



Original research

Prospective evaluation of intra-operative quick parathyroid hormone assay as an early predictor of post thyroidectomy hypocalcaemia



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HIGHLIGHTS

- Prospective study evaluating the utility of Intra operative serum quick parathyroid hormone level measurement twenty minutes after total thyroidectomy in predicting post-operative hypocalcemia.
- Prospective longitudinal study which included patients undergoing total thyroidectomy for benign or malignant thyroid disorders at tertiary hospital.
- Intra operative serum quick PTH level measurements were done twenty minutes after resection of thyroid.
- IOPTH level of 9 pmol/L, twenty minutes after total thyroidectomy, had the highest sensitivity and specificity of 92% and 83% respectively in predicting post-operative hypocalcemia.

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ABSTRACT

Background: Hypocalcaemia following total thyroidectomy is a major contributing factor in delayed hospital discharge and dissuading surgeons from day care thyroidectomy. We prospectively evaluated the utility of Intra-operative serum quick parathyroid hormone level measurement twenty minutes after total thyroidectomy in predicting post-operative hypocalcemia.

Material and methods: Prospective longitudinal study which included patients undergoing total thyroidectomy for benign or malignant thyroid disorders at SGPGIMS, Lucknow, India from November 2013 to February 2015. Patients who received calcium prophylaxis were excluded from the study. Intra-operative serum quick PTH level measurements were done twenty minutes after resection of thyroid. Serum calcium levels were estimated preoperatively and on three consecutive post operative days. Calcium supplementation was started in patients with symptomatic hypocalcemia.

Results: The study included 100 patients with a mean age of 41 years, range 17–72 years. 48 patients had Euthyroid multinodular goitre, 10 patients grave's disease and 42 patients had differentiated thyroid cancer. Total thyroidectomy was performed in 88 patients, total thyroidectomy with lymph node dissection in 12 patients. Post-operatively 23% patients experienced symptomatic hypocalcemia. The IOPTH level of 9 pmol/L, twenty minutes after total thyroidectomy, had the highest sensitivity and specificity of 92% and 83% respectively in predicting post-operative hypocalcemia.

Conclusion: Parathyroid hormone assay twenty minutes after thyroidectomy is an accurate and reliable means of predicting clinically relevant hypocalcemia. Patients with PTH values greater than 9 pmol/L twenty minutes after thyroidectomy, can be safely discharged on the same postoperative day as the probability of life threatening hypocalcemia is unlikely.

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1. Introduction

Thyroidectomy has evolved a long way since the 1970's. The technique of total thyroidectomy has shifted from lateral approach to capsular dissection in order to avoid injury to the recurrent laryngeal nerve and the parathyroids, and the completeness of

resection has progressed from anatomical dissection to embryological dissection with complete excision of the pyramidal remnants and tubercle of zuckerkanndl so as to prevent recurrence. With a significant decrease in the rates of postoperative hemorrhage, RLN palsy and permanent hypocalcaemia, there has been a subsequent reduction in hospital stay and thyroidectomy can now be performed as a day care surgery. However, temporary hypocalcaemia commonly occurring secondary to temporary hypoparathyroidism is one of the most frequent morbidities following thyroidectomy, with incidence ranging between 3 and 40% [1,2]. Additionally, as potentially life threatening hypocalcaemia may not develop for 24–48 h following surgery, besides postoperative bleeding, hypoparathyroidism is a major concern for delayed hospital discharge and dissuading surgeons from performing day care thyroid surgery.

To safely manage postoperative hypoparathyroidism/hypocalcaemia, various approaches have been adopted. The most common being serial calcium monitoring wherein calcium levels are typically drawn at 6–12 h intervals until a normocalcaemic plateau or a stable upward trend is demonstrated but this involves patients staying for at least 1–2 nights in the hospital [3]. In the era of cost containment, in order to avoid unnecessary prolonged hospital stay, there has been a gradual shift from Serial calcium monitoring to the other approaches like Routine calcium supplementation and Parathyroid hormone (PTH) directed supplementation. The availability of a perioperative method like PTH assay that can accurately identify patients who are at low risk to develop hypocalcaemia would be beneficial. These low risk patients, who comprise the majority of thyroidectomy patients, can undergo day care surgery. Similarly, those patients that can be identified early as high risk for developing hypocalcaemia can receive immediate prophylactic treatment there by mitigating troublesome symptoms and prolonged hospitalization. To detect hypocalcaemia, a comparison of decrease in serum PTH level after thyroidectomy to preoperative baseline PTH has been studied. However, this approach required the collection of several samples during and after surgery and the test's accuracy varied with preoperative PTH level [4,5]. Recently, a single PTH measurement some time after surgery has been advocated. Numerous PTH criteria with regards to timing of assay have been proposed but none have clearly been shown to be superior [5–7]. Recent reviews have suggested that measurement of a single PTH assay any time from 10 min to up to 6 h postoperatively seemed to provide equally accurate predictive results [5,7]. In our study, a single quick intraoperative PTH (ioPTH) level measurement was taken 20 min after thyroidectomy so that the PTH results would be available sooner and would facilitate ambulatory surgery. The aim of our study was to evaluate prospectively the utility of quick intraoperative PTH (ioPTH) assay in predicting clinically relevant postoperative hypocalcaemia [8–11].

