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The preoperative prediction of postoperative symptomatic hypocalcemia in patients with Graves' disease.

Shinichiro KOBAYASHI[1], Shigeki MINAMI[1], Kosho YAMANOUCHI[1], Naomi HAYASHIDA[2], Chika SAKIMURA[1], Susumu EGUCHI[1]

[1] Department of Surgery, Nagasaki University Graduate School of Biomedical Sciences
[2] Department of Global Health, Medicine and Welfare, Nagasaki University Graduate School of Biomedical Sciences

In Graves' disease, one of the postoperative complications of surgical treatment is symptomatic hypocalcemia, which is defined as symptoms of hypocalcemia such as tetany, paresthesia, and muscle cramps. The aim of this study was to evaluate the preoperative factors predicting the development of symptomatic hypocalcemia after thyroidectomy in Graves' patients. One hundred nine patients with Graves' disease underwent surgery between January 2005 and August 2010 in our department. We investigated the relationship between postoperative symptomatic hypocalcemia and the serum levels of preoperative thyroid hormones, preoperative biochemical tests, and operating states in these patients. A univariate analysis determined that the preoperative serum free triiodothyronine (T3), free thyroxin (T4), and alkaline phosphatase (ALP) levels before the administration of potassium iodide were significantly higher in the symptomatic hypocalcemia patients. A multivariate analysis shows the preoperative serum free T4 level before the administration of potassium iodide to also be significantly higher in the symptomatic hypocalcemia patients. In conclusion, the preoperative serum free T4 level before the administration of potassium iodide was thus determined to be a risk factor for developing postoperative symptomatic hypocalcemia.

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Introduction

Graves' disease is the most common cause of hyperthyroidism. In Europe and Japan, there has been a greater physician preference for antithyroid medication and surgery (1). If surgery is chosen as the primary therapy for Graves' disease, the American Thyroid Association and American Association of Clinical Endocrinologists recommend either a near-total or total thyroidectomy as the procedure of choice (1). Temporary symptoms of hypocalcemia, such as paresthesia of the distal extremities and circumoral area, the Chovostek and Trousseau sign, muscle cramps, laryngospasms, tetany, and seizures, are postoperative complications of the surgical treatment of Graves' disease. Hypocalcemic symptoms lead to patient distress and prolonged hospitalization (2). In addition, patients undergoing thyroidectomy for Graves' disease are more likely to have postoperative hypocalcemia than patients undergoing total thyroidectomy for other indications (3). In this study, we evaluated the factors associated with postoperative symptomatic hypocalcemia by examining the standard clinical parameters measured for all preoperative patients.

Patients and Methods

We studied 109 patients with Graves' disease who underwent near-total, or total thyroidectomy between January

Address correspondence: Kosho Yamanouchi, M.D. Ph.D., Department of Surgery, Nagasaki University Graduate School of Biomedical Sciences 1-7-1, Sakamoto, Nagasaki, Japan 852-8501
Tel: (81)-95-819-7316, Fax: + (81)-95-829-7319, E-mail: ymanouch@gk9.so-net.ne.jp

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2005 and August 2010. Graves' disease was defined by the presence of thyrotoxicosis, a diffuse goiter, and serum TSH receptor antibody or thyroid stimulating antibody. Forty patients were operated on due to side effects associated with the antithyroid medication. Twenty-four patients were operated on due to a poor control of the thyroid function. Fifteen patients were operated on due to a poor compliance of antithyroid medication. Thirty patients were operated on at the patients' requests, due to such factors as early remission, cosmetic deformity, and a desire to conceive a child soon after treatment

Potassium iodide (KI) was given for 1 or 2 weeks prior to surgery to all patients. Steroid treatment was added for patients who still exhibited hyperthyroidism on admission, despite the administration of KI.

