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ORIGINAL ARTICLE

Postoperative Serum Parathyroid Hormone Levels as a Predictor of Hypocalcemia in Patients Undergoing Total Thyroidectomy

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Abstract Postoperative hypocalcemia is a common complication of total thyroidectomy; the onset and severity of post-operative hypocalcemia is unpredictable. Various attempts have been made to identify predictors of hypocalcemia. There has been an increasing interest in serum levels of parathyroid hormone (PTH) as an early predictor of the development of hypocalcemia after total thyroidectomy. However, there is no consensus on the time intervals and cut-off levels of serum PTH to predict hypocalcemia. In this study, we intend to use serum PTH levels at 4th and 12th hour after total thyroidectomy to identify patients at risk of developing Postoperative hypocalcemia and to evaluate the role of PTH in predicting hypocalcemia. A Cross sectional analytical study conducted in 33 patients undergoing total/completion thyroidectomy from December 2018 to May 2020. Serum total calcium, Serum ionized calcium and Serum intact PTH levels were measured on three occasions (Preoperative and 4th and 12th hour Postoperative). Between both Postoperative levels of PTH, the one with better predictability of hypocalcemia was determined. Postoperative 4th hour PTH is a better predictor of transient hypocalcemia than Postoperative 12th hour PTH, as the association of the former with serum ionized calcium level was statistically highly significant with p value 0.005 and 0.021 respectively. Serum PTH determination after four hours of total thyroidectomy is a relatively better predictor of transient hypocalcemia, and can guide calcium supplementation for those at high risk in the Postoperative period. However, to determine the risk of hypocalcemia at the end of 1 month of follow-up, both the Postoperative 4th and post-operative 12th hour PTH have similar diagnostic accuracy.

Keywords PTH (parathyroid hormone) · Thyroidectomy · Post-thyroidectomy hypocalcemia · Parathyroid gland dysfunction

Introduction

Postoperative hypocalcemia is a common complication of total thyroidectomy and the incidence varies from 1 to 50%. Post-thyroidectomy hypocalcemia is due to parathyroid gland dysfunction, caused by devascularization, stunning or accidental removal of the glands along with the thyroid gland. Hypoparathyroidism manifests itself as hypocalcemia which can be transient (3–30%) or permanent (0.5–10.6%) [1].

Since the onset and severity of post-operative hypocalcemia is unpredictable, various attempts have been made to identify predictors of hypocalcemia. There has been an increasing interest in serum parathyroid hormone (PTH) levels as an early predictor of the development of hypocalcemia after total thyroidectomy. During the last few years, several researchers have measured PTH levels at various durations after thyroidectomy in an attempt to predict postoperative hypocalcemia [2–4].

However, there is no consensus among these studies on the time intervals and cut-off levels of serum PTH to predict hypocalcemia.

In this study we intend to use serum PTH levels on two occasions after total thyroidectomy to identify patients at

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risk of developing postoperative hypocalcemia and to evaluate the role of PTH in predicting the same.

Objectives

1. Estimate serum PTH levels before and after surgery in the 4th and 12th hour for patients undergoing total thyroidectomy.
2. Classify the patients as high risk (PTH < 12 pg/ml) or low risk (PTH > 12 pg/ml), based on the cut-off level of serum PTH.
3. To monitor and document the onset and severity of hypocalcemia in the high-risk group and the low-risk group.

Materials and Methods

This single center cross-sectional study was conducted in a tertiary care hospital and Research center attached to a medical college. The study was conducted between Dec 2018 to May 2020 after ethical clearance was obtained from institutional ethical committee (IEC) Ref No: DMC/KLR/IEC/758/20-21. Informed consent was obtained from all the participants.

Sample size of 33 patients was estimated using n' master 2.0 sample size calculating software, considering the reported percentage of 25.7% of patients developing hypocalcemia 24 h after thyroidectomy with a confidence interval of 95% and an absolute error of 15%.

The surgeries included 28 total thyroidectomies (Figs. 1 and 2) and 5 completion thyroidectomies (after hemithyroidectomy done elsewhere). Additional patient data evaluated were age, sex, preoperative diagnosis, number of parathyroid glands identified in the surgical specimen, and histological findings. All surgeries were performed by the same surgical team from the Department of Otorhinolaryngology and Head & Neck Surgery in our hospital.

