Effectiveness of Routine Supplement of Oral Calcium and Vitamin D to Prevent Postoperative Hypocalcemia after Total or Completion Thyroidectomy

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Background: *The incidence of hypocalcemia after total/completion thyroidectomy was 30 to 40% in recent studies. There is no consensus regarding the role of routine supplement of calcium and vitamin D.*
Objective: *To study the efficacy of routine oral calcium and vitamin D supplement to prevent postoperative hypocalcemia.*
Material and Method: *Sixty-eight patients who underwent total/completion thyroidectomy at the Division of Head Neck and Breast Surgery, Siriraj Hospital were included and randomized into two groups: Supplement and Control. Serum ionized calcium and total calcium were measured at 6 hour, and Days 1, 2, 3, 7 and 30 postoperatively. Clinical signs and symptoms of hypocalcemic state were recorded.*
Results: *The incidences of biochemical hypocalcemia were 74.3% and 96.9%, and of symptomatic hypocalcemia were 28.6% and 33.3%, in Supplement and Control groups, respectively. Most patients had hypocalcemia within the first postoperative days. Symptomatic hypocalcemia was related to ionized calcium less than 4.2 mg/dL or total calcium less than 7.9 mg/dL.*
Conclusion: *The incidence of post-thyroidectomy hypocalcemia was high. Most occurred within 24 hours but only 30% of these patients became symptomatic. The immediate postoperative calcium supplement may prevent this condition.*

Keywords: *Calcium, Hypocalcemia, Hypoparathyroidism, Thyroidectomy, Vitamin D*

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The incidence of postoperative hypocalcemia after total or completion thyroidectomy has been reported to vary from 1.6 to >50%[1,3], whereas symptomatic hypocalcemia occurs in 20 to 40% of hypocalcemic patients[1,2]. Clinical presentation of hypocalcemia were positive Chvostek's sign, positive Trousseau's sign, tetany or seizure, or circum-oral tingling or numbness. Hypocalcemia can occur during the first 24 hours up to several days after surgery. Prevention of this condition may decrease symptomatic hypocalcemia and its complications, and reduce length of hospital stay. The use of prophylactic calcium with or without vitamin D supplement was still controversial. There were few reports studying on this issue[1,2,4], and to our knowledge, there was no study on the relationship between clinical presentation of hypocalcemia and serum calcium level.

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The objective of this study was to assess the efficacy of routine oral calcium and vitamin D supplement for prevention of post-thyroidectomy hypocalcemia.

Material and Method

The study included patients who underwent total or completion of thyroidectomy between December 2007 and January 2009 at the Division of Head Neck and Breast Surgery, Department of Surgery, Siriraj Hospital, Bangkok, Thailand. The study was approved by the Siriraj Institutional Review Board.

The patients with the following were excluded from our study: (1) previous neck dissection, (2) previous neck irradiation, (3) parathyroidectomy had done or to be done, (4) serum creatinine >2 mg/dL, (5) bony metastasis, and (6) exposure to calcium or vitamin D within one month before this operation.

Sixty-eight patients were included in this study and given informed consents. After total or completion thyroidectomy, patients were randomized into two groups in the operation room; 1) patients not receiving the supplement (control group), and 2)

patients receiving oral calcium and vitamin D supplement (supplement group). The randomization was done by surgical staff or resident who attended the patient operation, using raffling.

The supplement included tablet calcium carbonate (1 gram/tablet) given 1 tablet every 8 hours (totally 3 grams per day) and capsule 1, 25 alpha-hydroxy vitamin D3 (0.25 microgram/capsule) given 1 capsule every 12 hours (totally 0.5 mcg per day)[2]. The supplement starts in the morning of postoperative day 1, and continues for 14 days. In control group, the oral supplement was given only when ionized calcium level is less than 4.6 mg/dl. And in both groups, intravenous calcium was also given if the patients had any symptoms or signs of hypocalcemia.

The definition of hypocalcemia was serum ionized calcium level <4.6 mg/dL (normal range of serum ionized calcium = 4.6 to 5.2 mg/dL). The symptoms and signs of hypocalcemia were (1) positive Chvostek's sign (2) positive Trousseau's sign (3) tetany or seizure, and (4) circumoral tingling or numbness.

Pre-operatively, all patients had the following pre-operative investigations: serum ionized calcium, total calcium, albumin, creatinine, phosphorus, alkaline phosphatase and parathyroid hormone.

Postoperatively all patients were taken serum parathyroid hormone once more in the morning of postoperative Day 1, and ionized calcium, total calcium, and phosphorus daily in the morning of postoperative Day 1, 2, 3, and the first OPD follow-up visit (postoperative day 7), and finally on postoperative day 30. Clinical signs and symptoms of hypocalcemia were monitored closely in all patients.

