

Utilizing Immediate Postoperative Serum Parathyroid Hormone in Predicting Severe Hypocalcemia Post-thyroidectomy

Nern H Kao¹, Adrian JH Koh²

ABSTRACT

Background: Postoperative hypocalcemia is a common complication of thyroid surgery. Serum parathyroid hormone (PTH) levels are a useful adjunct in predicting the likelihood of developing hypocalcemia. This can be used in identifying patients suitable for early discharge. However, there has been no consensus on the ideal timing of postoperative serum PTH.

Materials and methods: We retrospectively reviewed 122 patients who underwent completion or total thyroidectomy from January 2013 to October 2017. Patient's preexisting clinical data were collated and analyzed.

Results: The incidence of hypoparathyroidism and hypocalcemia was 36% and 48%, respectively, within the entire cohort. A normal serum PTH at skin closure was found to have a negative predictive value (NPV) of 96.5% for hypocalcemia with a sensitivity and specificity of 84.6% and 91.7%. The severity of hypocalcemia was found to be inversely related with the timing of the first dose of calcitriol replacement. Patients were more likely to develop severe hypercalcemia at a rate of 18.2% vs 16.7% vs 53.9% ($p = 0.05$) depending if they received it within 12 hours, between 12 hours and 24 hours, or after 24 hours from surgery.

Conclusion: Serum PTH at skin closure can identify patients who are unlikely to develop severe hypocalcemia. It is also useful to identify patients who will benefit from calcitriol replacement early so as to reduce the severity of hypocalcemia.

Keywords: Postoperative hypocalcemia, Thyroid, Thyroid surgery, Thyroidectomy.

World Journal of Endocrine Surgery (2020); 10.5005/jp-journals-10002-1282

INTRODUCTION

Postoperative hypocalcemia is a common complication after total or completion thyroidectomy. Studies have shown an incidence of 5–60% depending on the authors' criteria in defining hypocalcemia and the surgeons' experience.^{1–3} This occurs as a result of direct injury, devascularization, or inadvertent removal of the parathyroid glands. Hypocalcemia is typically transient but can result in paresthesia, muscle spasms, cardiac arrhythmias, or even be life-threatening in severe cases. This contributes to the patients' morbidity and length of hospital stay due to the need for calcium replacement and monitoring.

Hypocalcemia may not become clinically apparent until 24–48 hours after thyroidectomy. However, the parathyroid hormone (PTH) has a short half-life and has been reported to be a useful marker in identifying the patients at risk of developing hypocalcemia.⁴ Treatment can then be instituted early to avoid the complications of hypocalcemia.

This study takes a retrospective look at the data of our patients to identify the correlation between the drop in immediate and early postoperative PTH levels with hypocalcemia. We also evaluate if early calcitriol replacement reduces the severity of hypocalcemia and therefore the length of stay.

MATERIALS AND METHODS

This is a retrospective study of all patients who had undergone either a completion thyroidectomy or total thyroidectomy within our institution from January 2013 to October 2017. Patients were included if they had serial monitoring of the serum PTH and calcium levels. Patients were excluded if they had undergone

^{1,2}Department of General Surgery, Changi General Hospital, Simei Street 3, Singapore

Corresponding Author: Nern H Kao, Department of General Surgery, Changi General Hospital, Simei Street 3, Singapore, Phone: +65 69366734, e-mail: kao.nern.hoong@singhealth.com.sg

How to cite this article: Kao NH, Koh AJH. Utilizing Immediate Postoperative Serum Parathyroid Hormone in Predicting Severe Hypocalcemia Post-thyroidectomy. *World J Endoc Surg* 2020;12(2): 76–79.

Source of support: Nil

Conflict of interest: None

a planned parathyroidectomy concurrently. Other exclusion factors include a history of hyperthyroidism, preexisting hyperparathyroidism, or other concurrent surgery. The primary aim of the study is to identify which patients were likely to develop hypocalcemia based on the drop in PTH levels postoperatively. The secondary aim would be to assess if early calcitriol replacement in these patients reduce the severity of the hypocalcemia and the length of stay.

