

## PARATHYROID HORMONE ASSAY IN PREDICTING POST-OPERATIVE HYPOCALCEMIA AFTER TOTAL THYROIDECTOMY

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### ABSTRACT

**Objectives:** Injury to the parathyroids during thyroidectomy leads to either transient ischemia or even infarction of the glands which results in hypocalcemia. Early identification of post-operative hypocalcemia after thyroidectomy can be achieved by assessing parathormone (PTH) level. The present study correlates post-operative serum PTH at 4 h with serum calcium levels after total thyroidectomy and subsequent development of hypocalcemia. This study thus aims to determine the efficacy of parathyroid hormone assay in predicting post-operative hypocalcemia after total thyroidectomy.

**Methods:** After obtaining approval for the study from the Institutional Review Board, patients admitted in surgery department of Kottayam medical college for total thyroidectomy are evaluated with post-operative PTH levels at 4 h after surgery and serial monitoring of serum calcium levels. Patients are evaluated clinically for signs and symptoms of hypocalcemia and their association is studied.

**Results:** 20% of the study population developed hypocalcemia. Intact PTH was found to be lower in patients who developed symptoms of hypocalcemia. There was a statistically significant correlation between the two groups. A 4-h intact PTH value of 14 pg/mL was found to have high sensitivity (93.8%) and specificity (91.6%).

**Conclusion:** Hypocalcemia is one of the most feared complications after total thyroidectomy. Intact PTH measurement 4 h after total thyroidectomy can be used to predict the incidence of hypocalcemia after total thyroidectomy. Therefore, patients having low 4-h intact PTH value could be started on calcium supplementation and those having high PTH could be safely discharged early.

**Keywords:** PTH assay, Hypocalcemia, Thyroidectomy.

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### INTRODUCTION

Parathyroid dysfunction leading to hypocalcemia is common after total thyroidectomy and is often associated with significant patient morbidity and prolonged hospital stay. When parathyroids are removed intraoperatively, normal, devitalized glands should be auto-transplanted into the surrounding skeletal muscle. According to the study Kala *et al.*, more often though, the observed fall in parathormone (PTH) levels is a result of traumatic injury to the parathyroids during thyroidectomy leading to either transient ischemia or even infarction of the glands. Thus, the hyposecretion of PTH may be relatively transient (1.6%-68%) or may be permanent (0.4%-33%) [1].

Intact PTH is an 84-amino acid protein and control of its release is under direct feedback from extracellular calcium ions, as mediated through the cell surface calcium receptor of the parathyrocyte. The half-life of intact PTH is measured in minutes and can be reliably assayed. It is degraded into several smaller proteins with variable half-lives and biological activity [2]. The biologically active forms have very short half-lives, compared to the carboxyl-terminal fragments that have longer half-lives and accumulate in circulation as glomerular filtration declines [3]. The appearance of post-operative hypocalcemia may be delayed up to 48 h depending on the levels of such biologically active peptides. The first PTH receptor (PTH1R) was cloned in 1991. PTH1R recognizes intact PTH and parathyroid hormone-related peptide. A second, closely related receptor (PTH2R) selectively binds PTH. Activation of these receptors by PTH stimulates multiple cellular signaling pathways, which stimulate the release of intracellular calcium stores [4].

First, PTH stimulates the enzyme 1- $\alpha$ -hydroxylase (CYP27B1) which in turn increases intestinal absorption of calcium. Second, in the distal and proximal renal tubule, PTH binding to the PTH1R increases calcium absorption and decreases phosphate reabsorption. Third, PTH binding to PTH1R in the bones stimulates the release of phosphate and calcium from the bones into the circulation. Overall, these actions result in an increased calcium concentration [5].

