

Early Prediction of Post Thyroidectomy Hypocalcemia by Measuring Parathyroid Hormone

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ABSTRACT

Objective: To predict patients at risk of developing post-operative hypocalcemia by measuring parathyroid hormone (PTH) and serum calcium and early initiation of oral calcium and vitamin D in these patients to decrease complications.

Study Design: Prospective, observational study.

Place and Duration of Study: Department of Otolaryngology, Combined Military Hospital Rawalpindi, Pakistan, from Sep 2022 to Aug 2023.

Methodology: A total of 160 patients were included in the study group segregated into those who developed hypocalcemia (Group-A) versus normocalcemia (Group-B) post-operatively. Primary variables studied were mean levels of PTH for corresponding values of hypo or normocalcemia, frequency of patients presenting with normo versus hypocalcemia. Secondary variables of study were the sensitivity and specificity of PTH in predicting hypocalcemia.

Results: The incidence of hypocalcemia in the study group was seen in 63(39.4%) patients and normocalcemia was seen in 97 (60.6%) patients. The ability of PTH in predicting hypocalcemia at 01- and 24-hour intervals showed sensitivity of 90.5% and a specificity of 79.4% at one hour while the sensitivity at 24 hours was 95.2% with a specificity of 96.9%.

Conclusion: We conclude that falling levels of PTH hormones post-thyroidectomy showed excellent sensitivity and specificity in predicting hypocalcemia at 01 and 24 hours respectively.

Keywords: Calcium, Hypocalcemia, Parathyroid, Post-Thyroidectomy.

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INTRODUCTION

Hypocalcemia is the most frequent side effect after complete thyroidectomy due to the unstable blood flow to parathyroid glands and the injury to the laryngeal nerve.^{1,2} In recent studies, rates of transitory hypocalcemia as significant as 34%, and rates of persistent hypocalcemia as much as 0.6 to 6% have been recorded.³ Post-operative hypocalcemia is the most frequent complication seen in individuals undergoing total thyroidectomy, with reported occurrences ranging from 1.7% to 55%.⁴ Although in most individuals, hypocalcemia is self-limiting and does not require therapy, symptomatic hypocalcemia is of significant issue. It is typically difficult to anticipate which people are more likely to have this problem and will need calcium and vitamin D supplementation.^{5,6} Complaints typically appear 24 to 48 hours following surgery.⁷ Postoperative surveillance of serum calcium levels is the recommended protocol since no accurate indicator of clinically meaningful hypocalcemia following bilateral thyroid resections have been identified. To minimize the symptoms of hypocalcemia, several facilities

routinely administer oral calcium and vitamin D supplementation treatment to all patients after bilateral thyroid surgery but this approach has no scientific rationale.⁸

To reduce hospital, stay and readmission rates for symptomatic hypocalcemia, and allowing for early discharge without over-treating individuals, successfully recognizing the cohort of individuals at hazard for postsurgical hypocalcemia need to be identified. Individuals who do not carry complication risks may be eligible for early discharge. Since parathyroid insufficiency is the primary reason for chronic and clinical hypocalcemia, intra- and postoperative intact parathyroid hormone (iPTH) tests might help identify individuals at the risk for post-thyroidectomy hypocalcemia.^{9,10} This research aimed to see if fall in serum PTH levels assessed before and after one hour of total thyroidectomy could detect patients who would exhibit hypocalcemia helping us to define clinical treatment guidelines for calcium replacement.

METHODOLOGY

This prospective observational study was carried out at the Department of Otolaryngology, Combined Military Hospital Rawalpindi, Pakistan, from September 2022 to August 2023 after approval from

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the Institutional Ethical Review Board (vide letter no NBR 403).

Inclusion Criteria: Patients of either gender aged 12 to 65 years of age planned for an elective total, sub-total and retrosternal thyroidectomy were included.

Exclusion Criteria: Patients with metastatic thyroid cancer, extensive goiter involving the mediastinum, patients with advanced cardiac or respiratory disease, those already on calcium or vitamin D supplementation, those with renal disease/CKD, sepsis (SIRS), who required massive blood transfusion per-operatively, those receiving per-operative infusion of insulin, and patients lost to follow-up were excluded.