Thyroidectomy is usually performed as an open surgery with a lateral approach in our center. The superior thyroid artery is routinely taken at its terminal branches to the thyroid. Care is taken to preserve the inferior thyroid vessels to and from the parathyroid glands. In the event of an apparent devascularization or excision of a parathyroid gland, the involved gland is minced and reimplanted into the sternocleidomastoid muscle. Surgical drains are routinely placed into the thyroid bed.

Parathyroid hormone levels are routinely taken preoperatively. Parathyroid hormone and serum corrected calcium (CorrCa) levels are taken immediately after skin closure (0 hours), 6 hours postoperatively, and on postoperative day 1 (POD1). Parathyroid hormone and CorrCa levels are taken on subsequent postoperative days as needed.

Patients are always admitted after thyroid surgery in our center. Patients are discharged once the drain(s) are minimal and calcium levels remain stable. Symptoms suggestive of hypocalcemia such as peripheral or perioral paresthesia or muscle cramps are routinely assessed for during their stay.

Calcitriol and/or calcium replacement are not given routinely postoperatively. Oral calcium carbonate and calcitriol 0.5 µg BD are started if postoperative PTH value is ≤ 0.64 pmol/L. Intravenous (IV) calcium is given if the patient is symptomatic or if CorrCa levels is ≤ 1.90 mmol/L. Patient’s medication charts were reviewed for the prescription of calcitriol, oral or intravenous calcium replacement during their inpatient stay.

Data on the length of stay were also collected and patients were evaluated if early identification of hypoparathyroidism and therefore early calcitriol replacement resulted in a shorter length of stay.

For the purpose of this study, mild hypoparathyroidism (hypoPTH) is defined as < 1.30 pmol/L and severe as ≤ 0.64 pmol/L. Mild hypocalcemia is defined as < 2.10 mmol/L and severe hypocalcemia as ≤ 1.90 mmol/L.

This study was approved by the local institutional review board.

RESULTS

A total of 166 patients had undergone a total or a completion thyroidectomy within our institution. A total of 19 patients were excluded as they had concurrent planned parathyroidectomy. Another 25 patients were excluded because of previously undiagnosed hyperparathyroidism, previous hyperthyroidism, preexisting cholecalciferol replacement, or calcium monitoring via ionic calcium instead of serum corrected calcium, respectively. A final total of 122 patients were included into the study (Table 1).

The mean age of our patients was 56.5 years (19–85) with the majority being female at 82.8%. Fifty-eight (47.5%) of these patients had surgery for proven or likely thyroid cancer diagnosed preoperatively while another 12 (9.8%) had their surgery for follicular neoplasm on fine-needle aspiration cytology (FNAC). The remaining had surgery for benign disease.

Throughout the entire cohort, the incidence of postoperative hypoparathyroidism was 36.1% of which 18 (14.8%) and 26 (21.3%) patients had mild or severe hypoparathyroidism as defined above. The rate of hypocalcemia was higher with 59 (48.4%) patients having mild or severe hypocalcemia at 46 (37.7%) or 13 (10.7%), respectively.

Serum PTH levels were found to have a correlation with developing hypocalcemia. Patients were more likely to develop hypocalcemia the more profound the hypoparathyroidism. This was found to be the case regardless of the timing the PTH levels were taken (Table 2). In addition, patients whose serum PTH levels were normal (≥ 1.30 pmol/L) at skin closure were less likely to develop severe hypocalcemia. This had a negative predictive value (NPV) of 96.5% with a sensitivity and specificity of 84.6% and 91.7%, respectively. Of note, patients were still found to develop severe hypocalcemia even with a normal or mildly depressed PTH level. This is further discussed below.

