

Reliable Early Prediction for Different Types of Post-Thyroidectomy Hypocalcemia

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Objectives. High incidence of hypocalcemia after thyroidectomy is a major determinant in delay of discharge. Even though many studies have focused on the search for reliable early predictors of postoperative hypocalcemia, definitions of hypocalcemia are diverse; therefore, interpretation and application of previously reported findings may not be easy. We aimed to elucidate diverse patterns of post-thyroidectomy hypocalcemia and to provide reliable early predictors for these different types of hypocalcemia.

Methods. Retrospective chart review was performed and eligible 112 patients of thyroidectomy were categorized into four groups according to symptomatic and/or biochemical hypocalcemic criteria. A mismatch of occurrence and the timing of symptomatic or biochemical abnormalities were evaluated. Predictive values of commonly used biomarkers were compared in each group; levels of serum total calcium and ionized calcium, and intact parathyroid hormone (PTH).

Results. Among 62 hypocalcemic patients, 45 patients (72.5%) experienced both symptomatic and biochemical abnormalities during hospitalization. A mismatch on the timing of initial detection of symptomatic and biochemical hypocalcemia was observed in 21 patients (46.6%). Intact PTH level measured at 1 hour was a useful indicator in prediction of symptomatic hypocalcemia with 79.7-87.4% of diagnostic accuracy. Serum ionized calcium measured next morning after surgery was a reliable predictor of biochemical hypocalcemia with 77.9-94.8% of diagnostic accuracy.

Conclusion. For the safety of patients, the possibility of both symptomatic and biochemical hypocalcemia should be considered together before deciding early discharge. Using intact PTH for symptomatic hypocalcemia and day-1 ionized serum calcium level for biochemical hypocalcemia will be helpful for the reliable prediction of heterogeneous nature of postoperative hypocalcemia.

Key Words. *Hypocalcemia, Parathyroid hormone, Thyroidectomy, Early diagnosis, Postoperative complications*

INTRODUCTION

Hypocalcemia is one of the most common complications of thyroidectomy; the reported incidence of transient hypocalcemia

ranges from 0.3% to 49%, and that of permanent hypocalcemia ranges from 0% to 13% (1). Given the high incidence of transient hypocalcemia, concerns about postoperative hypocalcemia often become a major determinant in delay of early discharge (2). Even though close monitoring of serum calcium level is a standard of care for the patient who undergoes thyroidectomy (3-6), it has limitations as an early predictor of postoperative hypocalcemia, because the lowest concentration of serum calcium is usually not reached until 48 hours after thyroidectomy (7).

Many recent studies have focused on the search for reliable early predictors of postoperative hypocalcemia. Monitoring the level of serum total calcium (Ca) or ionized calcium (iCa⁺⁺), cal-

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culating slopes in the change of Ca or iCa^{++} levels, measuring intraoperative or standard intact parathyroid hormone (iPTH) level, and making a new algorithm by combining more than two of these values have all been reported as useful predictors (4, 8-11). However, the definitions of hypocalcemia that were used in these studies are diverse; therefore, the reported cut-off values of Ca, iCa^{++} , and PTH levels for prediction of hypocalcemia are also widely variable. Moreover, some studies focused only on the prediction of biochemical hypocalcemia (12, 13); however, in practice, observation of a mismatch between the presence of hypocalcemic symptoms and biochemical abnormalities is not uncommon. Therefore, there may be confusion in the interpretation of these data and limitations in the clinical application of previously reported findings.

In this study, we subdivided the study cohort into four groups according to symptomatic and/or biochemical hypocalcemic criteria. Chronological dissociation in the initial presentation of hypocalcemic symptoms and the initial detection of biochemical hypocalcemia was evaluated in order to understand the different characteristics of symptomatic and biochemical hypocalcemia. Predictive values of previously well-known biomarkers were compared in each group; Ca and iCa^{++} , iPTH, and the slopes of changes in Ca, iCa^{++} , and iPTH. A simple new algorithm is proposed for the early and reliable prediction of post-thyroidectomy hypocalcemia; for both symptomatic and biochemical hypocalcemia.

