoing total or completion thyroidectomy were enrolled into the study. Data collected on each patient included age; sex; previous surgical history; diagnosis; preoperative serum ionic calcium levels; type of operation; postoperative serum ionic calcium levels on days 1, 3, and 5 after surgery; and length of hospital stay and the histopathology reports. All patients were euthyroid at the time of surgery. In all patients, the parathyroid glands were carefully identified and preserved. Modified radical neck dissection was performed in patients with thyroid carcinoma. All patients had normal renal function at the time of surgery.

Two groups were formed: 24 patients (Group A) were serially selected who received oral calcium in the tablet form of calcium carbonate (2 gm/day in two divided doses) daily. 24 patients (Group B) received oral calcium carbonate

(2 gm/day) daily and vitamin D (60,000 IU thrice a week). Vitamin D was given in the form of 1 gm sachet (60,000 IU/sachet). Whole single sachet to be taken early morning dissolved in glass full of water thrice a week. In both groups, the supplement was started 1 week prior to surgery and continued for 2 weeks in the post operative period. Patients were assessed for hypocalcemic signs, symptoms and serum ionic calcium levels and compared between the two groups. Possible side effects of calcium with vitamin D like nausea, stomach cramps, dry mouth, increased thirst, increased urination were explained to the patients and were reported.

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 ionic calcium levels of ≤ 1.0 mmol/L or total calcium concentrations of ≤ 8.0 mg/dL, even if recorded only in a single measurement, either during the hospital stay or at any time after discharge from the hospital. This study protocol required hospitalization of all patients for a minimum of 5 days after surgery in order to perform the required blood tests. Patients with acute hypocalcemic symptoms like carpopedal spasms and/or ionic calcium level lower than 0.8 mmol/L were treated promptly with IV calcium gluconate. Ten milliliters of 10% solution (1 g) of calcium gluconate was administered over 10 min. A calcium infusion was started at a rate of 1–2 mg/kg/h if symptoms did not resolve. The infusion was titrated to the patient's symptoms and calcium levels. When adequate calcemia was achieved, urinary calcium excretion was measured to rule out hypercalciuria. A thiazide diuretic may be added to diminish calciuria and further increase the serum calcium level. All patients were reassessed after 1 week and at 1, 3, and 6 months. Calcium levels were measured at each follow-up visit. If the patient became clinically hypocalcemic after stopping the exogenous calcium with or without vitamin D, they restarted their supplements. Permanent hypocalcaemia was defined by the requirement for calcium with or without vitamin D supplement for more than 6 months postoperatively.

The t test was used when comparing continuous variables between different groups; and the χ^2 test was used for categorical data analysis, with SPSS 11.0 for Windows (SPSS Inc, Chicago, IL). $P \leq 0.05$ was regarded as statistically significant.

Results

48 Patients underwent total thyroidectomy over the study period. The ratio of males to females was 1:47. Patient' age ranged from 26 to 65 years, with a mean age of 45.5 years.

Each group included 24 patients; the clinical characteristics of the two groups are summarized in Table 1.

The thyroid diseases of the patients included multinodular goiter in 35 patients, papillary thyroid carcinoma in seven patients and hashimoto's thyroiditis in six patients. The pathology, operative procedure, and the histopathological diagnosis were comparable between patients of the two groups (Table 1, Figs. 1, 2). Symptomatic hypocalcemia developed in 10 patients (41.67%) of 24 in group A and in 3 of 24 (12.5%) in the group B ($P = 0.0230$) (Table 2). Laboratory hypocalcemia developed in 7 patients (29.16%) of 24 in the group A and 1 of 24 (4.16%) in the group B ($P = 0.0201$) (Table 3). The incidence of hypocalcemia was significantly lower in the group receiving oral calcium with vitamin D (Group-B) than in the group receiving only oral calcium (Group-A). Hypocalcemic symptoms were minimal in group B. These included perioral tingling in all 3 patients and tingling in the extremities in one patient. Hypocalcemic symptoms were more severe in the group A, including carpopedal spasms in three patients, Chvostek's sign was positive in two patients (Fig. 3). Decrease in serum calcium was also less in the group receiving oral calcium with vitamin D. In the group A, seven patients had serum calcium less than 1 mmol/L. Out of these 7, intravenous calcium was administered to three patients (Serum calcium <0.8 mmol/L). In the group B, only one patient had serum calcium less than 1 mmol/L (0.9 mmol/L) (Fig. 4). Serum calcium levels decreased by 2 days after thyroidectomy and nearly completely recovered approximately 10 days after surgery in both groups. Temporary hypocalcemia lasting for 3 months developed in two patients (8.33%) in group A. These two patients required Endocrinology consultation in monitoring of calcium and PTH levels and the medical management of the sequelae of hypoparathyroidism. Not a single patient developed permanent hypocalcemia. Hypercalcemia, hypercalciuria or other side effects did not