Early calcitriol replacement was found to reduce the severity of the hypocalcemia (Fig. 1). Approximately, 18% of patients who received calcitriol within 12 hours from the surgery did not develop hypocalcemia despite low PTH levels. Patients were more likely to develop severe hypocalcemia the later they received calcitriol replacement. This occurred at a rate of 18.2% vs 16.7% vs 53.9% ($p = 0.05$) depending if they received it within 12 hours, between 12 hours and 24 hours, or after 24 hours from surgery. This suggests that early serum PTH levels allow for earlier recognition of hypoparathyroidism and the earlier initiation of calcitriol replacement. This will therefore reduce the severity of subsequent hypocalcemia. Patients who developed hypocalcemia were also likely to have milder hypocalcemia the earlier the calcitriol replacement. This can be seen when comparing those with no or mild hypocalcemia vs severe hypocalcemia in those receiving calcitriol before or after 24 hours (82.6% vs 46.2%) (OR 5.54 [CI 1.20–25.68, $p < 0.05$]).

Serum PTH levels at skin closure was a useful marker in identifying those who require IV calcium replacement. Patients with a subnormal serum PTH level at skin closure were at a significantly increased risk of requiring IV calcium replacement (RR 6.39, CI 2.76–14.81, $p < 0.01$) (Table 3).

The average stay during the accrual period for patients without hypoparathyroidism or hypocalcemia ($n = 56$) was 2.1^{1-3} days. In comparison, patients who developed hypoparathyroidism had an expected longer length of stay. The length of stay was longer the later the patients received calcitriol from surgery. In the three patient populations studied, the average stay was 3.9 vs 4.0 vs 4.6 days (within 12 hours vs 12–24 hours vs after 24 hours) ($p = 0.31$).

Table 1: Sample descriptive statistics

Factor	n	Percentage
Gender		
Male	21	17.2%
Female	101	82.8%
Age	56.5 (19–85)	
Extent of surgery		
Completion thyroidectomy	17	13.9%
Total thyroidectomy	65	53.3%
Total thyroidectomy with unilateral CCC	36	29.5%
Total thyroidectomy with bilateral CCC	4	3.3%
Hypoparathyroidism		
No	78	63.9%
Mild	18	14.8%
Severe	26	21.3%
Hypocalcemia		
None	63	51.6%
Mild	46	37.7%
Severe	13	10.7%

*CCC, central compartment clearance

Table 2: Severity of hypocalcemia in relation to severity and timing of postoperative serum parathyroid hormone (PTH)

	Hypocalcemia					
	None		Mild		Severe	
HypoPTH—0 hours						
No	55	67.9%	24	29.6%	2	2.5%
Mild	5	21.7%	13	56.5%	5	21.7%
Severe	0	0.0%	9	60.0%	6	40.0%
HypoPTH—6 hours						
No	54	68.4%	22	27.8%	3	3.8%
Mild	5	26.3%	12	63.2%	2	10.5%
Severe	1	5.6%	9	50.0%	8	44.4%
HypoPTH—Postoperative day 1						
No	58	67.4%	25	29.1%	3	3.5%
Mild	2	14.3%	8	57.1%	4	28.6%
Severe	1	5.0%	13	65.0%	6	30.0%

