



Original Research

Predictors and risk factors of hypoparathyroidism after total thyroidectomy



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HIGHLIGHTS

- We were able to identify clinical and surgical risk factors for hypoparathyroidism after total thyroidectomy.
- Female gender, bilateral CND, malignancy, and inadvertent parathyroidectomy were risk factors for hypoparathyroidism.
- Relative changes in serum Ca and P levels appeared to be a reliable predictor of hypocalcemia after total thyroidectomy.

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ABSTRACT

Background: The aim of this study was to evaluate the risk factors for hypoparathyroidism after total thyroidectomy and to determine whether early postoperative serum levels of calcium and phosphorus could be used to predict its development.

Materials and Methods: The study group consisted of 1030 patients who had undergone total thyroidectomy at our institution between March 2008 and July 2014. The clinicopathologic characteristics, indications for the operation, and surgical details of normocalcemic and hypocalcemic patients were compared, and variations in serum calcium and phosphorus levels were measured every day after the operation.

Results: Of the 1030 patients, 291 (28.2%) were found to have transient hypocalcemia and 27 (2.6%) had permanent hypocalcemia. On univariate analysis, younger age ($P = 0.001$), female gender ($P < 0.001$), longer operative time ($P = 0.009$), extent of central neck dissection (CND) ($P = 0.003$), and malignancy ($P = 0.005$) were found to be significantly associated with transient hypocalcemia. On multivariate analysis, female gender ($P = 0.001$), extent of CND ($P = 0.017$), and the identification of parathyroid gland (PTG) tissue in permanent pathologic sections were significant factors. In addition, the occurrence of postoperative hypocalcemia was correlated with relative changes in serum calcium and phosphorus levels. Patients whose serum calcium levels decreased over 20% on postoperative day 2 were more likely to develop hypoparathyroidism, with 92% specificity.

Conclusion: Female gender ($P = 0.001$), extent of CND ($P = 0.014$), and PTG in permanent pathologic sections ($P = 0.035$) were found to be significant factors affecting the development of hypocalcemia. Despite some study limitations, we suggest that the relative changes in the serum levels of calcium (20%) and of phosphorus (40%) on the second postoperative day may be reliable predictors of post-thyroidectomy hypoparathyroidism.

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1. Introduction

Postoperative hypoparathyroidism is one of the most common complications following total thyroidectomy, with reports varying from 19 to 38% in patients with transient hypocalcemia and 0–3% in those with permanent hypocalcemia [1]. The primary cause of post-thyroidectomy hypocalcemia is secondary hypoparathyroidism after direct injury, devascularization, obstruction of venous drainage,

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or inadvertent excision of the parathyroid gland (PTG) [2,3]. Post-operative hypocalcemia increased both the hospital stay and the overall cost of treatment [4]. Also, patients who have had symptoms of hypocalcemia can be distressed over its possible recurrence, and others require long-term calcium (Ca) supplementation. Therefore, many surgeons are interested in ways to predict hypocalcemia and begin treatment early to prevent serious complications and avoid delaying the patient's discharge from the hospital.

Although many studies have looked for factors that might predict the development of hypocalcemia after total thyroidectomy, including the patients' clinical and biological characteristics and the different dissection techniques, a general consensus about which risk factors are valid is still lacking. Monitoring serum calcium levels is a traditional method for detecting post-thyroidectomy hypocalcemia [5], but absolute concentrations of serum calcium alone are not sufficient to predict its development [6]. Several researchers have now reported that intact parathyroid hormone (iPTH) levels are a significant predictor of hypocalcemia following total thyroidectomy [6–10]; however, the widespread use of an iPTH assay may be limited owing to its cost and lack of availability. Therefore, in our study, we analyzed clinical and surgical factors related to the development of hypoparathyroidism after total thyroidectomy and estimated the predictive value of relative changes in serum calcium and phosphorus levels, which can be measured in almost all hospitals that perform thyroidectomies.

2. Material and methods

2.1. Patients

All patients who underwent total thyroidectomy at the Kyung Hee University Medical Center, from March 2008 to July 2014 were included in the study. Patients with a history of previous neck surgery or concomitant parathyroid disease or renal failure were excluded. All thyroidectomies were performed by a single surgeon. The study protocol was approved by our institutional review board.