Sample size was calculated keeping the anticipated fall in parathyroid hormone levels between patients with normocalcemia versus hypocalcemia being 53.01% versus 86.19% respectively.¹¹ Minimum sample size comparing the two population proportions came out to be 27 patients. A total of 160 patients were included in the study group, segregated into those who developed hypocalcemia versus normocalcemia post-operatively.

Written informed high-risk consent was taken from all patients, with permission to be included in the study protocol, but they were not made aware of the study outcome to prevent bias and ensure blinding. Since the study required assessment of hypocalcemic versus normocalcemic patients for parathyroid hormone (PTH) level assessment, patients were added and observed till 48 hours of the post-operative period for presence or absence of hypocalcemia till completion of the minimum sample size for both groups mentioned. Patients exhibiting hypocalcemia were placed in Group-A while patient exhibiting normocalcemia were placed in Group-B (Figure). Baseline blood samples and levels of serum calcium and serum PTH were sent at 1-hour and 24-hours post-operatively and observed for development of hypocalcemia or normocalcemia and corresponding PTH levels. Hypocalcemia assessed post-operatively was defined as a serum Ca level of less than 2.22 mmol/l and normocalcemia was defined as serum level of Ca greater than 2.22 mmol/l.¹² PTH levels of less than 15 pg/ml were defined as hypoparathyroidism.¹³ Patients were further categorized on the degree of hypocalcemia based on calcium levels into mild (2.12-2.22 mmol/l), moderate (1.88-2.10 mmol/l) and severe (<1.88 mmol/l) hypocalcemia using the hypocalcemia severity index.

Assessment for hypocalcemia apart from laboratory findings included clinical signs (Chvostek's and Trousseau's signs). Patients with symptomatic hypocalcemia including numbness and or fits were treated with Ca supplementation as per protocol and endorsed accordingly. All patients with post-operative hypocalcemia after 24 hours of the procedure received supplemental Ca and Vitamin D as oral tablets and followed up with Ca levels assessed after 7 days post-procedure.

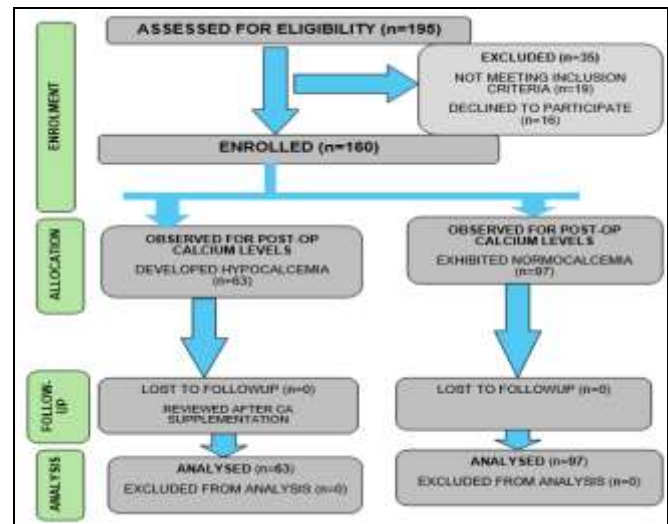


Figure: Patient Flow (n=160)

All statistical calculations were performed using Statistical Package for the Social Sciences 26. Primary variables studied were median levels of PTH for corresponding values of hypo or normocalcemia, frequency of patients presenting with normo versus hypocalcemia observed 48 hours post-operatively. Secondary variables of study were the sensitivity and specificity of PTH in predicting hypocalcemia and follow-up calcium levels in patients with hypocalcemia after 7 days post-procedure. Demographic data were statistically described in terms of median and inter quartile range, or frequencies and percentages where appropriate. Non parametric tests were used to compare means, and Chi-square test was used for frequency variables. Sensitivity and specificity were calculated for comparing levels of PTH and development of hypocalcemia. A *p*-value of <0.05 was considered statistically significant.

RESULTS

A total of 160 patients were included in the final assessment protocol after meeting the inclusion

criteria. Median age of patients was 46 (IQR 44-48) years and median weight was 68 (IQR 67-76). Gender distribution of the study group included 49(30.6%) males and 111(69.4%) females. The incidence of hypocalcemia in the study group was seen in 63(39.4%) patients and normocalcemia was seen in 97(60.6%) patients (Table-I).