Free free thyroxin (T4), free triiodothyronine (T3), thyroid stimulating hormone (TSH), alkaline phosphatase (ALP), albumin, phosphorus, and total calcium were examined before the administration of KI. After a week of the administration of KI, Free T4, free T3, TSH were examined again. ALP and total calcium were examined on the first postoperative day. After the patients were discharged, we followed hypocalcemia every 3 to 4 months until it improved.

Postoperative symptomatic hypocalcemia was defined as follows. The hypocalcemic symptoms such as a tingling or 'pins and needles' sensation in and around the mouth and lips, and in the extremities, muscular cramps, carpopedal spasms, and tetany developed during a week after the operation. Moreover, treatment of the hypocalcemia, which involved the infusion of calcium gluconate and oral calcium and vitamin D administration, improved the symptoms. There were no patients with permanent hypoparathyroidism, permanent recurrent laryngeal nerve paralysis, or postoperative bleeding. The serum calcium in all patients was greater than 2.25 mmol/l during the preoperative period.

The serum corrected calcium (mmol/l) level was calculated by the following formula:Calcium concentration (mmol/l) + 1 - (albumin (g/l)/40)

Statistical analysis

The 109 patients were separated into two groups; patients with postoperative symptomatic hypocalcemia (with hypocalcemia group) and patients without postoperative symptomatic hypocalcemia (without hypocalcemia group). The data were expressed as the means ± standard deviation (SD) or medians. Continuous valuables were evaluated by Student's *t*- test or Wilcoxon's test, as appropriate. Categorical variables were analyzed using the chi-square test or Fisher's exact test. Fisher's exact test was applied if the theoretical frequency was less than five. A multiple logistic regression analysis was used to assess simultaneous effects of factors on postoperative symptomatic hypocalcemia. The odds ratio and the 95% confidence interval were calculated for each covariate predictors included in the model. P value < 0.05 was considered to be statistically significant. These statistical analyses were performed using the SAS-JMP software programs for Windows (SAS Institute Inc. Cory, NC).

Results

Table 1 shows the clinical characteristics of the 109 patients, which included 80 females and 29 males, with Graves' disease. The median age of all patients was 34 years. The serum free T4 and T3 levels before the administration of KI were higher than the serum free T4 and T3 levels during the administration of KI ($P < 0.001$). Forty -four patients had high serum ALP concentrations during the preoperative period before the administration of KI. The median length of the operation was 180 minutes, and the median blood loss was 90 g.

Table 2 shows the differences in the symptomatic and non-symptomatic groups. Twenty-four patients (22%) developed symptomatic hypocalcemia during the postoperative period. There were no significant differences in the sex, age, length of operation, or blood loss between the two groups. The preoperative serum free T3 and free T4 levels before the KI administration were significantly higher in the with hypocalcemia group than the without hypocalcemia group ($P < 0.001$, both). The preoperative serum free T3 and free T4 levels on admission were also significantly higher in the with hypocalcemia group ($P = 0.03$ and $P < 0.01$, respectively). The preoperative serum calcium and corrected calcium levels were significantly also higher in the with hypocalcemia group ($P = 0.05$ and $P = 0.03$, respectively), as was the preoperative serum ALP ($P=0.01$).

When a multiple logistic regression analysis was performed to evaluate the confounding factors, the preoperative serum free T4 levels before the KI administration was found to be significantly associated with postoperative symptomatic hypocalcemia (Table 3).

Seventy-six patients had a high level of thyroid function (serum free T4 > 20.21 pmol/l) before the KI administration. The sensitivity and specificity of high level of thyroid function before the KI administration was 0.92 and 0.37 for predicting postoperative symptomatic hypocalcemia Hy-

perthyroidism provided reassuring information that patients with a normal thyroid function almost developed symptomatic hypocalcemia after surgery for Grave's disease (negative predictive values; NPV= 0.94).