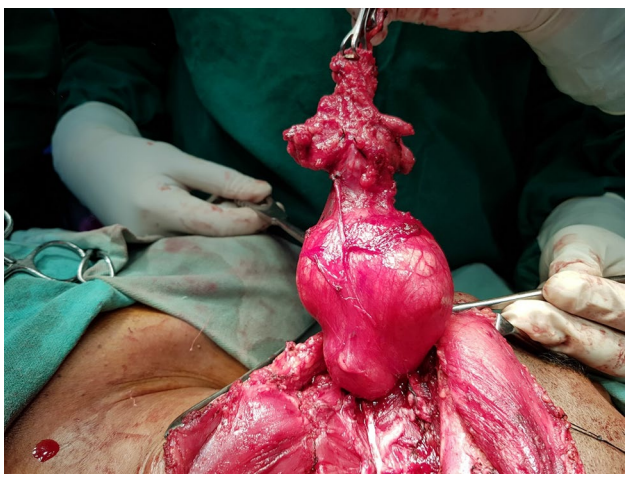

Fig. 1 Total thyroidectomy with central compartment clearance

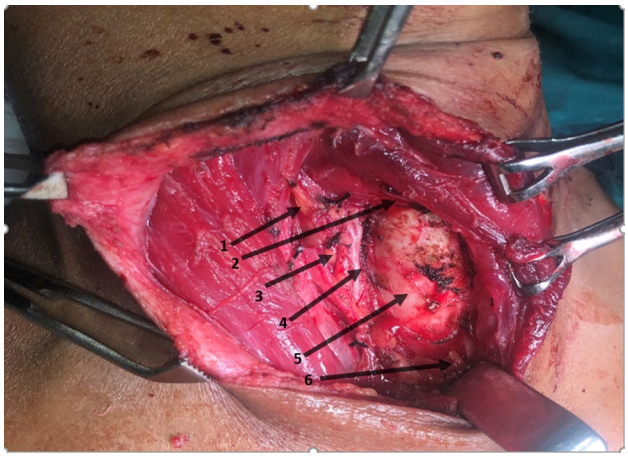

Fig. 2 Thyroid bed after total thyroidectomy showing, 1: superior parathyroid; 2: external br. superior laryngeal nerve; 3: inferior parathyroids; 4: RLN with bifurcation; 5: trachea; 6: central compartment nodes

Patients with parathyroid adenoma or hyperplasia, those with chronic renal disease, and patients receiving calcium and vitamin-D supplementation prior to surgery were excluded from the study.

This study involved the measurement of Serum ionized calcium, Serum total Calcium, Serum total Protein and serum albumin using Autoanalyzer, Serum intact PTH using Vitros Eci Immunodiagnostic systems (ortho-clinical diagnostics, United Kingdom).

The Serum ionized calcium, Serum total Calcium and PTH were measured preoperatively, 4th hour and 12th hour post operatively and expressed in mg/dl and pg/ml respectively.

PTH secreted into the blood stream undergoes extensive proteolysis to generate fragments, intact PTH is relatively independent of the glomerular filtration rate and reflects the biologically active portion of the hormone [5].

Serum total protein and albumin concentrations were measured only preoperatively to exclude patients with hypoproteinemia and/or hypoalbuminemia.

Reference ranges accepted as normal for ionized Calcium 4.5–5.6 mg/dl with hypocalcemia defined as < 4.5 mg/dl, serum total Calcium 8.6–10.2 mg/dl with hypocalcemia defined as < 8.6 mg/dl. serum total protein 6.4–8.3 g/dl, and serum albumin 3.5–5.2 g/dl.

Statistical methods: Hypocalcemia, high risk, low risk was considered as primary outcome variables. Post-operative 4th hour PTH and 12th hour PTH were primary explanatory variables.

Descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency and proportion for categorical variables. Shapiro wilk test p value of > 0.05 was considered as normal distribution. p value of < 0.05 was considered as statistically significant after assuming all the rules of statistical tests. Statistical software: IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.

Results

Thirty-three patients were enrolled in the study. Among them, 27 were women (81.82%) and 6 were males (18.18%). The mean age of the patients was 45 ± 10.37 (range: 21–64 years).

Of the 33 patients, 28 patients (84.85%) underwent Total thyroidectomy and 5 patients (5.15%) underwent Completion thyroidectomy. Total thyroidectomy was performed for malignancy in 17 (52%) patients. The most common malignancy in our series was papillary thyroid carcinoma seen in 14 cases followed by FTC in 2 cases and MTC in 1 case. Nine patients underwent total thyroidectomy for benign pathology. Among the patients with malignancy, central compartment clearance was performed in 11 (33%) patients.