MATERIALS AND METHODS

We retrospectively reviewed medical records of 123 consecutive patients who underwent total thyroidectomy with or without neck dissection (ND) and who were hospitalized for more than 3 days after the surgery between May 2004 and July 2005. At

that period of time, patients were usually hospitalized for more than 3 days after surgery and daily routine follow-up of biochemical markers were performed for screening of possible postoperative hypocalcemia. All the surgery was performed by one of the authors (YIS). Operation records, progression notes, nursing charts, and results of blood tests were noted. This study was approved by the Institutional Review Board of Samsung Medical Center (IRB-2010-05-068-001).

Because Ca or iCa^{++} is known to reach its lowest level on the third day after thyroidectomy in hypocalcemic patients (11), Ca and iCa^{++} levels were measured before surgery (within 2 month before surgery), at 1 hour, and every morning for 3 days after surgery. Immediate postoperative level was checked at 1 hour after surgery at PACU (post-anesthesia care unit). Using an immunoradiometric assay (ELSA-PTH, October 2004-model 13, Cis bio international, France), blood iPTH (reference value of our institution; 11-62 pg/mL) level was checked at 1 hour and the next morning after surgery. Slopes of changes in Ca, iCa^{++} , and iPTH levels were calculated using values obtained at 1 hour and the next morning after surgery (3). Routine biochemical tests were repeated at 3 month after the surgery. If there was an evidence of hypocalcemia, additional laboratory test was performed according to the patients' hypocalcemic status.

Among 123 patients, 11 patients were excluded from the study due to missing one or more of the laboratory tests described above. Twenty two male and 90 female patients (total 112 patients) were finally enrolled for this study. Their ages ranged from 17 to 79 years old, with a mean of 51. One hundred seven patients were diagnosed as papillary carcinoma, 4 patients as follicular carcinoma, and 1 patient as medullary carcinoma. Total thyroidectomy with ND (anterior compartment and/or lateral ND) was performed in 70 patients (62.5%). Autotransplantation of parathyroid glands was performed in 29 patients (25.9%). Patients' demographic characteristics are summarized at Table 1.

Table 1. Clinical characteristics of the patients

Variable	S-B- group	S+B+ group	S+B- group	S-B+ group	P-value
No. of patients (%)	50 (44.6)	45 (40.1)	9 (8.0)	8 (7.1)	
Sex (male : female)	10 : 40	8 : 37	2 : 7	2 : 6	0.979
Median age (years)	50.1	48.0	47.0	57.5	0.123
Histopathology of tumor					
Papillary carcinoma	48	42	9	8	0.770
Follicular carcinoma	2	2	-	-	
Medullary carcinoma	-	1	-	-	
Size of tumor (cm)	1.95±2.2	1.8±2.4	2.5±2.3	1.4±0.83	0.822
Types of surgery					
TT	29	7	4	2	0.001
TT with ACND	15	24	1	2	
TT with ACND and LND	6	14	4	4	
Parathyroid autotransplantation	7	15	4	3	0.236
Permanent hypocalcemia	0	2 (1.8%)	0	0	0.129

S-B-: normocalcemia group; S+B+: symptomatic and biochemical hypocalcemia group; S+B-: only symptomatic hypocalcemia group; S-B+: only biochemical hypocalcemia group; TT: total thyroidectomy; ACND: anterior compartment neck dissection; LND: lateral neck dissection.

Symptomatic hypocalcemia was defined when there was any episode of symptoms or signs of hypocalcemia during the hospital stay; perioral numbness, tingling sense or paresthesia of hands and/or feet, Chvostek sign, Trousseau sign, muscle cramp, or tetany. The patients were asked to report any postoperative symptoms and signs of hypocalcemia, which were educated by corresponding medical staffs when they admitted to an inpatient ward. If they reported their discomfort associated with hypocalcemia, an assigned nurse or a doctor determined whether it was a real hypocalcemic symptom or non-specific one. When it was regarded as a reliable hypocalcemic symptom, it was recorded in the nursing chart or in the progression note and those events were counted as symptomatic hypocalcemia in this study. Biochemical hypocalcemia was defined when any one of the checked Ca levels dropped below 8.0 mg/dL or when iCa^{++} level went under 1.05 mmol/L. These values have been used to define post-thyroidectomy hypocalcemia in much of the literature, although they are lower than the reference ranges. In our hospital, reference value of Ca is in between 8.4 mg/dL and 10.2 mg/dL, and that of iCa is in between 1.05 mmol/L and 1.35 mmol/L. Permanent hypocalcemia was defined as persistent symptomatic or biochemical hypocalcemia for more than 6 months after the surgery. Postoperatively, oral calcium supplements (calcium carbonate 1.5 g per day) were routinely provided for all patients. Patients who developed symptomatic hypocalcemia were managed with additional intravenous calcium gluconate and/or oral vitamin D supplementation in addition to oral calcium carbonate.