If the patients developed signs and/or symptoms of hypocalcemia, the patients were tested for ionized calcium to confirm the calcium level and given the standard treatment and investigations until ionized calcium more than 4.6 mg/dL and no any hypocalcemic signs and symptoms.

Data was prospectively recorded, including patients' demographic details, biochemistries (including serum ionized calcium levels, serum total calcium levels, serum phosphorus levels, parathyroid hormone levels, albumin, alkaline phosphatase, and creatinine), clinical presentations of hypocalcemia.

Statistical analysis

Data was analyzed using SPSS computer program (version 13.0 for Windows). Non-parametric nominal data were analyzed with χ^2 test, continuous data with t-test, and new cut point with binomial test. Statistical significance was *p*-value <0.05.

Results

Sixty-eight patients were included in our study. The ratio of female to male was 56 to 12. The mean age was 49.8 years (range 18 to 85). There were 33 patients in control group and 35 patients in supplement group. The demographic data among each group is shown in Table 1.

There was no difference between both groups in gender, age, type of thyroid operation, neck dissection, preservation of parathyroid glands, operator and pathology. In addition, there was no difference between both groups in albumin, alkaline phosphatase, creatinine, phosphorus and parathyroid hormone levels preoperatively, and phosphorus levels postoperatively during follow-ups (postoperative day 7 and 30). There were higher levels of phosphorus in the supplement group than in the control during postoperative day 1 to 3 (*p*-values <0.05). This increase in phosphorus levels may be related to a decrease in ionized calcium levels during this same period of time (Table 2).

The incidences of hypocalcemia in two groups were shown in Table 3. The incidences of biochemical hypocalcemia were high in both groups (74.3% in control and 96.9% in supplement). But the incidences of symptomatic hypocalcemia were similar to previous studies: 28.6% in control and 33.3% in supplement.

Most of patients developed hypocalcemia within 24 hours after operation in both groups. This made 27 patients (81.8%) in supplement group exposed to calcium and vitamin D as "therapeutic" not "prophylactic". Similarly, two-thirds of patients in control group developed hypocalcemia within the first 24 hours and received calcium and vitamin D supplement. These made us unable to evaluate the efficacy of the supplement as "prophylaxis".

Discussion

Our study was unable to assess the efficacy of routine oral calcium and vitamin D in term of prophylaxis. The problems were (1) there were about 80% of supplement group exposed to calcium and vitamin D after hypocalcemic events, (2) there were many patients in control group crossing over to supplement group since postoperative Day 1. This effect made two-thirds of the control group having the pattern of calcium exposure like the supplement group, and (3) assessment of prophylactic efficacy by using the incidences in postoperative day 2 or 3 as outcomes

Table 1. Demographic data between two groups

	Control n = 33	Supplement n = 35	*p*-value
Gender			0.468
Female (n = 56)	26	30	
Male (n = 12)	7	5	
Age			0.317
≥45 years (n = 41)	22	19	
<45 years (n = 27)	11	16	
Type of operation			0.941
Total thyroidectomy (n = 48)	23	25	
Completion thyroidectomy (n = 20)	10	10	
Neck dissection			0.118
No (n = 60)	27	33	
Yes (n = 8)	6	2	
Preservation of parathyroid glands			0.680
Complete (n = 41)	19	22	
Incomplete (n = 27)	14	13	
Operator			0.783
Staff (n = 53)	20	23	
Fellow/resident (n = 15)	13	12	
Pathology			0.623
Malignant (n = 29)	13	16	
Benign (n = 39)	20	19	

Table 2. Biochemistry results between two groups

	Control n = 33	Supplement n = 35	*p*-value
Biochemistry, mean (range)			
Albumin (3.5 to 5.5 g/dL)	4.13 (3.4 to 4.7)	4.27 (3.2 to 4.9)	NS
Alkaline phosphatase (39 to 117 U/L)	62.63 (37 to 97)	62.77 (32 to 116)	NS
Creatinine (0.5 to 1.5 mg/dL)	0.69 (0.4 to 1.1)	0.68 (0.5 to 1.2)	NS
Phosphorus (2.2 to 5.6 mg/dL)			
Pre-op	3.17 (1.1 to 4.3)	3.39 (2.5 to 4.6)	NS
Day1	3.87 (1.9 to 5.4)	4.35 (3 to 5.8)	<0.05
Day2	3.74 (2.3 to 5.3)	4.10 (2.1 to 5.8)	<0.05
Day3	3.99 (1.9 to 6.7)	4.43 (2.7 to 5.9)	<0.05
Day7	3.76 (2.7 to 5.2)	4.02 (2.9 to 5.2)	NS
Day30	3.24 (2.3 to 4.8)	3.37 (2.5 to 4.8)	NS
PTH (15 to 65 pg/mL)			
Pre-op	44.81 (17.65 to 112.9)	49.87 (24.5 to 99.86)	NS
Day1	21.46 (7.17 to 50.22)	21.09 (4.93 to 43.64)	NS