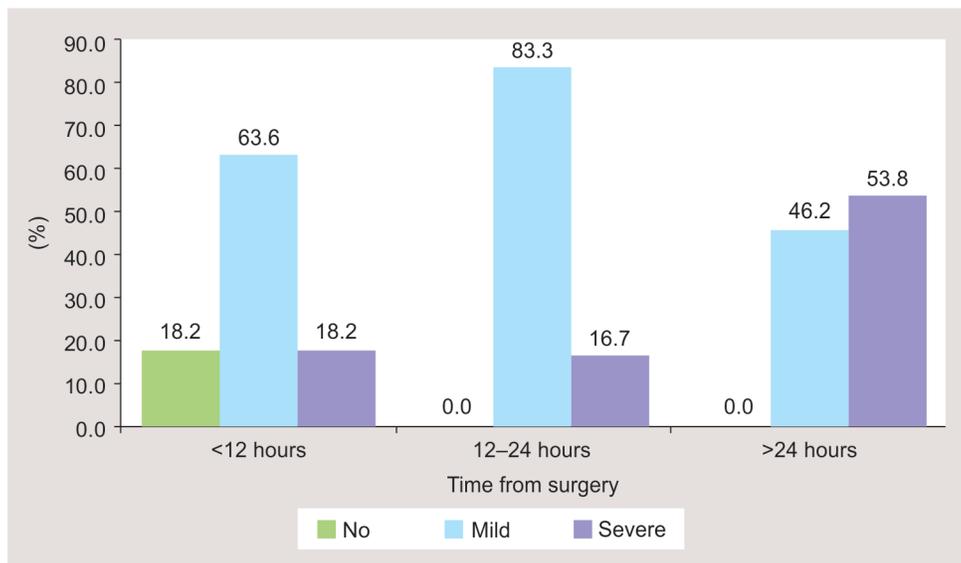


Fig. 1: Time of oral calcitriol replacement from surgery vs severity of hypocalcemia

Two patients were excluded from the first group as they had had concurrent lateral neck dissection, which inherently extends their length of stay. One patient was excluded from each of the latter two groups due to a prolonged stay in the intensive care unit as a result of failed extubation.

DISCUSSION

Hypocalcemia post-thyroidectomy is a recognized complication and has been described to occur anywhere between 5% and 60%.¹⁻³ There are numerous studies that describe the utility in using postoperative serum PTH levels in predicting the likelihood of developing hypocalcemia.⁵⁻⁷ Despite this, the recurring theme is that there is no agreement on the best time to perform postoperative PTH levels to accurately predict the hypocalcemia rate. Karatzanis et al. have shown that a decrease of 56% in PTH levels

on POD1 could accurately predict the likelihood of hypocalcemia with a sensitivity and specificity of 80%.⁷ In a systematic review by Mazotas et al. in 2017, there was ample data that POD1 PTH levels were a useful predictor of hypocalcemia. However, the authors did acknowledge that the limitations in performing PTH levels on POD1 were a potential delay in the treatment. As shown in this study, early identification and therefore treatment of hypoparathyroidism resulted in less severe hypocalcemia and a shorter length of stay. PTH levels performed as early as after skin closure can be a useful indicator to identify patients who are unlikely to develop a severe hypocalcemia value (NPV 96.5%, sensitivity 84.6%, specificity 91.7%). This can be used to guide the decision for repeated blood takings or the need for vitamin D3 or calcium replacement. Lang et al. in a prospective study also showed that PTH levels taken shortly after skin closure had a 82% sensitivity and 95% specificity in predicting hypocalcemia if PTH levels were less than 1.0 pmol/L.⁸

Table 3: Time of serum parathyroid hormone (PTH) vs intravenous calcium replacement

	<i>IV calcium replacement</i>		<i>IV calcium dose*</i>				
	No	Yes		<i>Min</i>	<i>Max</i>	<i>Average</i>	
HypoPTH—0 hours							
No	78	92.9%	6	7.1%	1	3	1.6
Mild	12	52.2%	11	47.8%	1	6	3.4
Severe	8	53.3%	7	46.7%	1	9	3.8
HypoPTH—6 hours							
No	79	92.9%	6	7.1%	1	2	1.3
Mild	8	44.4%	10	55.6%	1	6	2.9
Severe	9	50.0%	9	50.0%	1	9	3.7
HypoPTH—Postoperative day 1							
No	82	93.2%	6	6.8%	1	2	1.4
Mild	7	50.0%	7	50.0%	1	6	3.0
Severe	9	45.0%	11	55.0%	1	9	4.0