Because of the lag between the hyposecretion of PTH and the development of symptomatic hypocalcemia, early pharmacologic support with calcium, magnesium, and calcitriol can potentially keep high-risk patients eucalcemic and asymptomatic, thereby avoiding morbidity. Early prophylactic administration of calcitriol is important in maintaining eucalcemia in high-risk patients. Thus, the early identification of post-thyroidectomy patients at risk of hypoparathyroidism and hypocalcemia would allow for the early introduction of calcitriol. Conversely, patients at low risk of post-thyroidectomy hypocalcemia can be spared the discomfort of excessive blood tests and can reliably be discharged without fear of symptomatic hypocalcemia [2].

Study conducted by Nabeel *et al.* showed that intact PTH was found to be lower in patients who developed symptoms of hypocalcemia. A 1-h intact PTH value of 14 pg/mL was found to have high sensitivity (92.3%) and specificity (91.9%) [6].

The present study correlates post-operative serum PTH with serum calcium (Ca<sup>2+</sup>) levels obtained at 4 h after total thyroidectomy and hence to determine the efficacy of parathyroid hormone assay in predicting post-operative hypocalcemia and as an indicator to facilitate early discharge.

Table 1: Frequency distribution of age, sex, symptomatic hypocalcemia, and length of hospital stay

Age		Sex		Symptomatic hypocalcemia		Length of hospital stay	
18–54 years	>54 years	Male	Female	No	Yes	<7 days	>6 days
106	5	9	102	89	22	94	17
95.5%	4.5%	8.1%	91.9%	80.18%	19.82%	84.68%	15.32%

## METHODOLOGY

### Type of study

Prospective observational study

### Period of study

12 Months

### Ethical permission number

40/2020.

### Study setting

Patients admitted in surgery department of Kottayam medical college for total thyroidectomy are evaluated with post-operative PTH levels at 4 h after surgery and serial monitoring of serum calcium levels.

### Sample size

According to the study conducted by Nabeel *et al.* [6], sensitivity and specificity of PTH assay in predicting post-operative hypocalcemia after total thyroidectomy with a value of <14 pg/mL were 92.3% and 91.9%. Using the data, the sample size was calculated using the formula:

$$N = \frac{Z^2 \times \text{Sensitivity} (1 - \text{Sensitivity})}{d^2 \times p}$$

p=Prevalence of hypocalcemia (proportion of people developing post-operative hypocalcemia in the study)

p=30%

d=precision=10% of sensitivity=0.092

$$N = \frac{2.58^2 \times 0.3 \times (1 - 0.3)}{0.092^2 \times 0.3} = 111$$

Sample Size is taken as 120.

## METHODS

### Study population

Patients who are admitted to surgical unit for total thyroidectomy who are >18 years in the Department of General Surgery in Government Medical College, Kottayam, during the study period.

### Study procedure

The study involves the determination of serum calcium, creatinine, and albumin pre-operatively. Serum PTH 4 h after total thyroidectomy and serum calcium levels on days 2, 3, 4 are monitored. Symptomatic hypocalcemia is defined when there was any episode of symptoms or signs of hypocalcemia during the hospital stay: Perioral numbness, tingling sense or paresthesia of hands or feet, Chvostek's sign, Trousseau's sign, muscle cramp, tetany, or seizures. Biochemical hypocalcemia is defined when anyone of the checked Ca levels <8 mg/dL. Operational definition of hypocalcemia for this research topic is based on biochemical level of calcium. Parent study has found that the PTH value of <14pg was found with higher sensitivity and specificity. Hence, this value has taken in this study too. Immunochemiluminometric measurement of serum intact PTH is used which belongs to the second generation assay. Samples were collected in plane bottle and sent to laboratory with icepack.

### Study tool

Pro forma.