Table-I Demographic and Clinical Variables (n=160)

Variable	Values
Age in years, Median (IQR)	46 (44-48)
Weight in kg, Median (IQR)	68 (67-76)
Gender	
Male	49 (30.6%)
Female	111 (69.4%)
Patients with normocalcemia after 48 hours	97 (60.6%)
Patients with hypocalcemia after 48 hours	63 (39.4%)

Patients with hypocalcemia were designated as Group-A (n=63) while those with normocalcemia were designated as Group-B (n=97). Median levels of calcium taken 01 hour post-operatively were 2.1 (IQR 2.0-2.3) mmol/l versus 2.2 (IQR 2.1-2.4) mmol/l between both groups ($p<0.001$), and levels taken 24 hours post-operatively were 2.2 (IQR 2.0-2.3) versus 2.2 (IQR 2.1-2.4) mmol/l between Group A and Group B ($p<0.001$). Similarly, median levels of PTH (parathyroid hormone) taken at 1 hour post-operatively were 34.0 (IQR 9-38) versus 43.0 (IQR 37.0-46.0) pg/ml ($p<0.001$), while levels taken 24 hours post-operatively were 34.0 (IQR 7.0-38.0) pg/ml ($p<0.001$), which can be seen in Table-II.

Table-II: Calcium and Corresponding Parathyroid Hormone (PTH) Levels between Patients with Normocalcemia versus Hypocalcemia (n=160)

Variables	Group-A (n=63) Median (IQR)	Group-B (n=97) Median (IQR)	p-value
Serum calcium levels (mmol/l)			
1 hour post-surgery	2.1(2.0-2.3)	2.2(2.1-2.4)	<0.001
24 hours post-surgery	2.2 (2.0-2.3)	2.2(2.1-2.4)	<0.001
Serum parathyroid hormone levels (pg/ml)			
1 hour post-surgery	34.0 (9.0-38.0)	43.0 (37.0-46.0)	<0.001
24 hours post-surgery	34.0 (7.0-38.0)	43.0 (37.0-46.0)	<0.001

The ability of PTH in predicting hypocalcemia at 01- and 24-hour intervals showed a sensitivity of 90.5% and a specificity of 79.4% at one hour while the sensitivity at 24 hours was 95.2% with a specificity of 96.9% (Table-III).

One-four-hour post-thyroidectomy showed a positive predictive value (PPV) of 0.74, and negative predictive value (NPV) of 0.93. Twenty-four-hour post-thyroidectomy showed a positive predictive

value (PPV) of 0.95 and negative predictive value (NPV) of 0.97.

Table-III: Sensitivity and Specificity of Parathyroid Hormone (PTH) Levels in Predicting Hypocalcemia (n=160)

Variable	At 01 Hour	At 24 Hours
Sensitivity	90.5%	95.2%
Specificity	79.4%	96.9%

When comparing the severity of hypocalcemia, there were no reported cases of mild hypocalcemia. Moderate hypocalcemia was reported in 43(68.3%) patients after 24 hours, while severe hypocalcemia was reported in 20(31.7%) patients. After treatment in the hypocalcemia group (Group-A, n=63) after 7 days post-operatively, normocalcemia was reported in 43(68.3%) patients, mild hypocalcemia in 02(3.2%), moderate hypocalcemia in 16 (25.4%) and severe hypocalcemia was reported in 02 (3.2%) patients. Median values for serum ionized calcium were 2.2(IQR 2.0-2.3) mmol/l after 24 hours post-operatively versus 2.2(IQR 2.1-2.4) mmol/l after 7 days post-operatively on Ca supplementation ($p<0.001$), as seen in Table-IV.

