Original Article

The Prediction of Low Four-Hour Parathyroid Hormone Level After Total Thyroidectomy on Hypocalcemia

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Abstract

Objective: The purpose of the study is to study parathyroid hormone (PTH) level in prediction of early post-thyroidectomy hypocalcemia and long term hypoparathyroidism or hypocalcemia outcome six months after surgery.

Method: Patients who underwent total thyroidectomy or completion thyroidectomy procedure from July 2015 to July 2018 were studied. Corrected serum calcium and PTH levels were measured 4-hour after thyroidectomy and monitored from 24 to 48 hours. The levels of PTH and calcium were graded as normal or low levels. These data were analyzed using validation tools; sensitivity, specificity, positive predictive value, negative predictive value, and accuracy.

Result: Out of a total of 66 patients, 24 cases were detected with low PTH levels after total thyroidectomy. The sensitivity and specificity of low PTH levels in the prediction of hypocalcemia were 45% and 79%, respectively, with a 79% positive predictive value and 58% accuracy. Prediction of permanent hypoparathyroidism after total thyroidectomy was with 53% sensitivity, 81% specificity and 66% accuracy.

Conclusion: The low PTH levels may be an indicator of hypocalcemia after total thyroidectomy, in which the evidence shows high specificity and positive predictive value. Therefore, if hypoparathyroidism is detected after total thyroidectomy, hypocalcemia is high likely, so calcium or vitamin D replacement should be provided to prevent severe hypocalcemia.

Keywords: Postoperative hypoparathyroid, Postoperative hypocalcemia

Received: 25 May 2020 **Revised: 21 May 2021** **Accepted: 25 May 2021**

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Introduction

Total thyroidectomy is associated with many postoperative complications, for example, bleeding, airway obstruction, recurrent laryngeal nerve injury, and hypocalcemia. Hypocalcemia is one of the most frequent morbidity as the result of parathyroid gland injury or unintentional excision. Although the surgeon takes care dissecting during total thyroidectomy procedure, transient hypocalcemia may occur about 1.6 - 50%.[1, 2] The incidence of permanent hypocalcemia is 0-2%.[3-6] Early postoperative hypocalcemia can cause mild to severe symptoms such as numbness, muscle cramping, seizure, or cardiac arrhythmia. Increased length of hospital stay as a consquence of symptomatic hypocalcemia may occur between 24 and 48 hours after a total thyroidectomy operation.[7, 8] Thus the patient is observed and calcium level is corrected for at least 48 hours to prevent hypocalcemia at discharge.

At present the prevention of post thyroidectomy hypocalcemia is practiced into three different ways. Firstly, the calcium level is monitored post operatively and if hypocalcemia occurs, calcium or vitamin D supplement is prescribed to the patient.[9, 10] Secondly, calcium or vitamin D supplement is routinely given in every post-thyroidectomy patient. However about 50% of cases receive unnecessary calcium supplement.[11, 12] Third, PTH level-directed supplementation, the PTH level is monitored postoperatively; when low PTH level is detected, the calcium supplement is given to the patient even if the calcium level is still normal because low PTH level may reflect hypocalcemia over the next 24 to 48 hours.[13]

The primary objective of this study is to evaluate PTH level as a predictor of early post-thyroidectomy hypocalcemia and the secondary objective was to determine long term hypoparathyroidism or hypocalcemia outcome six months after surgery.

Method

This retrospective study was approved by the human research ethics committee of Thammasat University. The sample size was calculated by two independent proportions (two-tailed test) with $\alpha = 0.05$, $\beta = 0.20$ (power 80%). Finally, at least 23 patients in each group were required. Sixty-six patients who had undergone total or completion thyroidectomy between July 2015 and July 2018 were reviewed. Completion thyroidectomy is defined as the surgical removal of the remnant thyroid tissue following procedures of less than total or near-total thyroidectomy. Inclusion criteria were those diagnosed with benign or malignant thyroid disease and underwent total or completion thyroidectomy by head, neck and breast surgeons in Thammasat University Hospital. Exclusion criteria were any one of the followings: those with some conditions (chronic renal insufficiency, hyperparathyroidism, hyperthyroidism, abnormal preoperative serum calcium or vitamin D deficiency) that might affect calcium or PTH level, those with prior calcium or vitamin D supplementation before surgery.

The level of PTH was graded as normal or low levels as followed: normal level is between 15 to 65 pg/ml and low level was less than 15 pg/ml. For calcium level, the value of low calcium was less than 8.5 mg/dl or appearance of hypocalcemic symptoms and normal calcium level was between 8.5 to 10.1 mg/dl.Hypoparathyroidism was indicated by PTH level less than 15 pg/ml. Corrected calcium level using the formula 0.8 x (4 - serum albumin) + serum calcium less than 8.5 mg/dl indicated hypocalcemia. In this study our protocol was parathyroid-directed supplementation. The patient were checked for PTH, albumin and serum calcium levels at 4 hours post-operatively.[14] If hypoparathyroidism was detected, patient received calcium supplementation and serum calcium levels were repeated every 6-8 hours for 24 to 48 hours to ensure normocalcemia prior to discharge.In case of normocalcemia, the serum calcium would continue to be monitored for at least 48 hours to detect any further hypocalcemia. After discharge, patients were followed at surgical out patient clinic regularly for six months in order to detect any long-term hypoparathyroidism. At 6 months, the patients who remained on calcium carbonate and/or vitamin D supplementation, were defined to have permanent hypoparathyroidism.