Patients who underwent compartment clearance had significantly higher rates of transient hypoparathyroidism whereas no statistical significance was obtained between the central compartment clearance technique and development of prolonged hypocalcemia.

The mean Preoperative PTH, mean Postoperative 4th Hour PTH and mean Postoperative 12th Hour PTH was 18.16 ± 10.18, 12.77 ± 7.25 and 9.71 ± 5.31 respectively, the mean Preoperative total Calcium, the mean postoperative 4th Hour total Calcium and the mean Postoperative 12th Hour total Calcium was 9.3 ± 0.84, 8.45 ± 0.96 and 8.17 ± 1.17 respectively and the mean Preoperative ionized Calcium, the mean postoperative 4th hour ionized Calcium and the mean Postoperative 12th hour ionized Calcium was 4.82 ± 0.47, 4.35 ± 0.52 and 4.19 ± 0.46 respectively. There was a significant decrease in mean serum Calcium levels at the 4th hour and 12th hour compared to preoperative Calcium levels in both groups, which explained the development of symptoms of transient hypocalcemia in approximately half of the study participants, Table 1.

We have categorized post-thyroidectomy patients as high risk of developing hypocalcemia based on postoperative 4th hour PTH of less than 12 pg/ml. With a cut-off value of 12 pg/ml at the Postoperative 4th hour as the cut-off value, 18 patients were classified as high risk and 15 as low risk of developing hypocalcemia. 14 patients in the high-risk group and 3 patients in low-risk group developed transient hypocalcemia. At 1 month Postoperative follow-up, 10 patients in the high-risk group had persistent hypocalcemia (mildly symptomatic) and received oral calcium and vitamin-D treatment. None of the patients in the low-risk group were hypocalcemia.

The Postoperative 4th hour PTH had fair predictive validity in predicting follow-up ionized calcium, as indicated by the area under the curve of 0.780 (95% CI 0.621 to 0.938, p value 0.012), similarly the Postoperative 12th hour PTH had good predictive validity in predicting follow-up ionized calcium, as indicated by the area under the curve of 0.891 (95% CI 0.782 to 1.000, p value < 0.001), Table 2.

PTH value of ≤ 13.7 at 4th hour had highest sensitivity and specificity in predicting hypocalcemia at 4th hour

Table 2 Predictive validity of Post Op 4Th Hour PTH and Post Op 12Th Hour PTH in predicting follow-up ionized calcium (ROC analysis) (N = 32)

Test result variables: post op 4th hour PTH and post op 12th hour PTH					
Area under the curve		SE	95% CI of AUC		p value
			Lower bound	Upper bound	
Post op 4th hour	0.780	0.081	0.621	0.938	0.012
Post op 12th hour	0.891	0.056	0.782	1.000	< 0.001

Table 1 Descriptive analysis of PTH, Total calcium and Ionized calcium in study population (N = 33)

	Mean ± SD	Median	Minimum	Maximum	95% CI	
					Lower	Upper
Pre-op PTH	18.16 ± 10.18	17	4.3	47.5	14.55	21.77
Post-op 4th hour	12.77 ± 7.25	11	3.4	29.1	10.2	15.34
Post-op 12th hour	9.71 ± 5.31	8.9	3.4	26.1	7.82	11.59
Pre-op total calcium	9.3 ± 0.84	9.5	7.2	10.8	9	9.6
Post-op 4th hour total calcium	8.45 ± 0.96	8.4	6.2	10	8.1	8.79
Post-op 12th hour total calcium	8.17 ± 1.17	8.3	4	9.8	7.75	8.58
Post-op 4th hour ionized Ca^{2+}	4.35 ± 0.53	4.3	3.17	5.17	4.17	4.54
Post-op 12th hour ionized Ca^{2+}	4.2 ± 0.65	4.22	1.9	5.1	3.97	4.43

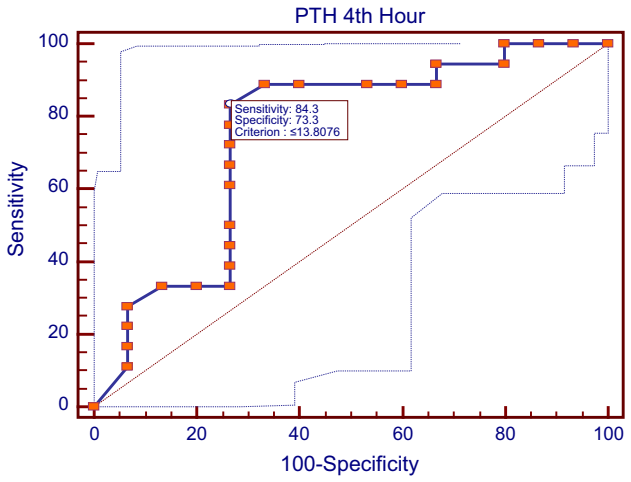

Fig. 3 ROC curve showing validity of PTH at 4th hour in predicting hypocalcaemia at 4th hour (ionized calcium)