Table 2: Association of post-operative hypocalcemia with PTH assay

PTH at 4 hours after thyroidectomy	Caonpostop day 2		CaonPostop day 3		Caonpostop day 4		Asymp. Sig. (two-sided)
	<8	>7.9	<8	>7.9	<8	>7.9	
PTH 4 h							
<14	19	1	19	1	18	2	
≥14	2	89	2	89	1	90	0.000
Total	21	90	21	90	19	92	

Table 3: Relation between PTH assay at 4 h and symptomatic hypocalcemia

PTH at 4 hours after thyroidectomy	Symptomatic hypocalcemia		Total
	No	Yes	
PTH 4 h			
<14			
Count	1	19	20
% within symptomatic hypocalcemia	1.1	86.4	18.0
>13			
Count	88	3	91
% within symptomatic hypocalcemia	98.9	13.6	82.0
Total			
Count	89	22	111
% within symptomatic hypocalcemia	100.0	100.0	100.0

### Inclusion criteria

Patients who are admitted to surgical unit for total thyroidectomy who are >18 years in the Department of General Surgery in Government Medical College, Kottayam, during the study period were included in the study.

### Exclusion criteria

1. Coexisting renal dysfunction, i.e., serum creatinine >1.4
2. Hypoalbuminemia, i.e., serum albumin <3
3. Presumptive treatment with calcium.

### Data management and statistical analysis

Data will be entered in Microsoft Excel and statistical analysis will be done with SPSS-21 software and sensitivity, specificity, and predictive values will be derived.

## RESULTS

In this study, 106 patients out of 111 were aged between 18 and 54 years, and the rest of 5 patients were 55 years or more, the eldest being 79 years (Table 1).

Diseases related to thyroid gland are commonly seen in females. In this study also, females constitute the larger proportion, i.e., 102 out of 111 (91.9%). Among the 9 male patients, 2 patients were diagnosed to have follicular carcinoma.

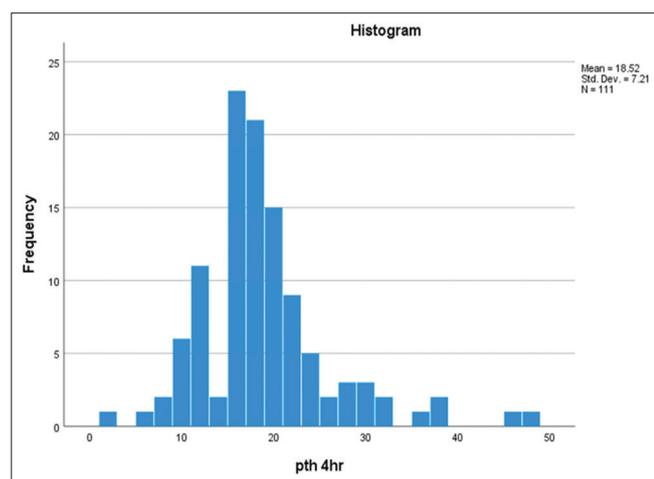
There is no significant difference in the incidence of symptomatic hypocalcemia in patients with hypo or hyperthyroidism or euthyroid status with p value of 0.418, 0.413, and 0.547, respectively.

Comorbidities associated with thyroid disease were also studied. 8 patients among 111 patients were found to have diabetes mellitus and 14 patients have hypertension and only 2 patients had history of coronary artery disease.

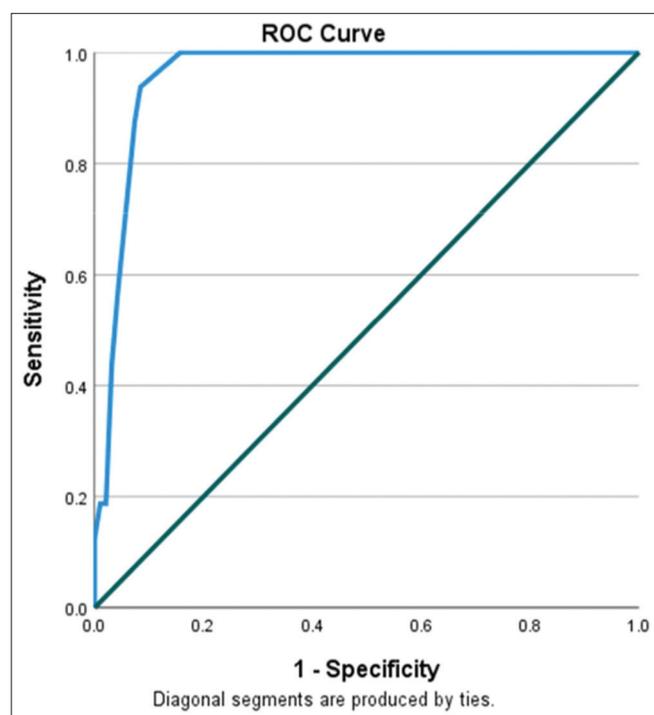
The sensitivity and specificity of PTH values were noted at different threshold values (Table 4). The best sensitivity and specificity were observed at a threshold PTH value of 14. Table 4 presents the relation

