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Original Article

Percentage Decline of Parathyroid Hormone Level is a Predictor for Post-thyroidectomy Symptomatic Hypocalcemia

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Conflict of Interest

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

ABSTRACT

Purpose: Postoperative hypocalcemia is one of the most common complications after thyroid surgery. However, the predictive efficacy of parathyroid hormone (PTH) level was still controversial. We investigated the cut-off value of perioperative PTH level for postoperative hypocalcemia after total thyroidectomy.
Methods: Four hundred eighty-two patients performed total thyroidectomy from January 2015 to December 2016 were enrolled. Demographics, operative variables and the development of symptomatic hypocalcemia were collected and evaluated.
Results: Transient symptomatic hypocalcemia occurred in 83 (17.2%) patients and 5 (1.0%) patients have progressed to the permanent hypocalcemia. Patients with transient symptomatic hypocalcemia showed significantly lower postoperative day 1 PTH level than those without hypocalcemia (7.7±6.5 vs. 13.1±10.4 pg/mL; P<0.001), while correlation between postoperative PTH level and development of symptomatic hypocalcemia was not found in a multivariate analysis (P=0.122). Percentage decline of the preoperative PTH only showed significant association with transient hypocalcemia and the recommended cut-off value was 75.0%. When percentage decline of 75.0% was used, the incidence of transient hypoparathyroidism was 3.4 times (95% confidence interval, 2.1–5.6) higher in high percentage decline group (P<0.001). In regard to the permanent hypoparathyroidism, there were no significant differences in all factors.
Conclusion: Percentage decline of PTH can be used as a predictive factor for postoperative hypocalcemia. Cautions against preventing injury of the parathyroid glands with careful surgical technique should be recommended.

Keywords: Parathyroid hormone; Hypoparathyroidism; Thyroidectomy; Hypocalcemia; Sequelae

INTRODUCTION

Thyroid cancer is the most prevalent cancer in Korea, and its incidence has rapidly increased over the past 10 years (1). As thyroidectomy is the mainstay of therapy for thyroid cancer, postoperative complication is the major concern of surgeons and patients (2). Postoperative hypocalcemia is one of the most common complications after thyroid surgery, with the varying incidence from 1.6% to >50.0% (3-6). The causes of the postoperative hypocalcemia

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included surgical trauma to the parathyroid glands, large extent of surgery, inexperience of the surgeon, and concomitant thyroid disease including Graves' disease.

As postoperative hypocalcemia can cause increased length of hospital stay, additional medication, extra blood test, and cost burden on the patients, many researchers have tried to predict postoperative hypocalcemia after thyroid surgery (3). Recent systematic review indicated that perioperative parathyroid hormone (PTH) level, preoperative vitamin D, and postoperative changes of calcium were biochemical predictors of postoperative hypocalcemia (7). Of these factors, postoperative PTH was considered as the most useful predictor of hypocalcemia. However, the predictive ability of PTH level can be affected by the timing of PTH measurement and the cut-off value.

In this context, we evaluated the predictive value of perioperative PTH level for postoperative hypocalcemia after total thyroidectomy.

METHODS

1. Patients

The Institutional Review Boards of the Ewha Womans University Medical Center (Approval No. 2017-09-056) approved this retrospective cohort study. Between January 2015 and December 2016, 485 patients with thyroid cancer underwent total thyroidectomy by a single surgeon. After exclusion of 3 patients with concomitant parathyroid disease, 482 patients were finally included in the present study. Demographic data, preoperative thyroid function, extent of operation, stage of tumor, numbers of removed lymph nodes (LNs), and numbers of sacrificed parathyroid glands were analyzed as well as the development of postoperative symptomatic hypocalcemia.

2. Management protocols

Serum levels of calcium, phosphorus, ionized calcium, and PTH were measured on preoperative day 1, postoperative day 1, postoperative day 14, and postoperative 3 months. Postoperative symptomatic hypocalcemia was defined as an ionized calcium level lower than 4.6 mg/dL (normal range, 4.6–5.4 mg/dL) associated with hypocalcemic symptoms. Hypocalcemic symptoms include perioral numbness, tingling sensations in the fingers or toes, and muscle cramps. In case of mild symptomatic hypocalcemia, patients were supplemented with 1,000–2,000 mg of oral calcium and 1,000 IU of cholecalciferol. When hypocalcemic symptoms were severe or showed no improvement after medication, patients received 2.0 g of intravenous calcium gluconate and were supplemented with 3,000–4,000 mg of oral calcium and 1,000–2,000 IU of cholecalciferol for 2 weeks. Hypocalcemia was considered permanent in patients who required calcium and vitamin D supplementation for longer than 6 months after surgery. All patients were followed-up at 2 weeks, 3 months, 6 months, and annually.