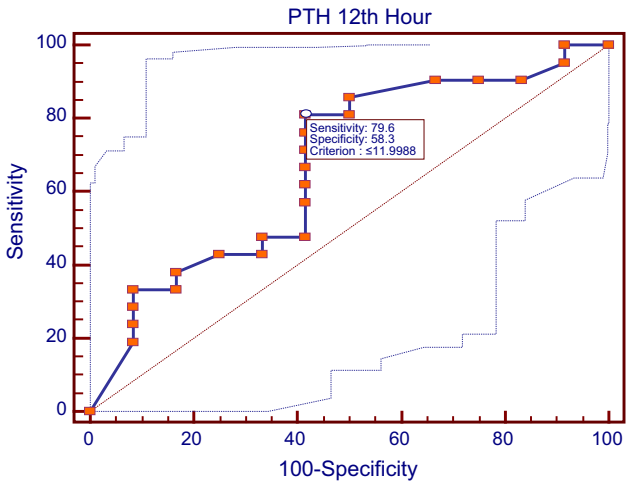

Fig. 4 ROC curve showing validity of PTH at 12th hour in predicting hypocalcaemia at 12th hour (ionized calcium)

postoperative. Sensitivity was 83.3%, specificity was 73.33%, positive predictive value was 78.9% and negative predictive value was 78.6%, (Fig. 3). Similarly, PTH value of ≤ 12.4 at 12th hour had highest sensitivity and specificity in predicting hypocalcemia at 12th hour postoperative. Sensitivity was 80.95%, specificity was 58.33%, Positive predictive value was 77.3% and negative predictive value was 63.6% (Fig. 4).

No significant relation was observed in the occurrence of hypocalcemia with respect to the number of parathyroid visualized or saved within the risk groups (p value 0.697) and (p value 0.101) respectively.

Among the 27 women enrolled in the study, 12 (44%) developed transient hypocalcemia, which was significantly higher than that detected in men, 2 out of 6 (33%).

Both Post-operative 4th and 12th hour PTH had similar sensitivity, specificity, negative predictive value and positive predictive value to predict prolonged hypocalcemia.

Discussion

Thyroidectomy though considered safe, carries risks especially, in terms of hypo-functioning of the parathyroid glands. Along with thyroid surgeries, any surgery of the anterior neck (central compartment) predisposes the parathyroid glands to the risk of being accidentally removed along with the thyroid specimen, or having vascular compromise leading to a decrease in the serum parathormone (PTH, Parathyroid hormone) levels [6].

The fall in serum parathyroid hormone levels after thyroidectomy often manifests as hypocalcemia with an incidence of 1–50% [7]. In our study, the estimated rate of transient hypocalcemia was 42%. This hyposecretion of PTH can be relatively transient [1.6–68%] or permanent [0.4–33%] [8].

Serum calcium is not an accurate predictor of hypocalcemia as levels do not undergo significant changes until one to two days after thyroidectomy and also hypocalcemia symptoms might not appear for 24 to 48 h.

Hence, post-operatively it is difficult to predict whether a patient is at a higher risk of developing hypocalcemia based only on calcium levels or surgical events [9].

So, as a common practice in our center, calcium and/or Vitamin-D are administered prophylactically to patients after total thyroidectomy [10].

To reliably predict the risk of developing hypocalcemia in patients undergoing total thyroidectomy more specific biochemical tests can be performed such as the estimate of the serum parathyroid hormone as studies have shown that the postoperative serum PTH levels can be a predictor of the occurrence and severity of hypocalcemia after thyroidectomy. During the last few years, several researchers have measured PTH levels within minutes or hours after thyroidectomy procedure to predict the onset and severity of postoperative hypocalcemia.

In our pilot study, we have measured PTH levels at two-time intervals; post-op 4 h and post-op 12 h, given the fact that at our center processing of the samples for PTH measurement is available only during afternoon hours. Also, the selection of two timings was done in order to assess the better of the two, so that it can be incorporated in the protocol for management of the patients undergoing Total thyroidectomy.