For comparison of the characteristics of symptomatic vs. biochemical hypocalcemia, patients were categorized into four groups; patients who presented with both symptomatic and biochemical hypocalcemia (S+B+ group), patients with only symptomatic hypocalcemia (S+B- group), patients with only biochemical hypocalcemia (S-B+ group), and patients without symptomatic or biochemical evidence of hypocalcemia (S-B- group). Occurrence and onset timing of biochemical and symptomatic hypocalcemia are plotted in Fig. 1. Obtained values (mean \pm standard deviations) of the candidate biomarkers, which included Ca, iCa^{++} , and $iPTH$ levels at 1 hour or 1 day after surgery, and slopes of the changes in Ca, iCa^{++} , and $iPTH$ levels are compared in Table 2. Predictive accuracy of these biomarkers in each group are summarized in Table 3.

Statistical analysis was performed using a commercially available software package (SPSS ver. 13.0; SPSS Inc., Chicago, IL, USA). ANOVA test was used when comparing group means or frequencies. Chi-square test was used for the analysis of diagnostic accuracy of different biomarkers between each group.

RESULTS

Incidence of hypocalcemia (Table 1)

Transient symptomatic or biochemical hypocalcemia developed

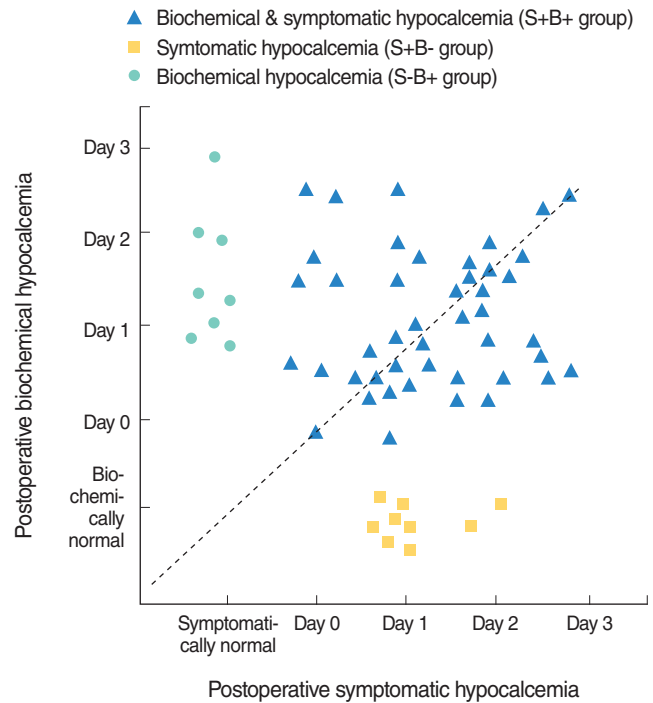


Fig. 1. Mismatch on the occurrence of symptomatic and biochemical hypocalcemia. In 45 patients of the S+B+ group (triangles), 24 patients presented with symptomatic and biochemical abnormalities on the same day (triangles along a dotted line) and the remaining 21 patients on different days of the hospital stay (scattered triangles). Nine patients presented with only symptomatic hypocalcemia (S+B- group, rectangles), while 8 patients revealed only biochemical hypocalcemia (S-B+ group, circles).

in 62 patients (62/112, 55.3%) and permanent hypocalcemia in 2 patients (1.8%). Among the 62 hypocalcemic patients, 45 patients (45/62, 72.5%) experienced both symptomatic and biochemical abnormalities during the hospital stay; thus, they were subgrouped into the S+B+ group. Nine patients (14.5%) met the criteria for symptomatic hypocalcemia only (S+B- group), while 8 patients (12.9%) showed only biochemical hypocalcemia (S-B+ group).