2. Patient and methods

2.1. Study design

This was a single-center prospective cohort study conducted at a tertiary referral center from November 2013 to February 2015. One hundred patients who underwent total thyroidectomy for benign as well as malignant pathologies of thyroid gland were studied. The protocol was approved by the Institution's Ethics Committee, and written informed consent were obtained from all participants.

2.2. Patients

Inclusion criteria included all patients who underwent either a total or a completion total thyroidectomy for benign or malignant

thyroid disease. Exclusion criteria included patients who received postoperative calcium prophylaxis, patients with known hyperparathyroidism, chronic renal insufficiency, pregnancy or those with concomitant serious illnesses requiring hospitalization during the perioperative period and those with incomplete biochemical values. Patients on medications known to affect calcium or PTH levels such as lithium, octreotide, antiepileptics, glucocorticoids, bisphosphonates, diuretics and estrogens were excluded from the study.

2.3. Methods

Total thyroidectomy was defined as excision of both lobes and isthmus of the thyroid gland. Completion thyroidectomy was defined as a patient who had a previous thyroid lobectomy and who was presenting for excision of the remaining thyroid lobe. All surgeries were performed according to the department protocol, the recurrent laryngeal nerves were carefully identified and dissected, and the superior thyroid artery and vein were separately identified and ligated close to the thyroid gland. Parathyroid glands were routinely identified and preserved, with meticulous dissection to preserve their blood supply. If the parathyroid glands could not be readily identified, further dissection was not undertaken to identify them. Any devascularized parathyroid glands were immediately minced and auto transplanted to the ipsilateral sternocleidomastoid muscle. Operative findings such as the weight of the thyroidectomy specimen and the number of parathyroid glands identified and auto transplanted were recorded. The quick ioPTH level measurements were taken twenty minutes after excision of the thyroid, while the patient was still anesthetized. Serum Calcium levels were checked preoperatively and on post-operative days 1, 2 and 3. All patients were observed for the development of either asymptomatic (biochemical) or symptomatic (clinical) hypocalcaemia. The decision of calcium supplementation was not dependent on the ioPTH levels. Asymptomatic/biochemical hypocalcaemia was defined as a serum calcium of less than 8.0 mg/dL in the absence of clinical signs or symptoms. Symptomatic/Clinical hypocalcaemia was defined as the presence of clinical signs or symptoms of hypocalcaemia with a serum calcium less than 8.0 mg/dL, or the presence of signs and symptoms of hypocalcaemia in patients with a serum calcium equal to or greater than 8.0 mg/dL. Patients who developed biochemical hypocalcaemia were treated with elemental oral calcium supplementation. Patients who developed clinically relevant hypocalcaemia were treated with intravenous calcium gluconate and/or oral vitamin D supplementation in addition to elemental oral calcium.

All post thyroidectomy patients were followed up within 1 week and were asked specifically about hypocalcaemic symptoms after hospital discharge. They were then followed up every 2–3 months for the first year. Those patients who discontinued all supplements in the presence of normocalcaemia within 6 months of surgery were regarded as having temporary hypoparathyroidism, whereas those who continued on the supplements for more than 6 months with low serum PTH at 6 months were categorized as having permanent hypoparathyroidism.

2.4. Laboratory

The Siemens Immulite Immunoassay System, a rapid assay based upon chemiluminescence for intact parathyroid hormone, was utilized in our study. The result is usually available within 15–30 min, and all serum utilized was obtained from peripheral venipuncture. The lower and higher limits of detection range from 5 to 2500 pg/ml with an analytical sensitivity of 4.0 pg/ml. The intraassay and interassay precision are <12% and <10% respectively.