Also, an in-depth review of literature was carried out before opting for two post-op timings for PTH measurement.

However, no common guidelines have been established on the use of PTH, nor has its use been universally adopted

in common practice. The widespread application of the PTH assay is expensive and many centers do not have access to the PTH assay kits or the technical feasibility to run the tests.

Studies have evaluated possible risk factors that include patient characteristics, disease related factors or surgical procedures that can influence the development of post-thyroidectomy hypoparathyroidism. In the literature, different opinions have been expressed about the correlation between the development of postoperative hypocalcemia and the age of the patient. Similarly, a systematic review found no correlation between patients age and postoperative hypocalcemia [11].

In most studies, the female sex has been identified as a significant risk factor for hypocalcemia. In the present study, female patients developed transient hypocalcemia in 44% (12/27) of cases, which was significantly greater than that detected in men, 33% of cases (2/6). The extent of thyroidectomy, and malignant neoplasm are commonly considered to be risk factors for hypocalcemia after thyroidectomy. Multivariate analyses by various authors confirmed that the extent of resection is a major risk factor for transient and permanent hypoparathyroidism after thyroid surgery, even when surgical technique and surgeon expertise are controlled for [12].

In our statistical analysis, the pathological finding of malignancy was significantly associated with the development of hypocalcemia as can be shown by comparing the risk groups.

The current study also shows that the extent of resection remains the strongest independent risk factor for postoperative hypoparathyroidism.

One of the largest series in the literature on the complications of central compartment clearance performed in 1087 patients over a 30-year period, found that central compartment clearance had a significantly higher rate of transient hypoparathyroidism (51.9% vs. 27.7%, respectively) and permanent hypoparathyroidism (16.2% vs. 6.3%, respectively) than total thyroidectomy alone [13].

In this study, patients undergoing total thyroidectomy with central compartment clearance had a higher rate of transient [69.2% vs. 20%, respectively] and prolonged hypoparathyroidism [46% vs. 20%, respectively] compared to patients undergoing total thyroidectomy alone. However, central compartment clearance was found to be a significant risk factor for transient hypoparathyroidism alone.

There was no statistically significant difference in the occurrence of hypocalcemia with respect to the number of parathyroids visualized or saved within the risk groups. (P value 0.697) and (P value 0.101) respectively.

Furthermore, we have also taken into account another time interval i.e., post-operative 12th hour PTH, to evaluate its ability to predict hypocalcemia. Based on the ROC the Post Op 12Th hour PTH had good predictive validity in predicting the risk, as indicated by area under the curve of 0.906 (95% CI 0.779 to 1.000, p value < 0.001).

The postoperative 12Th Hour PTH had good predictive validity in predicting follow-up ionized calcium levels, as indicated by the area under the curve of 0.891 (95% CI 0.782 to 1.000, p value < 0.001). Therefore, the utility of postoperative 12th hour PTH as an additional time interval to predict hypocalcemia after 1 month after total thyroidectomy can be considered.

Both post-op 4th and 12th hour PTH levels were found to have almost similar ability to predict transient and prolonged hypocalcemia in patients undergoing total thyroidectomy and either of them can be used as a predictor with similar results.

However, we found that post-operative 4th hour PTH is better than the post-operative 12th hour PTH as a predictor of transient hypocalcemia. The association of the former with the development of hypocalcemia in the immediate post-operative period is statistically more significant than the latter.

Furthermore, with further analysis of our results, we suggest that a PTH value of ≤ 13.7 at 4th hour and a PTH value of ≤ 12.4 at the 12th hour can be taken into account as cut-off value to predict hypocalcemia, however prospective studies with a larger sample size are required to validate the reliability of each of these predictors of hypocalcemia.

Conclusions

The study suggests that the PTH value of ≤ 13.7 at 4th hour and the PTH value of ≤ 12.4 at the 12th hour Postoperatively can be considered as cut-off levels to predict transient hypocalcemia for the early initiation of prophylactic treatment to reduce the risk of development of hypocalcemia. However, prospective studies with a larger sample size are required to validate the reliability of each of these predictors of hypocalcemia.

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Declarations

Conflict of interest The authors have no conflicts of interest.

Ethics Approval Institutional Ethical Committee approval was obtained for: The start of study (IEC No: SDUMC/KLR/IEC/169/2018-19) and, Publication (IEC No: DMC/KLR/IEC/758/2020-21).

Informed Consent Patients were invited to participate and the consent for participation in the study was obtained from all the patients prior to the start of study.

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