Anterior compartment ND was performed in 42 patients. Both anterior compartment and lateral ND was performed in 28 patients (totally 70 patients). Lateral ND was performed as a therapeutic intent in all patients. In contrast, clinical suspicion of anterior compartment lymph node metastasis was given in only 13 patients (31%). In overall, therapeutic ND was performed in 41 patients and prophylactic ND was performed in 29 patients. In a prophylactic ND group (n=29), number of S-B- group was 10, S+B+ group was 13, S+B- group was 1, S-B+ group was 1 patient respectively. In a therapeutic ND group (n=41), S-B- group was 11, S+B+ group was 25, S+B- group was 4, S-B+ group was 5 patients respectively. This was not a statistically significant difference.

Table 2. Comparison of measured parameters (mean ± standard deviation) in each group

	S-B- (n=50)	S+B+ (n=45)	S+B- (n=9)	S-B+ (n=8)	P-value
Total calcium (mg/dL)					
Postop-1H	8.68 ± 0.42 ^a	8.31 ± 0.58 ^a	8.72 ± 0.67	8.36 ± 0.74	^a < 0.05
Next morning	8.27 ± 0.39 ^b	7.54 ± 0.44 ^{b, c}	8.00 ± 0.39 ^c	7.95 ± 0.45	^b < 0.001 ^c < 0.05
Ionized calcium (mmol/L)					
Postop-1H	1.12 ± 0.04	1.10 ± 0.05	1.11 ± 0.05	1.10 ± 0.04	NS
Day 1	1.11 ± 0.05 ^{d, e}	0.99 ± 0.07 ^{d, f}	1.06 ± 0.04 ^f	1.01 ± 0.05 ^e	^{d, e} < 0.001 ^f < 0.05
Slope of changes (postop-1H & day 1)					
Total calcium	-0.25 ± 0.22 ^g	-0.46 ± 0.34 ^g	-0.50 ± 0.57	-0.28 ± 0.46	^g < 0.05
Ionized calcium	-0.13 ± 0.67 ^h	-1.44 ± 1.23 ^h	-0.65 ± 0.60	-1.17 ± 0.36	^h < 0.001
Standard iPTH (pg/mL)					
Postop-1H	20.7 ± 12.7 ^{i, j}	4.04 ± 2.82 ^j	5.62 ± 3.55 ^j	13.8 ± 9.87	^{i, j} < 0.001
Day 1	20.1 ± 7.78 ^{k, l}	4.31 ± 3.23 ^k	9.22 ± 6.08 ^l	12.5 ± 10.6	^k < 0.001 ^l < 0.05

S-B-: normocalcemic group; S+B+: symptomatic and biochemical hypocalcemic group; S+B-: symptomatic hypocalcemic group; S-B+: biochemical hypocalcemic group; Postop-1H: levels measured at 1 hour after surgery; NS: not significant; a to l: each alphabet indicate that the certain P-value was calculated from comparing the corresponding values that have been the same upper-note alphabet.

Table 3. Predictive abilities (%) of tested parameters in each hypocalcemic group

	Sensitivity	Specificity	PPV	NPV	DA
Total calcium (mg/dL) at day 1					
S+B+	44.4	96.0	90.9	65.8	71.6
S+B-	22.2	96.0	50.0	87.3	84.7
S-B+	0.0	96.0	0.0	85.7	82.8
Ionized calcium (mmol/L) at day 1					
S+B+	53.3	100.0	100.0	70.4	77.9
S+B-	0.0	100.0	0.0	84.7	84.7
S-B+	62.5	100.0	100.0	94.3	94.8
Slope of changes between 1 hour and 1 day after surgery					
Total calcium					
S+B+	88.9	24.0	51.3	70.6	54.7
S+B-	77.8	24.0	15.6	85.7	32.2
S-B+	87.5	24.0	15.6	92.3	32.8
Ionized calcium					
S+B+	93.3	44.0	60.0	88.0	67.4
S+B-	88.9	44.0	22.2	95.7	50.8
S-B+	100.0	44.0	22.2	100.0	51.7
Standard intact PTH (pg/mL)					
One hour after surgery					
S+B+	100.0	76.0	78.9	100.0	87.4
S+B-	100.0	76.0	42.9	100.0	79.7
S-B+	50.0	76.0	25.0	90.5	72.4
Day 1					
S+B+	81.4	91.1	89.7	83.7	86.4
S+B-	57.1	83.7	33.3	93.2	80.4
S-B+	50.0	83.7	33.3	91.1	78.9

PPV: positive predictive value; NPV: negative predictive value; DA: diagnostic accuracy; S+B+: symptomatic and biochemical hypocalcemic group; S+B-: symptomatic hypocalcemic group; S-B+: biochemical hypocalcemic group; PTH: parathyroid hormone.