3. Statistical analysis

All results are expressed as mean and standard deviation, absolute numbers, or proportions. Statistical analysis including the Student's t-test, Fisher's exact test, and Mann-Whitney U test was performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). Multivariate logistic regression was used to analyze the relationship between PTH level and development of symptomatic hypocalcemia. Recursive Partitioning And Regression Trees (RPART)

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classification algorithm in R 3.4.2 (R Development Core Team, Vienna, Austria) was used to find the optimal cutting points for PTH level. A 2-sided P value of 0.05 or less were considered statistically significant.

RESULTS

Of the enrolled 482 patients, 406 (84.2%) were female and 76 (15.8%) were male. Mean age of patients was 48.2±12.1 (range, 20–83 years). Total thyroidectomy without neck dissection was performed in 114 patients (23.7%), while combined central neck dissection was done in 368 patients (76.3%). Mean number of retrieved LNs was 5.0±4.2 (range, 0–23), and the median number of sacrificed parathyroid glands was 1.0 (range, 0–3). Preoperative vitamin D level was 36.4±11.3 pg/mL. The mean serum PTH level at preoperative day1 and postoperative day 1 was 32.3±15.2 pg/mL and 23.2±17.0 pg/mL, respectively. Transient symptomatic hypocalcemia occurred in 83 (17.2%) patients and 5 (1.0%) patients have progressed to the permanent hypocalcemia.

Table 1 showed the characteristics of the patients with or without transient symptomatic hypocalcemia. There were no differences in risk factors including extent of surgery, pathologic stage and number of sacrificed parathyroid glands, except laboratory findings at postoperative day 1. Patients with transient symptomatic hypocalcemia showed significantly lower postoperative day 1 PTH level than those without hypocalcemia (7.7±6.5 vs. 13.1±10.4 pg/mL; P<0.001). In a multivariate analysis, however, there was no correlation between postoperative PTH level and development of symptomatic hypocalcemia (odds ratio, 0.965; 95% confidence interval [CI], 0.923–1.009; P=0.122).

Table 1. Comparison of clinicopathological features between patients with and without symptomatic hypocalcemia

Characteristics	Patients with symptomatic hypocalcemia (n=83)	Patients without symptomatic hypocalcemia (n=399)	P value
Age at operation (yr)	47.7±12.0	48.2±11.9	0.720
Female sex	75 (90.4)	331 (83.0)	0.092
Extent of surgery			0.643
Total thyroidectomy	18 (21.7)	96 (24.1)	
Total thyroidectomy with central LN dissection	65 (78.3)	303 (75.9)	
Operative findings			
Tumor size (cm)	0.9±0.6	0.9±0.6	0.844
No. of LN retrieval	4.8±3.7	5.1±4.3	0.682
Median No. of parathyroid glands sacrificed	1.0 (0–3)	1.0 (0–3)	0.170
Pathologic TNM stage			0.429
T1N0	24 (28.9)	92 (23.1)	
T1N1a	6 (7.2)	36 (9.0)	
T1Nx	3 (3.6)	18 (4.5)	
T2N1a	0 (0.0)	2 (0.5)	
T2Nx	1 (1.2)	0 (0.0)	
T3N0	23 (27.7)	108 (27.1)	
T3N1a	21 (25.3)	115 (28.8)	
T3Nx	5 (6.0)	28 (7.0)	
Laboratory findings			
Preoperative vitamin D level (ng/mL)	35.6±10.9	36.6±11.8	0.596
Preoperative day 1 PTH level (pg/mL)	31.5±14.6	32.5±15.3	0.592
Postoperative day 1 PTH level (pg/mL)	7.7±6.5	13.1±10.4	<0.001
Postoperative day 1 ionized calcium level (pg/mL)	1.0±0.1	1.1±0.1	<0.001
Postoperative day 1 total calcium level (pg/mL)	7.5±0.5	8.1±0.6	<0.001

Data shown are mean±standard deviation, number (%), or mean (range).
LN = lymph node; PTH = parathyroid hormone; TNM = tumor, node, and metastasis.