Statistical analysis

For numerical variable the student's t test was applied to detect significant differences between groups. Chi-square and Fisher's exact tests were applied for categorical variables. Results of

4-hour PTH levels for prediction of hypocalcemia were analysed by sensitivity, specificity, positive predictive value, negative predictive value, and accuracy. All statistical tests were performed using Stata version 12.0.

Results

Baseline characteristics of patients including age, sex, main diagnosis, operative procedure and rate of unintentional parathyroid gland excision were described in percentage, mean and standard deviation (SD), as shown as Table 1.

Table 1 Baseline characteristics between normal parathyroid and low parathyroid groups

	All (n = 66)	Normal 4-hour PTH (n = 42)	Low 4-hour PTH (n = 24)	*P*-value
Gender				0.306
Female (%)	56 (84.85)	34 (80.95)	22 (91.67)	
Male (%)	10 (15.5)	8 (19.05)	2 (8.33)	
Age, mean ± SD	46.84 ± 15.97	48.5 ± 16.75	43.95 ± 14.38	0.270
Pathology				0.429
Benign (%)	41 (62.12)	28 (66.67)	13 (54.17)	
Malignant (%)	25 (37.87)	14 (33.33)	11 (45.83)	
Operation				0.645
Total thyroidectomy (%)	61 (92.42)	38 (90.48)	23 (95.83)	
Completion thyroidectomy (%)	5 (7.58)	4 (9.52)	1 (4.17)	
Parathyroid tissue present on pathology report (%)	4 (6.06)	1 (2.38)	3 (12.5)	0.133

Hypocalcemia were found in 19 of the 24 patients (79.17%) who had low 4-hour PTH levels in the early post-operative peroid. However, 23 of the 42 patients with normal PTH levels (54.76%) had the conditions. The sensitivity and specificity of low 4-hour PTH level in the detection of early post-operative hypocalcemia were 45% and 79%, respectively, with a 79% positive predictive value and 58% accuracy as shown in Table 2.

Table 2 Early postoperative hypocalcemia based on four-hour parathyroid hormone level

	Normal 4-hour PTH (n = 42)	Low 4-hour PTH (n = 24)	*P*-value
4-hour PTH level (pg/ml), mean ± SD	48.49 ± 27.56	4.73 ± 4.61	< 0.01
4-hour Ca level (mg/dL), mean ± SD	8.61 ± 0.43	8.39 ± 0.39	0.05
24-hour Ca level (mg/dL), mean ± SD	8.52 ± 0.48	8.12 ± 0.70	< 0.01
Early post-op. Hypocalcemia, n (%)	23 (54.76%)	19 (79.17%)	0.047

After six months of thyroidectomy procedures, 8 patients had lost their follow-ups. Among 58 patients, 77% and 42% of the patients in the low and normal 4-hour PTH group respectively had encountered permanent hypoparathyroidism, the sensitivity and specificity in the detection of long-term hypoparathyroidism were 53% and 81%, respectively, with a 77% positive predictive value and 66% accuracy as shown in Table 3.

Table 3 Long term hypoparathyroidism based on four-hour parathyroid hormone level

	Normal 4-hour PTH (n = 36)	Low 4-hour PTH (n = 22)	*P*-value
6-month PTH level (pg/ml), mean ± SD	70.09 ± 36.04	28.54 ±17.01	< 0.01
6-month Ca level (mg/dL), mean ± SD	9.05 ± 0.41	8.58 ± 0.65	< 0.01
Permanent hypoparathyroidism, n (%)	15 (41.67%)	17 (77.27%)	< 0.01

Discussion

Our results have shown high specificity and high positive predictive value of low PTH level at 4 hours after operation to detect early post-operative hypocalcemia. Therefore, it is a strong indicator for calcium or vitamin D supplementation. However, even normal PTH patients should continue to be monitored for calcium level for at least 48 hours, if hypocalcemia is detected calcium supplementation should be given later.

The result of the six months follow up suggested that the low 4-hour PTH level after thyroidectomy could predict long-term hypoparathyroidism. Consequently, those patients should be advised to continue their calcium or vitamin D supplementation with 81% specificity.

The previous studies have shown many predictors of the early post-operative hypocalcemia such as single intraoperative intact PTH (iPTH) level,[15-17]% iPTH decline from baseline,[14] calcium slope,[10] preoperative vitamin D status,[18] number of identified parathyroid glands[19] and types of operation.[20] Additionally, Suwannasarn M. et al found that the patients who had developed a significant immediate post-operative hypocalcemia had a significantly lower iPTH4hr ($P < 0.01$) and a significantly greater %iPTH decline ($P < 0.01$). The sensitivity, specificity, positive, and negative predictive values of the iPTH4hr were 92%, 87.5%, 82.1%, and 94.6%, respectively, including overall accuracy of 89.2%. The iPTH4hr ($P < 0.01$) and % iPTH decline ($P = 0.02$) were also significantly different between patients with and without permanent hypoparathyroidism.[21]

However, there is a possibility that our study is less accurate than other previous studies due to several limitations such as the small sample size, the loss of patients during the follow-up period and the use of retrospective study design.

A low level of PTH at the four-hours after thyroid surgery could predict the occurrence of postoperative hypocalcemia, enabling the patient to receive replacement drugs immediately before severe hypocalcemia occurs. However, for normal four-hour PTH level there is still the need to check calcium level before discharge to prevent hypocalcemia at home. Patients with low PTH levels at six-month after thyroidectomy have higher risk to develop long term hypoparathyroidism and calcium supplementation should not be stopped.

Acknowledgements

The author would like to thank Boonying Siribumrungwong, MD, PhD. for assisting with the statistical analysis, and Mr.Ake-atthaphon Inthaviwat for language editing.

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