Fig. 1 Thyroid disease in Group-A (supplement with calcium)

Fig. 2 Thyroid disease in Group B (supplement with calcium and vitamin D)

Table 2 Comparison of symptomatic hypocalcemia between two groups

	Group-A (calcium)	Group-B (calcium + vitamin D)
Symptamatic hypocalcemia		
Present	10	3
Absent	14	21
Total	24	24

χ^2 test value = 5.169 with 1 degree of freedom

P value = 0.0230 (<0.05)

Table 3 Comparison of laboratory hypocalcemia between two groups

	Group-A (calcium)	Group-B (calcium + vitamin D)
Laboratory hypocalcemia		
Present	7	1
Absent	17	23
Total	24	24

χ^2 test value = 5.400 with 1 degree of freedom

P value = 0.0201 (<0.05)

Table 1 Characteristics of patients with oral calcium with and without vitamin D supplement

Variable	Group A (calcium)	Group B (calcium + vitamin D)	P value
Number of patients	24	24	NS
Age (years) -mean	44.5	42.7	NS
Sex (M/F)	1/23	0/24	NS
Thyroid disease			
A. Benign	17	18	NS
B. Malignancy	4	3	NS
C. Hashimoto's thyroiditis	3	3	NS
Temporary hypocalcemia			
A. Symptamatic	10	3	0.0230 (< 0.05) Significant
B. Laboratory	7	1	0.0201 (< 0.05) Significant
C. IV Calcium	3	0	NS
Permanant hypocalcemia	0	0	NS

P value <0.05 is significant

Laboratory hypocalcemia is defined as serum ionic calcium level of <1.0 mmol/L or total calcium level of <8.0 mg/dL

NS not significant, M male, F female

X-axis- Number of patients.

Y-axis:

- 1st Qtr- Perioral tingling.
- 2nd Qtr- Tingling in the extremities.
- 3rd Qtr- Carpopedal spasms.
- 4th Qtr- Positive Chvostek's sign.

Fig. 3 Severity of symptomatic hypocalcemia in both groups. *Group-A*: Supplement with oral calcium. *Group-B*: Supplement with oral calcium and vitamin D. X-axis: Number of patients. Y-axis: 1st Qtr- Perioral tingling. 2nd Qtr- Tingling in the extremities. 3rd Qtr- Carpopedal spasms. 4th Qtr- Positive Chvostek's sign

X-axis- Number of patients.

Y-axis- Serum Calcium in mmol/L.

Fig. 4 Severity of laboratory hypocalcemia in both groups. *Group-A*: Supplement with oral calcium. *Group-B*: Supplement with oral calcium and vitamin D. X-axis: Number of patients. Y-axis: Serum Calcium in mmol/L

develop in any of the patients receiving oral calcium with or without vitamin D supplements.

Discussion

Thyroid surgery has a history of significant changes in the technique and the incidence of complications. Hypoparathyroidism is a feared complication of thyroid surgery. Up to one-third of patients develop hypocalcemia following thyroidectomy. Although 97% of cases are self-limiting, hypocalcemia causes significant and distressing symptoms and increases in medical costs [2, 3].

The parathyroid glands produce parathyroid hormone (PTH), which is intimately involved in the regulation of serum calcium. PTH increases serum calcium levels by causing bone resorption, increasing renal absorption of calcium, and stimulating the synthesis of the biologically active form of vitamin D (1,25-dihydroxy vitamin D) in kidneys [2]. The most dramatic effect of 1,25-dihydroxy vitamin D is to facilitate intestinal absorption of calcium even in healthy individuals with no apparent vitamin D deficiency [8].

In the absence of vitamin D, dietary calcium is not absorbed at all efficiently. The vitamin D hormone, 1,25-dihydroxycholecalciferol [1,25(OH)₂D₃], stimulates the synthesis of the epithelial calcium channels [9] and the plasma membrane calcium pumps [10, 11] and induces the formation of the calbindins. Calbindin is an intracellular protein that ferries calcium across the intestinal epithelial cell [12]. Thus vitamin D increase the overall rate of trans-cytosolic diffusion of calcium.