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Table 2. Comparison of clinicopathological features between patients with high percentage decline of PTH and control group

Characteristics	PTH decline over 75% (n=195)	Control (n=287)	P value
Age at operation (yr)	49.3±11.1	47.3±12.4	0.081
Female sex	171 (87.7)	235 (81.9)	0.086
Extent of operation			0.643
Total thyroidectomy	44 (22.6)	70 (24.4)	
Total thyroidectomy with central neck dissection	151 (77.4)	217 (75.6)	
Pathologic characteristics			
Tumor size (cm)	0.9±0.7	0.9±0.6	0.188
No. of LN retrieval	5.1±4.2	5.0±4.3	0.763
Median No. of parathyroid glands sacrificed	1.0 (0–3)	1.0 (0–3)	0.488
Laboratory data			
Preoperative vitamin D level (ng/mL)	35.4±10.8	37.4±11.8	0.179
Preoperative day 1 PTH level (pg/mL)	38.3±13.8	28.3±14.7	<0.001
Postoperative day 1 PTH level (pg/mL)	5.8±2.2	16.5±10.9	<0.001
Transient hypoparathyroidism	54 (27.7)	29 (10.1)	<0.001

Data shown are mean±standard deviation, number (%), or mean (range).
PTH = parathyroid hormone; LN = lymph node.

Using the tree classification algorithm by RPART model, there was no cut-off value for postoperative day 1 PTH measurement. In RPART model, percentage decline of the preoperative PTH only showed significant association with transient hypocalcemia and the recommended cut-off value was 75.0%. When percentage decline of 75.0% was used, the incidence of transient symptomatic hypocalcemia was 3.4 times (95% CI, 2.1–5.6) higher in high percentage decline group (P<0.001). There were no differences in other risk factors, including age, sex, combined central neck dissection, and number of sacrificed parathyroid glands (**Table 2**). There was no significant difference in all factors, because only 5 patients experienced permanent hypocalcemia.

DISCUSSION

In the present study, percentage decline of PTH can be used as a predictive factor for postoperative hypocalcemia and percentage decline of 75.0% showed 3.4 times higher incidence for developing symptomatic hypocalcemia. Postoperative hypocalcemia can be divided into 3 types according to the symptom and laboratory status (8). Symptomatic biochemical hypocalcemia is the most critical problem and may progress to the permanent hypocalcemia. Asymptomatic biochemical hypocalcemia has been presumed to be a stunning of parathyroid during the thyroidectomy or perioperative hemodilution. This condition is not a predisposing factor of permanent hypocalcemia. Some patients experienced hypocalcemic symptoms with mismatched biochemical hypocalcemia, defined as decrease of calcium levels despite normal parathyroid function. Asymptomatic or mismatched hypocalcemia can be managed conservatively and make no significant problems. Therefore, prediction of the symptomatic biochemical hypocalcemia is a matter of great interest.

Many studies have tried to predict and prevent postoperative symptomatic hypocalcemia. Laboratory tests including perioperative PTH level, total calcium, ionized calcium, and phosphorus level were evaluated (3,9-16). In most of these studies, postoperative serum PTH was recommended as the most powerful predictor for post-thyroidectomy hypocalcemia, with a sensitivity ranging from 64% to 100% and a specificity ranging from 72% to 100%. However, some studies questioned the role of the postoperative PTH. Lombardi et al. (17) showed that PTH lacked accuracy to predict hypocalcemia. Del Rio et al. (18) also demonstrated that measurement of PTH was not predictive of hypocalcemia

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by evaluating more than 1,000 patients. These results indicated that the postoperative PTH alone was not sufficient as a predictor of hypocalcemia. In the present study, PTH level at postoperative day 1 also showed no predictive cut-off value for detecting symptomatic hypocalcemia after total thyroidectomy for thyroid cancer.

The single measurement of PTH conflicted with a lack of sensitivity or specificity, depending on the threshold maintained (17,19). To resolve this threshold problem, some investigators studied the PTH decline of the perioperative periods. Lecerf et al. (19) indicated that the PTH decline was more precise than the PTH level alone in early diagnosis of hypocalcemia. Other several studies also have reported that percentage decline of the perioperative PTH level in the immediate postoperative period was useful to predict hypocalcemia, using the thresholds of PTH decline from 50.0% to 75.7% (20-23). We demonstrated that the percentage decline of preoperative PTH level, using the cut-off value 75.0%, showed significant difference in the chance of transient hypocalcemia ($P<0.001$). Our result suggested that clinicians could use the percentage decline of PTH level, to predict symptomatic hypocalcemia early and properly after thyroid surgery.