*1 dose = 10 mL 10% calcium gluconate (2.3 mmol/10 mL) in 100 mL normal saline

Interestingly, 20 (25.6%) and 2 (2.6%) of our patients who had normal PTH levels developed mild and severe hypocalcemia, respectively. We speculate that these patients experienced a mild injury to the parathyroid glands during surgery possibly from manipulation. As a result, the affected glands were able to maintain sufficient function to produce a “normal” laboratory value. However, despite this “normal” value, the parathyroid glands were in actual fact unable to produce sufficient hormonal levels to meet the body’s demand to correct the hypocalcemia. The significance is that there is a risk that a small subset of patients can still develop severe hypocalcemia despite normal PTH levels. We suggest that serum calcium levels should also be performed postoperatively to identify these patients. This would largely impact centers that aim for same-day discharge and rely on intraoperative or early postoperative PTH levels in identifying patients at risk.

There are numerous weaknesses to our study. One such weakness is the low population number. This affects the statistical power and predisposed the study to type II errors. This was also a retrospective study with data collated from the daily management of our patients. As a result, there was no fixed written protocol for the management of the patients especially with regards to the hypoparathyroidism and hypocalcemia. Our surgical team strives to maintain a similar practice for all of our patients to the best of our ability. However, variances tend to occur especially when there is a change in the primary surgical team as well as the unfamiliarity of the overnight on-call surgical team to the standard practice. The management and medications prescribed may therefore veer from the usual.

SUMMARY

Hypoparathyroidism is a common complication of thyroid surgery. Normal serum PTH levels at skin closure are a useful tool in identifying patients who are unlikely to develop hypocalcemia. This can be used to minimize blood taking and to identify patients who are safe for early discharge. Early identification of hypoPTH

allows for early calcitriol replacement, which is shown to reduce the severity of the hypocalcemia.

REFERENCES

1. Hundahl SA, Cady B, Cunningham MP, et al. Initial results from a prospective cohort study of 5583 cases of thyroid carcinoma treated in the United states during 1996: US and German thyroid cancer study group. An American college of surgeons Commission on cancer patient care Evaluation study. *Cancer* 2000;89(1):202–217. DOI: 10.1002/1097-0142(20000701)89:1<202::AID-CNCR27>3.0.CO;2-A.
2. 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(8):971–975. DOI: 10.1007/s002680010160.
3. Rosato L, Avenia N, Bernante P, et al. Complications of thyroid surgery: analysis of a multicentric study on 14,934 patients operated on in Italy over 5 years. *World J Surg* 2004;28(3):271–276. DOI: 10.1007/s00268-003-6903-1.
4. Mazotas IG, Yen TWF, Park J, et al. A postoperative parathyroid hormone-based algorithm to reduce symptomatic hypocalcemia following completion/total thyroidectomy: a retrospective analysis of 591 patients. *Surgery* 2018;164(4):746–753. DOI: 10.1016/j.surg.2018.04.040.
5. Philips R, Nulty P, Seim N, et al. Predicting transient hypocalcaemia in patients with unplanned parathyroidectomy after thyroidectomy. *Am J Otolaryngol* 2019;40(4):504–508. DOI: 10.1016/j.amjoto.2019.04.006.
6. Galy-Bernadov C, Lallemand B, Chambon G, et al. Parathyroid hormone assays following total thyroidectomy: is there a predictive value? *Eur Thyroid J* 2018;7(1):34–38. DOI: 10.1159/000484689.
7. Karatzanis AD, Ierodiakonou DP, Fountakis ES, et al. Postoperative day 1 levels of parathyroid as predictor of occurrence and severity of hypocalcaemia after total thyroidectomy. *Head Neck* 2018;40(5):1040–1045. DOI: 10.1002/hed.25081.
8. Lang BH, Yih PC, Ng KK. A prospective evaluation of quick intraoperative parathyroid hormone assay at the time of skin closure in predicting clinically relevant hypocalcaemia after thyroidectomy. *World J Surg* 2012;36(6):1300–1306. DOI: 10.1007/s00268-012-1561-9.