2.2. Lymph node dissection

Cervical lymph node dissections included central neck dissection (CND) and CND combined with lateral neck dissection (LND). LND involved the usual method of removing lymph nodes from levels II to IV or levels II to V, sparing the internal jugular vein, spinal accessory nerve, and sternocleidomastoid muscle.

2.3. Measurements of serum calcium and phosphorus

Serum calcium and phosphorus concentrations (normal ranges = 8.4–10.2 mg/dL and 2.5–5.5 mg/dL, respectively) were measured in all patients prior to thyroidectomy and in the morning on each postoperative day. Serum level of calcium which used for this study was ionic calcium not the corrected serum calcium. Serum levels of iPTH (normal range = 13–65 pg/mL) were measured on postoperative day 2 and were quantified on electrochemiluminescence immunoassay using the sandwich principle.

2.4. Hypocalcemia treatment

At our institution, the policy for treating hypocalcemia was to administer Ca with vitamin D to symptomatic patients only. Ca was injected intravenously until symptoms disappeared, and oral Ca and vitamin D were then administered simultaneously, and oral supplements were included with the patient's 14-day discharge medications. Daily laboratory evaluations were conducted for

patients with symptomatic hypocalcemia until normalization, after which they were discharged. Abnormal sequelae related to hypocalcemia were routinely assessed 2 weeks after the operation, and these evaluations continued on an outpatient basis for 1 year after the operation.

Hypocalcemic signs and symptoms included numbness of the extremities, facial paresthesias, muscular spasms, and Chvostek's or Trousseau's signs. In this study, we defined a "transient hypocalcemia" group, consisting of patients who received Ca replacement to treat such signs and symptoms and who had serum iPTH levels <13 pg/mL regardless of their serum calcium levels. "Permanent hypocalcemia" was defined as iPTH levels <13 pg/mL and the need for Ca or vitamin D supplements for more than 6 months after total thyroidectomy. Of the patients who were treated with oral or IV Ca replacement for hypocalcemia-like symptoms (e.g., paresthesias), 101 had iPTH levels of 13 pg/mL or higher on postoperative day 2 and were therefore reclassified as normocalcemic.

2.5. Statistical analysis

The statistical analysis was conducted with SPSS version 18.0 (SPSS, Chicago, IL, USA) and MedCalc Software bvba version 15.11.4 (MedCalc, Ostend, Belgium). Categorical variables were indicated as frequency, parametric continuous variables with values expressed as means \pm SD, and non-parametric variables expressed as medians with ranges. The Kolmogorov–Smirnov test was used to assess the normality of the data distribution. Differences in frequencies between groups were calculated using Fisher's exact test. Continuous variables between groups were compared using the independent sample *t*-test or the Mann–Whitney *U* test. All statistical tests were two-sided, and a *P* value of <0.05 was considered statistically significant. The predictive ability of the laboratory parameters was tested using the area under the receiver operating characteristic (ROC) curves.

3. Results

3.1. Factors affecting to the development of hypoparathyroidism

Table 1 shows the characteristics of the 1030 patients, 291 (28.2%) of whom had transient hypocalcemia and 27 (2.6%) of whom had permanent hypocalcemia. Factors found on univariate analysis that significantly increased the risk of developing transient hypocalcemia were younger age ($P = 0.001$), female gender ($P < 0.001$), longer operative time ($P = 0.009$), lymph node dissection (CND [$P = 0.003$] and LND [$P = 0.010$]), the extent of CND ($P = 0.003$), PTG autotransplantation ($P = 0.002$), malignant pathology ($P = 0.005$), and evidence of PTG tissue in the permanent pathologic sections ($P < 0.001$). No factors correlated significantly with permanent hypocalcemia (Table 1).

These parameters were analyzed using a logistic regression model to determine the risk of hypocalcemia, and the estimated relative risk was calculated (Table 2). After logistic regression analysis, female gender ($P = 0.001$; odds ratio [OR] = 2.285 [range = 1.391–3.751]), the extent of CND ($P = 0.014$; OR = 1.556 [range = 1.094–2.212]), and the presence of PTG tissue in the permanent pathologic sections ($P = 0.035$; OR = 1.509 [range = 1.030–2.212]) were the significant factors that affected the development of hypocalcemia.

3.2. Relative changes in serum calcium and phosphorus levels

Fig. 1 shows the relative changes in serum calcium and phosphorus levels in normocalcemic and hypocalcemic patient groups. The relative decreases in serum calcium on postoperative days 1

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