There are some limitations in this study. First of all, the definition of hypocalcemic symptom is subjective and arbitrary, and many previous studies have used their own definitions (13,24-29). The result of this study may be biased by the threshold for pain or tingling sensation of the patients. Second, we did not evaluate the role of intraoperative or immediate postoperative PTH measurement. As early measurement of PTH can allow patients early and safe discharge, further study for the role of early PTH measurement is warranted.

CONCLUSION

Percentage decline of PTH can be used as a predictive factor for postoperative hypocalcemia. Cautions against preventing injury of the parathyroid glands with careful surgical technique should be recommended.

REFERENCES

1. Jung KW, Won YJ, Kong HJ, Oh CM, Seo HG, Lee JS. Cancer statistics in Korea: incidence, mortality, survival and prevalence in 2010. Cancer Res Treat 2013;45:1-14.
PUBMED | CROSSREF
2. Cannizzaro MA, Lo Bianco S, Picardo MC, Provenzano D, Buffone A. How to avoid and to manage post-operative complications in thyroid surgery. Updates Surg 2017;69:211-5.
PUBMED | CROSSREF
3. Pattou F, Combemale F, Fabre S, Carnaille B, Decoulx M, Wemeau JL, et al. Hypocalcemia following thyroid surgery: incidence and prediction of outcome. World J Surg 1998;22:718-24.
PUBMED | CROSSREF
4. Reeve T, Thompson NW. Complications of thyroid surgery: how to avoid them, how to manage them, and observations on their possible effect on the whole patient. World J Surg 2000;24:971-5.
PUBMED | CROSSREF
5. Fahmy FF, Gillett D, Lolen Y, Shotton JC. Management of serum calcium levels in post-thyroidectomy patients. Clin Otolaryngol Allied Sci 2004;29:735-9.
PUBMED | CROSSREF
6. Demeester-Mirkine N, Hooghe L, Van Geertruyden J, De Maertelaer V. Hypocalcemia after thyroidectomy. Arch Surg 1992;127:854-8.
PUBMED | CROSSREF