Inadequate production of PTH leads to hypocalcemia due to inadequate production of active form of vitamin D. Hypoparathyroidism, and the resulting hypocalcemia, may be transient or permanent [2, 7]. In the literature, the incidence of temporary hypocalcemia after thyroid surgery ranges from 1.6% to 50%, and permanent hypocalcemia occurs after 1.5% to 4% of surgeries [13–16]. Permanent hypoparathyroidism may be due to direct trauma to the parathyroid glands, devascularization of the glands, or removal of the glands during surgery. The cause of transient hypocalcemia after surgery is not clearly understood. It may be attributable to temporary hypoparathyroidism caused by reversible ischemia to the parathyroid glands, hypothermia to the glands, or release of endothelin-1. Endothelin-1 is an acute-phase reactant known to suppress PTH production, and levels have been elevated in patients with transient hypoparathyroidism [14]. Transient hypocalcemia secondary to the impairment of parathyroid function recovers in 10–15 days after surgery. Serum calcium levels begin to recover in parallel with the increase of PTH levels [13]. Calcium with vitamin D supplements in

this period effectively reduces the incidence and progression of hypocalcemia.

Other hypotheses have been put forth to account for transient hypocalcemia not caused by hypoparathyroidism. These include haemodilution or increased urinary calcium excretion secondary to surgical stress, calcitonin release secondary to thyroid gland manipulation, hungry bone syndrome. Calcitonin is produced by the thyroid and inhibits bone breakdown while stimulating renal excretion of calcium. Hungry-bone syndrome occurs in patients with preoperative hyperthyroidism. These patients have increased bone breakdown in their hyperthyroid state. When a patient's thyroid hormone level drops acutely after surgery, his or her stimulus to break down bone is removed. The bones, now "hungry" for calcium, remove calcium from the plasma, decreasing serum calcium levels [1, 14].

Most patients who are hypocalcemic after thyroidectomy are initially asymptomatic. Symptoms and signs of hypocalcemia include increased neuromuscular irritability, circumoral paresthesias, mental status changes, tetany (repetitive neuromuscular discharge after a single stimulus), carpopedal spasm, laryngospasm, seizures, QT prolongation on ECG, and cardiac arrest [14]. Twitching of the ipsilateral facial musculature (perioral, nasal, and eye muscles) by tapping over cranial nerve VII at the ear is known as Chovstek's sign. Contraction at the oral angle alone is seen in 10–25% of the normal population. Trousseau's sign consists of carpal spasm provoked by ischemia, induced by inflation of the blood pressure measuring cuff around the arm. Spontaneous muscle cramps are commonly seen in hypocalcemia. Prolonged contraction of the respiratory and laryngeal muscles causes stridorous breathing and can cause cyanosis [17–19].

The present study compared the incidence and severity of post-thyroidectomy hypocalcemia in the two groups of patients undergoing total thyroidectomy. Group A received oral calcium (2 gm/day in 2 divided doses) daily while group B received oral calcium with vitamin D (60,000 IU/day three times a week) 1 week prior to surgery and continued for 2 weeks after surgery as parathyroid function usually recovers in 10–15 days after surgery. The study shows that perioperative supplement with oral calcium and vitamin D prevented a significant decrease of serum calcium levels as well as the subsequent development of major hypocalcemic symptoms after total thyroidectomy. In the group receiving calcium with vitamin D, the symptoms were minimal and patients did not experience hypocalcemic crisis. By contrast, hypocalcemic symptoms were more severe in the group that received only calcium supplement (Fig. 3). In this group, three patients suffered from carpopedal spasms and two patients showed positive chovstek's sign. Laboratory hypocalcemia was also significantly less in the group B. In this group only one patient

had decreased serum calcium (0.9 mmol/L). In group A, seven patients had decreased serum calcium (Fig. 4). Out of these, three had serum calcium less than 0.8 mmol/L and required intravenous calcium administration after their persistent significant hypocalcemia failed to respond to subsequent administration of oral calcium. Therefore, our data suggest that routine oral calcium with 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. The dosages and durations of calcium and vitamin D given to our patients were within standard pharmacological limits. Hypercalcemia, hypercalciuria or other side effects were not observed.

Conclusion

Our data suggest that oral calcium (2 gm/day) daily with vitamin D (60,000 IU/day three times a week) supplement 1 week prior to surgery and for 2 weeks in the postoperative period is effective in reducing the incidence and severity of hypocalcemia after total thyroidectomy. Symptomatic as well as laboratory hypocalcemia was significantly less in the group receiving calcium with vitamin D than the group receiving only calcium. We therefore recommend oral calcium with vitamin D supplements in the perioperative period for the prevention of post-thyroidectomy hypocalcemia and its life threatening consequences. It increases the likelihood of a safe and early discharge from the hospital. This will ultimately lead to improved patient satisfaction and significant cost savings.

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