Mismatch on the occurrence of symptomatic and biochemical hypocalcemia (Fig. 1)

Of 45 patients in the S+B+ group, 24 patients (24/45, 53.3%) presented with symptomatic and biochemical abnormalities on the same day. A mismatch on the occurrence timing of symptomatic or biochemical hypocalcemia was observed in the other 21 S+B+ patients (21/45, 46.6%), which corresponded to 33.9% of all transient hypocalcemic patients (21/65). There was a 1-day gap between the initial occurrence of symptoms/signs and biochemical abnormality in 11 patients (17.7%), a 2-day gap in 8 patients (12.9%), and a 3-day gap in 2 patients (3.2%).

Comparison of biomarkers in each group (Table 2)

Mean values of Ca and iCa⁺⁺ measured at 1 hour after surgery in the recovery room were in the range of 8.31-8.68 mg/dL and 1.10-1.12 mmol/L, respectively, which were all above the hypocalcemic criteria in the every group. However, Ca and iCa⁺⁺ measured on the morning after surgery (day 1) showed wide ranges across the hypocalcemic criteria. Day 1 iCa⁺⁺ level of S-B- patients (1.11 ± 0.05 mmol/L) was within the reference value and was statistically higher than that of S-B+ (1.01 ± 0.05 mmol/L) and S+B+ (0.99 ± 0.07 mmol/L) patients, which belonged to the criterion for biochemical hypocalcemia (1.05 mmol/L). Slopes of changes in Ca or iCa⁺⁺ levels were helpful in differentiation of the S-B- group and S+B+ group, but not between the other groups. Standard iPTH levels of the S+B+ and S+B- groups measured either 1 hour or 1 day after surgery were all statistically lower than those of the S-B- group and were below the reported useful criterion, 10 pg/mL (14). However, those of the S-B+ group were 13.8 ± 9.87 pg/mL and 12.5 ± 10.6 pg/mL, respectively, which were not different from those of the S-B- group and above the level of 10 pg/mL. None of the patients experienced symp-

tomatic hypocalcemia when their postoperative iPTH level was higher than 10 pg/mL.

Prediction of postoperative hypocalcemia (Table 3)

Overall diagnostic accuracy of day 1 Ca and iCa^{++} levels ranged from 71.6% to 84.7% and 77.9% to 94.8%, respectively. Standard iPTH level measured 1 hour or 1 day after surgery exhibited diagnostic accuracies ranging between 72.4% and 87.4%. However, slopes of changes in Ca or iCa^{++} levels showed much poorer diagnostic accuracies ranging from 32.2% to 67.4%. In the meanwhile, PTH level obtained at one hour after surgery and iCa^{++} slope obtained at the next morning showed relatively higher sensitivity than the other biomarkers.

DISCUSSION

This study demonstrated the heterogeneous nature of symptomatic and biochemical hypocalcemia. Among 62 hypocalcemic patients, 17 patients (27.4%) exhibited either symptomatic or biochemical hypocalcemia. Even though 45 of 62 hypocalcemic patients (72.5%) experienced both symptomatic and biochemical abnormalities during their three-day hospital stay, 21 of these patients (33.9%) had mismatches in the timing of initial presentation or occurrence between symptomatic and biochemical hypocalcemia. Therefore, for reliable prediction of postoperative hypocalcemia, both symptomatic and biochemical hypocalcemic criteria should be considered together.

The reason for these mismatches in the timing of initial presentation or in the occurrence of symptomatic and biochemical hypocalcemia is not clear. We speculate that routine postoperative oral calcium supplementation might influence on developing symptomatic hypocalcemia and/or biochemical hypocalcemia. Routine supplementation of oral calcium might obscure an early detection of hypocalcemia as well. Velocity of calcium reduction also influence on the onset of symptoms of hypocalcemia, since hypocalcemic symptoms are usually influenced not only by serum total calcium level but also by the velocity of calcium reduction (15). Another possibility is an over-diagnosis of symptomatic hypocalcemia in this study since we defined as symptomatic hypocalcemia if there is any event of tingling sensation regardless of its severity. In our study, numbness or tingling sense of the lip, hands, or feet was the most common symptom. The Chvostek sign was observed only in 5 patients. None of the patients experienced myalgia, muscle spasm, hypotension, or abnormal findings on EKG that were attributable to the low level of serum calcium. In most of the cases, postoperative symptomatic hypocalcemia was easily controlled with intravenous infusion of calcium gluconate \pm oral vitamin D administration.