https://doi.org/10.16956/jes.2017.17.4.168

7. Edafe O, Antakia R, Laskar N, Uttley L, Balasubramanian SP. Systematic review and meta-analysis of predictors of post-thyroidectomy hypocalcaemia. Br J Surg 2014;101:307-20.
PUBMED | CROSSREF
8. Yoon JH. Prediction for development of hypocalcemic symptoms and signs after total thyroidectomy. Proceedings of the First Asian Master Course of Thyroid Cancer; 2011 Sep 1–3; Seoul, Korea. Seoul: Korean Thyroid Association; 2011. p.75-80.
9. Watson CG, Steed DL, Robinson AG, Deftos LJ. The role of calcitonin and parathyroid hormone in the pathogenesis of post-thyroidectomy hypocalcemia. Metabolism 1981;30:588-9.
PUBMED | CROSSREF
10. Chia SH, Weisman RA, Tieu D, Kelly C, Dillmann WH, Orloff LA. Prospective study of perioperative factors predicting hypocalcemia after thyroid and parathyroid surgery. Arch Otolaryngol Head Neck Surg 2006;132:41-5.
PUBMED | CROSSREF
11. Erbil Y, Barbaros U, Temel B, Turkoglu U, Işsever H, Bozbora A, et al. The impact of age, vitamin D(3) level, and incidental parathyroidectomy on postoperative hypocalcemia after total or near total thyroidectomy. Am J Surg 2009;197:439-46.
PUBMED | CROSSREF
12. Karamanakos SN, Markou KB, Panagopoulos K, Karavias D, Vagianos CE, Scopa CD, et al. Complications and risk factors related to the extent of surgery in thyroidectomy. Results from 2,043 procedures. Hormones (Athens) 2010;9:318-25.
PUBMED | CROSSREF
13. Asari R, Passler C, Kaczirek K, Scheuba C, Niederle B. Hypoparathyroidism after total thyroidectomy: a prospective study. Arch Surg 2008;143:132-7.
PUBMED | CROSSREF
14. Harness JK, Fung L, Thompson NW, Burney RE, McLeod MK. Total thyroidectomy: complications and technique. World J Surg 1986;10:781-6.
PUBMED | CROSSREF
15. McHenry CR, Speroff T, Wentworth D, Murphy T. Risk factors for postthyroidectomy hypocalcemia. Surgery 1994;116:641-7.
PUBMED
16. Mittendorf EA, Merlino JI, McHenry CR. Post-parathyroidectomy hypocalcemia: incidence, risk factors, and management. Am Surg 2004;70:114-9.
PUBMED
17. Lombardi CP, Raffaelli M, Princi P, Dobrinja C, Carrozza C, Di Stasio E, et al. Parathyroid hormone levels 4 hours after surgery do not accurately predict post-thyroidectomy hypocalcemia. Surgery 2006;140:1016-23.
PUBMED | CROSSREF
18. Del Rio P, Arcuri MF, Ferreri G, Sommaruga L, Sianesi M. The utility of serum PTH assessment 24 hours after total thyroidectomy. Otolaryngol Head Neck Surg 2005;132:584-6.
PUBMED | CROSSREF
19. Lecerf P, Orry D, Perrodeau E, Lhommet C, Charretier C, Mor C, et al. Parathyroid hormone decline 4 hours after total thyroidectomy accurately predicts hypocalcemia. Surgery 2012;152:863-8.
PUBMED | CROSSREF
20. Toniato A, Boschin IM, Piotto A, Pelizzo M, Sartori P. Thyroidectomy and parathyroid hormone: tracing hypocalcemia-prone patients. Am J Surg 2008;196:285-8.
PUBMED | CROSSREF
21. Alía P, Moreno P, Rigo R, Francos JM, Navarro MA. Postresection parathyroid hormone and parathyroid hormone decline accurately predict hypocalcemia after thyroidectomy. Am J Clin Pathol 2007;127:592-7.
PUBMED | CROSSREF
22. Di Fabio F, Casella C, Bugari G, Iacobello C, Salerni B. Identification of patients at low risk for thyroidectomy-related hypocalcemia by intraoperative quick PTH. World J Surg 2006;30:1428-33.
PUBMED | CROSSREF
23. Khafif A, Pivoarov A, Medina JE, Avergel A, Gil Z, Fliss DM. Parathyroid hormone: a sensitive predictor of hypocalcemia following total thyroidectomy. Otolaryngol Head Neck Surg 2006;134:907-10.
PUBMED | CROSSREF
24. Pfleiderer AG, Ahmad N, Draper MR, Vrotsou K, Smith WK. The timing of calcium measurements in helping to predict temporary and permanent hypocalcaemia in patients having completion and total thyroidectomies. Ann R Coll Surg Engl 2009;91:140-6.
PUBMED | CROSSREF

https://doi.org/10.16956/jes.2017.17.4.168

25. Roh JL, Park JY, Park CI. Prevention of postoperative hypocalcemia with routine oral calcium and vitamin D supplements in patients with differentiated papillary thyroid carcinoma undergoing total thyroidectomy plus central neck dissection. Cancer 2009;115:251-8.
PUBMED | CROSSREF

26. Henry JF, Gramatica L, Denizot A, Kvachenyuk A, Puccini M, Defechereux T. Morbidity of prophylactic lymph node dissection in the central neck area in patients with papillary thyroid carcinoma. Langenbecks Arch Surg 1998;383:167-9.
PUBMED | CROSSREF

27. Palestini N, Borasi A, Cestino L, Freddi M, Odasso C, Robecchi A. Is central neck dissection a safe procedure in the treatment of papillary thyroid cancer? Our experience. Langenbecks Arch Surg 2008;393:693-8.
PUBMED | CROSSREF

28. Steinmüller T, Klupp J, Wenking S, Neuhaus P. Complications associated with different surgical approaches to differentiated thyroid carcinoma. Langenbecks Arch Surg 1999;384:50-3.
PUBMED | CROSSREF

29. Sywak M, Cornford L, Roach P, Stalberg P, Sidhu S, Delbridge L. Routine ipsilateral level VI lymphadenectomy reduces postoperative thyroglobulin levels in papillary thyroid cancer. Surgery 2006;140:1000-5.
PUBMED | CROSSREF

https://doi.org/10.16956/jes.2017.17.4.168