Discussion

Calcium is present in serum in a form bound to albumin (40-45%), ionized (45-50%) or complexed to inorganic anions (5-10%). The ionized calcium is physiologically the most important fraction (4). The symptoms of hypocalcemia generally correlate with the magnitude and speed of the decrease in the serum calcium level (5). Manifestations of neuromuscular irritability develop, and hypocalcemia can cause paresthesia of the distal extremities and circumoral area, the Chovostek and Trousseau sign, muscle cramps, laryngospasms, tetany, and seizures (5). In acute symptomatic hypocalcemia, these symptoms usually occur at concentrations of 1.88 mmol/l or less and warrant rapid parenteral administration of calcium (5). In this study, we targeted symptomatic hypocalcemia, because hypocalcemia needs to be treated as soon as possible when patients develop symptoms. Furthermore, the postoperative serum calcium levels in all patients decreased despite supplementation with calcium and the patients developing symptomatic hypocalcemia had significantly lower serum calcium levels than the non-symptomatic patients in a postoperative state ($P < 0.001$).

Table 1. Basic characteristics of 109 patients with Graves' disease

Factor	Value	normal range
Sex : female/male	80:29	
Age (year)	34.7 ± 13.9	
Preoperative State (before KI administration)		
calcium (mmol/l)	2.41 ± 0.11	2.25-2.65
corrected calcium (mmol/l)	2.42 ± 0.12	2.25-2.65
phosphorus (mmol/l)	1.19 ± 0.22	0.81-1.52
albumin (g/dl)	42.3 ± 3.5	40.0-50.0
alkaline phosphatase (IU/l)	357.8 ± 186.4	115-359
free T3 (pmol/l)	16.7 ± 12.1	3.0 - 6.5
free T4 (pmol/l)	39.5 ± 27.7	10.0 - 23.0
TSH (mIU/l)	0.0013 ± 0.0078	0.450-5.080
Preoperative State (during KI administration)		
free T3 (pmol/l)	2.63 ± 1.59	3.0 - 6.5
free T4 (pmol/l)	22.1 ± 13.3	10.0 - 23.0
TSH (mIU/l)	0.0013 ± 0.0045	0.450-5.080
Operating state		
Operation time (minutes)	187.2 ± 53.1	
Blood loss in operation (g)	155.1 ± 202.0	
valume of resection (g)	65.08 ± 74.1	
valume of the rest (g)	3.38 ± 1.71	
Postoperative State (post operative day 1)		
calcium (mmol/l)	2.14 ± 0.17	2.25-2.65
decreased level of calcium (mmol/l)	0.28 ± 0.2	

Values were given as mean ± standard devision for normal distribution or median (interquartile range) for skew distribution, except for sex. The serum corrected calcium (mmol/l) level was calculated by the following formula: Calcium concentration (mmol/l) + 1 - (albumin (g/l)/40). KI: potassium Iodide, free T3: free triiodothyronine, free T4: free thyroxin, TSH: thyroid stimulating hormone

Table 2. Comparison between patients with and without postoperative hypocalcemia

Factor	With hypocalcemia group (n=24)	Without hypocalcemia group (n=85)	P-value
Sex female : male	17:7	63:22	0.75
Age (year)	33.3 ± 10.3	35.1 ± 14.8	0.84
Preoperative State (before KI administration)			
calcium (mmol/l)	2.44 ± 0.13	2.40 ± 0.10	0.21
corrected calcium (mmol/l)	2.45 ± 0.12	2.41 ± 0.11	0.03
phosphorus (mmol/l)	1.25 ± 0.25	1.17 ± 0.21	0.14
albumin (g/dl)	41.4 ± 3.3	42.6 ± 3.5	0.13
alkaline phosphatase (IU/l)	448.4 ± 228.6	332.2 ± 165.4	0.01
free T3 (pmol/l)	25.3 ± 12.9	14.3 ± 10.8	<0.001
free T4 (pmol/l)	61.5 ± 28.6	33.3 ± 24.1	<0.001
TSH (mIU/l)	0.012 ± 0.016	1.70 ± 8.78	0.78
Preoperative State (during KI administration)			
free T3 (pmol/l)	11.5 ± 7.74	8.09 ± 5.03	0.03
free T4 (pmol/l)	31.0 ± 16.8	19.5 ± 11.1	<0.01
TSH (mIU/l)	0.011 ± 0.009	1.67 ± 4.98	0.52
Operating state			
Operation time (minutes)	179.5 ± 44.0	189.3 ± 55.5	0.80
Blood loss in operation (g)	105.0 ± 93.5	169.2 ± 221.8	0.20
valume of resection (g)	49.5 ± 35.2	69.5 ± 81.4	0.85
valume of the rest (g)	2.89 ± 1.84	3.52 ± 1.67	0.13
Postoperative State (post operative day 1)			
calcium (mmol/l)	2.03 ± 0.06	2.17 ± 0.15	<0.001
decreased level of calcium (mmol/l)	0.41 ± 0.20	0.23 ± 0.17	<0.001