**Table 4: Sensitivity and specificity at different cut-off values of PTH**

PTH value	Sensitivity	Specificity
13.0	87.5	92.6
14.0	93.8	91.6
15.5	100	84.2
16.5	100	68.4



**Fig. 1: Frequency distribution of PTH assay at 4 h after total thyroidectomy**



**Fig. 2: ROC with area under curve of 95.6%**

between symptomatic patients and threshold PTH value. 86.4% of patients had symptoms of hypocalcemia with a PTH value of  $\leq 14$ . 98.9% of patients with PTH value  $\geq 14$  did not develop any symptoms of hypocalcemia.

## DISCUSSION

Thyroidectomy is one of the most common surgeries performed worldwide and hypocalcemia is one of the most common complications following total thyroidectomy. To minimize post-operative complications due to hypocalcemia and to permit an early and safe discharge, it is important to identify a method to predict patients at high risk of developing significant hypocalcemia. Multiple studies have examined the role of a single measurement of serum PTH level on POD1 that would predict the development of post-operative hypocalcaemia after total thyroidectomy

Cayo *et al.* concluded that a POD1 PTH  $< 10$  pg/mL had a sensitivity of 86% and negative predictive value of 90% for symptomatic hypocalcemia [7]. According to Tredici *et al.*, the sensitivity of serum calcium measurement as a predictor of hypocalcaemia is too low to be used as a reliable screening test [8].

The study by Landry *et al.* was to identify specific parameters to use as a guide for selective calcium with/without calcitriol supplementation in patients who have undergone completion or total thyroidectomy. According to this study, selective, rather than routine, calcium replacement therapy may be safe and achievable. Patients who have a PTH level of  $< 6$  pg/mL or a serum calcium level of  $< 8$  mg/dL at the time of hospital discharge should be sent home with calcium and/or calcitriol supplementation [9].

The high cost of serum PTH assay makes its serial measurement less feasible. Hence, it would be desirable if a single PTH measurement predicts the development of post-thyroidectomy hypocalcaemia. Several studies were conducted measuring the sensitivity of PTH done intraoperatively, immediate post-operatively and in the morning, after thyroidectomy. A study was done by Lombard *et al.* in which PTH was measured pre-operatively, at the end of the surgical procedure, and at 2, 4, 6, 24, and 48 h after the operation. It was concluded that a single PTH levels below the normal range ( $< 10$  pg/mL) between 4 and 6 h after the operation correctly predicted post-operative hypocalcaemia (sensitivity 94% and specificity 100%) [10].

In the present study, a 4-h post-operative serum intact PTH value of  $< 14$  pg/mL has a sensitivity of 93.8% and a specificity of 91.6% for predicting patients at risk for developing post total thyroidectomy hypocalcaemia. PTH value of  $> 15.5$  pg/mL is taken as a criteria for safe early discharge.

## CONCLUSION

Hypocalcemia is one of the most feared complications after total thyroidectomy. Intact PTH measurement 4 h after total thyroidectomy can be used to predict the incidence of hypocalcemia after total thyroidectomy. Even though the best sensitivity and specificity are obtained at a PTH threshold value of 14 pg/mL, the highest sensitivity at a lowest PTH threshold obtained is at 15.5 pg/mL which can be taken as criterion for early safe discharge.

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