might not be unreliable because most of patients were exposed to calcium since postoperative day 1 and there were too few patients who were not exposed to any supplement (10 patients as new control group vs. 58 patients as new supplement group).

The cause of these problems was the "timing" of giving initial prophylactic calcium and vitamin D. Because in our study, the hypocalcemia occurred within the first 24 hours, earlier than other studies in which the hypocalcemia occurred after 24 hours to several days after operation[2,3,5]. Another reason may be the cut point to diagnose hypocalcemia. This is because

Table 3. Incidences of hypocalcemia

	Incidences of hypocalcemia	
	Control n = 33	Supplement n = 35
Biochemical hypocalcemia, n (%)		
Overall	32 (96.9)	26 (74.3)
Day 1	27 (81.8)	23 (65.7)
Day 2	4 (12.1)	1 (2.9)
Day 3	1 (3.0)	2 (5.7)
Symptomatic hypocalcemia, n (%)	11 (33.3)	10 (28.6)

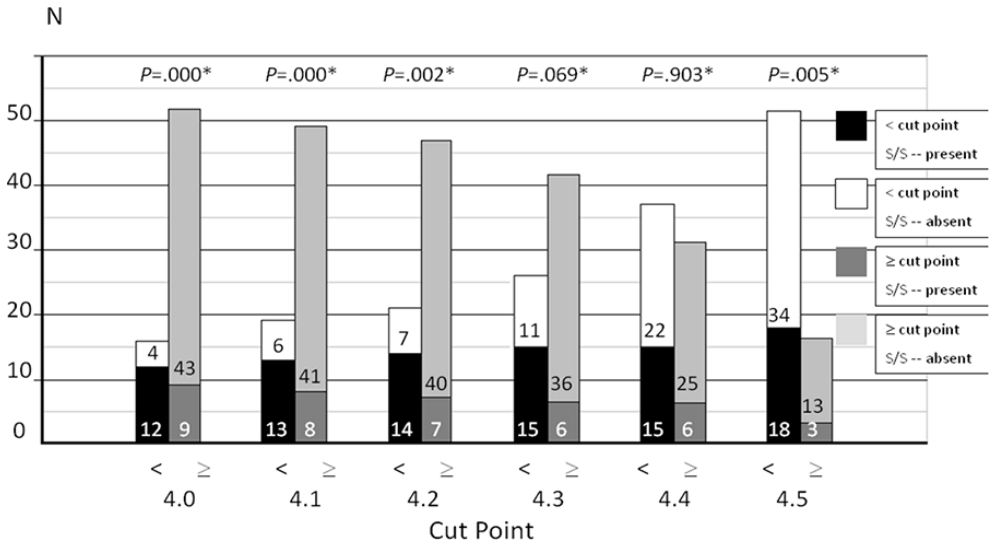

Fig. 1 Cut points.

even biochemical hypocalcemia occurred very often, but it might not be clinically significant. Symptomatic hypocalcemia may be more important in terms of prevention and therapy.

With binomial test, we assessed the relationship between any certain cut points and symptomatic hypocalcemia. At the ionized calcium levels at 4.0, 4.1, 4.2 and 4.5 mg/dL, the *p*-value was <0.05. But at the ionized calcium level of 4.5, the sample size of group whose ionized calcium ≥4.5 mg/dL and that of group whose ionized calcium <4.5 mg/dL were too much different. The *p*-value of the cut point of 4.5 mg/dL was unreliable. We considered the cut point of 4.2 mg/dL was related to symptomatic hypocalcemia (Fig. 1) and should be used as new threshold level for "therapeutic" calcium supplement. Using a new cut point as 4.2 mg/dL of ionized calcium, its sensitivity, specificity, positive predictive value and negative predictive value are 71.43%, 87.23%, 71.43% and 87.23%, subsequently.

Binomial test

Because of less laboratory availability of ionized calcium and familiarity of physicians to interpret ionized calcium level, total calcium level may be more useful than ionized calcium level in clinical practice. The levels of total and ionized calcium were consistent along whole courses. With regression analysis, their strong association was confirmed statistically with *p*-value <0.001 in every postoperative day.