Relatively strict criteria for hypocalcemia adopted in this study, inclusion criteria of more than 3 days of hospitalization and selection of the patient cohort who received total thyroidectomy \pm

ND, thus inducing a bias of selecting more patients with complications, might explain the relatively higher incidence of transient hypocalcemia (58%) observed in this study. Also, designated study period belongs to an early experience of thyroidectomy of the author (YIS). And relatively higher rate of ND is also attributed to higher incidence of hypocalcemia. Anterior compartment ND \pm lateral ND was performed in 70 of 112 patients (63%) and hypocalcemia developed in 51 of these 70 patients (72.8%). Permanent hypocalcemia occurred in 2 patients (1.8%) of ND, and these two patients belonged to the S+B+ group.

We performed autotransplantation of the parathyroid gland in sternocleidomastoid muscle when discolored tissue was confirmed as a parathyroid gland by frozen biopsy. One or two parathyroid glands was autotransplanted in 29 of 112 patients (25.9%), and 22 of them (75.9%) experienced postoperative hypocalcemia. As noted before (16), higher incidence of hypocalcemia was observed in this patient group of parathyroid autotransplantation (Table 1, $P=0.016$).

Many studies have focused on the search for reliable early predictors of postoperative hypocalcemia in the hope of safe early discharge after thyroidectomy, including continuous monitoring of serum calcium level for at least postoperative 23 hours (16) and routine oral calcium supplementation for all patients (17). Even though an upward-sloping curve of Ca level is reported to be predictive of no occurrence of postoperative hypocalcemia (3, 18), upward-sloping of Ca or iCa^{++} was an infrequent event (14% or 21%, respectively) in this study and their diagnostic accuracies, specificities, and positive predictive values were relatively poor. Because iPTH has a very short half life (less than 5 minutes) (19, 20) and a high sensitivity and high specificity ranging between 80% to 100%, intraoperative iPTH is currently the most emphasized biomarker (11, 12, 14, 21). In this study, iPTH level measured at 1 hour after surgery showed high sensitivity and high negative predictive value in the S+B+ and S+B- groups. And none of the patients experienced symptomatic hypocalcemia when postoperative iPTH level was higher than 10 pg/mL. However, its ability for prediction of the S-B+ group widely ranged from 25.0% to 90.5%. Therefore, measurement of iPTH alone will not be sufficient for safe and reliable prediction of heterogeneous types of postoperative hypocalcemia.

Given that 1) none of the patients was symptomatic when postoperative iPTH level was higher than 10 pg/mL, 2) postoperative iPTH level was a useful biomarker in differentiation of normocalcemic patients from S+B- or S+B+ patients with high diagnostic accuracies, and 3) day 1 iCa^{++} level was also useful in differentiation of normocalcemia from hypocalcemia of S-B+ or S+B+ patients with the highest diagnostic accuracy, we propose a relatively simple guideline for an early and reliable prediction of postoperative hypocalcemia by combining iPTH level and day 1 iCa^{++} levels. When iPTH level measured about 1 hour after surgery is equal to or higher than 10 pg/mL, none of the patients will develop symptomatic hypocalcemia; therefore, early

discharge can be considered for them. If iPTH level is lower than 10 pg/mL, discharge should be decided according to the level of iCa⁺⁺ measured at next morning after the surgery. When iCa⁺⁺ level is less than 1.05 mmol/L, more attention including careful observation with calcium supplementation is highly recommended.

In summary, we retrospectively demonstrated that symptomatic and biochemical hypocalcemia after thyroidectomy may differ in their occurrence and onset timing. Therefore, for the safety of patients, the possibility of both symptomatic and biochemical hypocalcemia should be considered together before deciding an early discharge from the hospital. Intact PTH level checked at 1 hour after surgery was useful in prediction of symptomatic hypocalcemia. Serum ionized calcium measured on the morning after surgery was a reliable predictor for biochemical hypocalcemia. Using both iPTH and postoperative iCa⁺⁺ levels will increase the diagnostic accuracy for the early and reliable prediction of postoperative hypocalcemia.

CONFLICT OF INTEREST

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

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