Values were given as mean ± standard devision for normal distribution or median (interquartile range) for skew distribution, except for sex. The serum corrected calcium (mmol/l) level was calculated by the following formula: Calcium concentration (mmol/l) + 1 - (albumin (g/l)/40). KI: potassium iodide, free T3: free triiodothyronine, free T4: free thyroxin, TSH: thyroid stimulating hormone

Table 3. Odds ratio (OR) and 95% confidence interval (CI) for postoperative symptomatic hypocalcemia ,as assessed using multiple logistic regression analysis

Factor	Unit	OR	95% CI	p Value
age	every 10 years	1.12	0.74 to 1.63	0.6
Sex (male/female)		0.97		0.96
Free T4	every 10 pmol/L	1.43	1.18 to 1.76	<0.001
ALP	every 100 IU/L	1.22	0.94 to 1.62	0.14

Free T4: free thyroxin, ALP: alkaline phosphatase
Free T4 and ALP were mesured before the administration of Potassium iodide.

According to a multivariate analysis, we showed the free T4 levels to be a risk factor for postoperative symptomatic hypocalcemia. This finding is supported by the fact that thyroid hormones have been associated with the bone metabolism due to thyroid hormone receptors in human bone (6). Accelerated bone turnover caused by the direct stimulation of bone cells triggers bone loss in patients with hyperthyroidism (6-8). In the hyperthyroid state, increased bone resorption leads to increased serum calcium concentrations and suppression of circulating parathyroid hormone (PTH) (9). According to Pantazi et al, after treatment for hyperthyroidism, the serum calcium concentrations tend to decline (9). At this time, increased PTH concentrations seem to play a role in calcium deposition to the bone (9). The abnormal calcium deposition to the bone is often observed as long as a year after the beginning of antithyroid treatment, despite the euthyroid conditions (9). Therefore, it is important to carefully evaluate to thyroid functions before preparation with KI when considering the status of preoperative bone metabolism, Postoperative normalization of bone metabolism cause calcium deposition (10). These phenomena were kwon as hunger bone syndrome.

Our current study showed that there is a relationship between hyperthyroidism and the incidence of postoperative symptomatic hypocalcemia. Preoperative hyperthyroidism were considered to be the risk of postoperative symptomatic hypocalcemia, although there were hardly postoperative symptomatic hypocalcemia in the patients with preoperative euthyroidism.

Some limitations associated with this study include its retrospective nature, and the fact that it was done in a single center. Accordingly, a prospective study in a larger number of patients will be required using well-matched groups of patients to confirm our findings. Moreover, for effective prevention of postoperative symptomatic hypocalcemia, it will be necessary to evaluate bone metabolism, such as by monitoring bone density and bone turnover markers, such as PTH and 25-hydroxy vitamin D3 (11). The serum calcium levels and intact PTH were also required when symptoms of hypocalcemia develop after the operation for correctly diagnosing the symptomatic hypocalcemia

In conclusion, the free T4 level before the administration of KI was found to be a risk factor for postoperative symptomatic hypocalcemia. Patients who have hyperthyroidism and before the KI administration might therefore have insufficient calcium in their bones and thereby may easily develop postoperative symptomatic hypocalcemia.

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