We calculated an equation of association between them as:

$$[Ca2+] = 0.134 + 0.512\,[Catot]$$

When [Ca2+] is serum ionized calcium level and [Catot] is serum total calcium level,with this equation, we found that total calcium level of 7.9 mg/

dL was related to ionized calcium level of 4.2 mg/dL; thus. we can use total calcium level of 7.9 mg/dL instead of ionized level of 4.2 mg/dL.

Conclusion

The incidence of hypocalcemia after total or completion of thyroidectomy is high and about one-third of hypocalcemic patients experienced hypocalcemia-related signs or symptoms. The hypocalcemia in our study occurred early within 24 hours, suggesting the importance of immediate postoperative calcium and vitamin D supplement. Unfortunately, this study could not demonstrate the efficacy of the prophylaxis.

What this study adds?

The biochemical hypocalcemia may not be clinically significant because most of them were asymptomatic. The ionized calcium level at 4.2 mg/dL or total calcium level at 7.9 mg/dL were related to symptomatic hypocalcemia, and should be used as threshold levels to start calcium therapy regardless of signs or symptoms.

Acknowledgements

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Potential conflicts of interest

None.

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ประสิทธิภาพของการให้แคลเซียมและวิตามินดีเสริมเพื่อป้องกันการเกิดภาวะแคลเซียมในเลือดต่ำภายหลังการผ่าตัดต่อมไทรอยด์ออกทั้งหมด

เอกราช ลิ่วธนมงคล, วราภรณ์ อิ่มฤทัยเจริญโชค, พรชัย โอเจริญรัตน์

ภูมิหลัง: *อุบัติการณ์ของภาวะแคลเซียมในเลือดต่ำภายหลังการผ่าตัดต่อมไทรอยด์ออกทั้งหมดพบได้สูงถึงประมาณ 30 ถึง 40% ในปัจจุบันยังไม่มีแนวทางที่ชัดเจนเกี่ยวกับบทบาทของการให้แคลเซียมและวิตามินดีเสริมเพื่อป้องกันในผู้ป่วยเหล่านี้*

วัตถุประสงค์: *เพื่อศึกษาประสิทธิภาพของการให้แคลเซียมและวิตามินดีเสริมเพื่อป้องกันภาวะแคลเซียมในเลือดต่ำภายหลังการผ่าตัด*

วัสดุและวิธีการ: *ผู้ป่วยจำนวน 60 รายที่เข้ารับการผ่าตัดต่อมไทรอยด์ออกทั้งหมดที่สาขาวิชาศัลยศาสตร์ศีรษะ คอ และเต้านม ภาควิชาศัลยศาสตร์ คณะแพทยศาสตร์ ศิริราชพยาบาลได้รับการสุ่มแบ่งออกเป็นสองกลุ่ม: กลุ่มที่ได้รับยาเสริม และกลุ่มควบคุม ระดับแคลเซียมในเลือดได้รับการตรวจที่ระยะเวลา 6 ชั่วโมง และวันที่ 1, 2, 3, 7 และ 30 ภายหลังการผ่าตัดอาการและอาการแสดงของภาวะแคลเซียมต่ำในเลือดได้รับการบันทึก*

ผลการศึกษา: *อุบัติการณ์ของภาวะแคลเซียมในเลือดต่ำเท่ากับ 74.3% และ 96.9% และอาการทางคลินิกของภาวะแคลเซียมต่ำเท่ากับ 28.6% และ 33.3% ในกลุ่มที่ได้รับยาเสริมและกลุ่มควบคุมตามลำดับ ผู้ป่วยที่มีภาวะแคลเซียมในเลือดต่ำส่วนใหญ่เกิดขึ้นภายในวันแรกหลังการผ่าตัด อาการและอาการแสดงของภาวะแคลเซียมต่ำเกิดขึ้นในผู้ป่วยที่มีระดับไอโอไนซ์แคลเซียมต่ำกว่า 4.2 มก./ดล. หรือระดับแคลเซียมรวมต่ำกว่า 7.9 มก./ดล.*

สรุป: *อุบัติการณ์ของภาวะแคลเซียมในเลือดต่ำภายหลังการผ่าตัดต่อมไทรอยด์ออกทั้งหมดเกิดขึ้นบ่อยมาก โดยส่วนใหญ่เกิดขึ้นภายใน 24 ชั่วโมงแรกหลังการผ่าตัด การให้แคลเซียมและวิตามินดีเสริมในผู้ป่วยทุกราย อาจป้องกันภาวะแทรกซ้อนนี้ได้*