Table-IV: Change in Serum Calcium Levels in Hypocalcemia Group after Oral Supplementation 7 DAYS post-procedure (n=63)

Variables	At 24 hours (n=63) n(%)	At 7 days (n=63) n(%)	p-value
Frequency of hypocalcemia severity			
Normocalcemia	00(0.0%)	43(68.3%)	-
Mild hypocalcemia	00(0.0%)	02(3.2%)	-
Moderate hypocalcemia	43(68.3%)	16(25.4%)	-
Severe hypocalcemia	20(31.7%)	02(3.2%)	-
Serum calcium levels (mmol/l), Median (IQR)	2.2(2.0-2.3)	2.2(2.1-2.4)	<0.001

DISCUSSION

Our study concluded very positive results to recommend the use of PTH hormone levels in patients undergoing thyroidectomy. The results showed that PTH levels show excellent sensitivity and specificity for diagnosing hypocalcemia earlier and this finding may prevent related complications if therapy is started in patients prone to develop hypocalcemia in the next 12-24 hours.¹¹ Local studies done by Aimon *et al.* have proposed similar results.¹² Prior research has favored routinely prescribing oral calcium following surgery to avoid post-thyroidectomy hypocalcemia and permit a quicker hospital departure. This regimen, nevertheless, could cause hypercalcemia sometimes and needless therapy in some individuals.¹³

In our medical setting, we started a new technique for PTH assessment to foretell postoperative hypocalcemia in patients having TT. PTH was tested at 01 and then 24 hours following the procedure. First-hour measurements were used to identify patients who might soon acquire hypocalcemia, and 24-hour measurements were used to monitor any substantial alterations in PTH concentrations. Findings concluded that pre-operative levels were comparable between both groups while PTH levels were considerably lower in patients with hypocalcemia done at 01 and then at 24 hours being corroborated by various studies done internationally.¹⁴ The levels of PTH corresponding to hypocalcemia were 2-4 times lower than the ranges in seen with people who exhibited normocalcemia showing a good correlation between the two parameters assessed post-operatively. The results of our research indicated that measuring PTH concentrations on the post-surgery first hour was accurate and credible in predicting post-surgery hypoparathyroidism because there were no statistically substantial variations between mean serum PTH concentrations at the postoperative first and twenty-four hours. As a result, patients with appropriate PTH values in the first hour might be released from the hospital without risk. This has been supported by international studies as well.¹⁵

Comparing the outcomes between the two groups revealed a statistically significant difference concerning hypocalcemia. We propose that the development of both symptomatic and asymptomatic hypocalcemia can be prevented by diagnosing individuals with hypoparathyroidism during the first postoperative hour and administering preventive calcium and vitamin D as a treatment protocol keeping the falling levels of PTH as reference in these patients. The effectiveness of preventive calcium and vitamin D in averting the onset of symptomatic and non-symptomatic hypocalcemia in individuals with hypoparathyroidism discovered after 24 hours following surgery has also been demonstrated in several trials, along with being reported in our study as well.^{16,17}

The PTH test could be cost-effective by lowering postoperative hospital stay. While the assay itself is not cost-effective, the burden of hypocalcemia induced complications and the resulting prolongation in hospital stay far exceeds the cost of the test. Secondly, as individuals who had a decrease in PTH levels showed complications later on, we can reserve 24-hour

sample testing only in susceptible individuals in resource constrained settings and start prophylactic Ca treatment accordingly after the first hour of the procedure. Even though a more extensive study is required for its full validation, it should be employed in clinical management as a highly accurate tool for the earlier detection, prevention, and therapy of medically necessary post-thyroidectomy hypocalcemia.¹⁸

The excellent sensitivity and specificity of PTH levels in predicting hypocalcemia offers a new avenue of treatment strategies which can help mitigate hypocalcemia-induced complications, resulting in effective and better patient care.

We recommend PTH hormone assay as an excellent predictive marker for segregating patients which may develop hypocalcemia and starting treatment accordingly to prevent complications and decreasing hospital stay.

LIMITATIONS OF STUDY

The fact that ours was a single center study is the main limitation. Secondly, cost-affectivity and broader availability of PTH assays still remain issues. The sensitivity needs to be studied in specific thyroid malignancies and non-malignant cases to see any changes or co-relation between hypocalcemia and PTH levels.

CONCLUSION

We conclude that falling levels of PTH hormones post-thyroidectomy showed excellent sensitivity and specificity in predicting hypocalcemia at 01 and 24 hours respectively.

Conflict of Interest: None.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

FM & AIZS: Data acquisition, data analysis, critical review, approval of the final version to be published.

AAS & MUA: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

MUAM & AY: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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