Table 1
Demographic, Clinical, and Biochemical Characteristics of patients.

| Characteristic | Value |
|---|-----------------------------|
| Age (yrs) \pm SD (range) | 41.78 \pm 14.79 (17–72) |
| Sex (male/female) | 29/71 |
| Clinical presentation | |
| Multi-nodular Goiter | 47 |
| Solitary thyroid nodule | 33 |
| Diffuse goiter | 18 |
| Lateral neck mass | 2 |
| Duration of illness in months; Median, Range | 36 (1–600) |
| Thyroid functional status | |
| Euthyroid | 81 |
| Hyperthyroid | 13 |
| Hypothyroid | 6 |
| Preoperative serum calcium (mg/dL) \pm SD (range) | 9.11 \pm 0.54 (8.1–10.30) |
| Thyroidectomy | |
| Total | 91 |
| Completion | 9 |
| Histopathology | |
| Malignant | 42 |
| Benign | 58 |
| Intra-operative PTH @ 20 min post thyroidectomy (pg/mL) \pm SD (range) | 24.92 \pm 26.75 (5–167) |

2.5. Statistics

χ^2 test and Fisher's exact test were used for comparison of dichotomous variables between the two groups. Student *t*-test and the Mann-Whitney *U* test were used for comparison of parametric and non parametric continuous variables respectively. Preoperative and postoperative day one biochemical variables that were significant in the univariate analysis were entered into multivariate analysis to determine independent factor. Youden's index was used to calculate the best cutoff value for predicting hypocalcaemia. The area under a receiver characteristic (ROC) curve (AUC) was used to measure the relative predictability of these variables or criteria. AUC values close to 1.00 meant better predictability and those close to 0.500 meant poorer predictability. All statistical analyses were conducted using SPSS version 18.0 (SPSS, Inc., Chicago, IL, USA). *P* < 0.05 was considered statistically significant.

3. Results

A total of 100 patients were included in the statistical analysis of the study; 29 males and 71 females, with age ranging from 17 to 72 years (median age 48.5 years). Total thyroidectomy was performed in 91 patients, while 9 patients underwent completion thyroidectomy. The demographic, clinical and biochemical characteristics of the patients are represented in Table 1.

Mean preoperative total calcium level was 9.11 \pm 0.54 (range- 8.1– 10.30) mg/dL with a preoperative ionic calcium level of 4.57 \pm 0.23 (range-4.0– 5.2) mg/dL. The intra operative PTH, 20 min after thyroidectomy was 24.92 \pm 26.75 (range 5–167) pg/mL (Table 1).

Out of the 100 patients, 23 patients developed symptomatic hypocalcaemia, 52 patients developed biochemical hypocalcaemia and 25 patients were normocalcaemic. On comparing the two

Table 2
Comparison of Clinicopathological and Biochemical Parameters between Group I (Normocalcaemia) and Group II (Clinical hypocalcaemia).

| | Group I (n = 77) | Group II (n = 23) | P value |
|---|----------------------------|---------------------------|---------|
| Age \pm SD (yrs) (range) | 42.96 \pm 14.50 | 37.83 \pm 14.55 | 0.14 |
| Sex (male/female) | 22/55 | 7/16 | 0.94 |
| Hyperthyroidism (yes/no) | 9 | 4 | 0.73 |
| Preoperative serum calcium (mg/dL) \pm SD (range) | 9.17 \pm 0.53 (8.3–10.3) | 8.91 \pm 0.51 (8.1–9.8) | 0.04 |
| Preoperative ionized calcium (mg/dL) \pm SD (range) | 4.59 \pm 0.22 (4.0–5.2) | 4.50 \pm 0.27 (4.0–4.9) | 0.12 |
| Thyroidectomy | | | |
| Total | 68 | 23 | 0.08 |
| Completion | 9 | 0 | |
| Lymph node dissection (yes/no) | 8/69 | 4/19 | 0.36 |
| No. of parathyroid glands identified and preserved | | | |
| \leq 2 glands | 13 (8%) | 2 (16%) | 0.04 |
| $>$ 2 glands | 64 (83%) | 21 (82%) | |
| No. of parathyroid glands auto-transplanted | | | |
| None | 63 | 18 | 0.64 |
| 1 | 11 | 3 | |
| 2 | 3 | 2 | |
| Weight of excised gland (gm) | 102.63 \pm 105.87 | 122.73 \pm 111.96 | |
| Histopathology | | | |
| Malignant | 32 | 10 | 0.58 |
| Graves' disease/toxic MNG | 9 | 1 | |
| Benign | 36 | 12 | |
| Thyroiditis (yes/no) | 7/77 | 4/23 | 0.26 |
| Intra-operative PTH, @20 min post-thyroidectomy (pg/mL) \pm SD (range) | 30.61 \pm 28.06 (5–167) | 5.88 \pm 2.64 (5–15) | <0.001 |

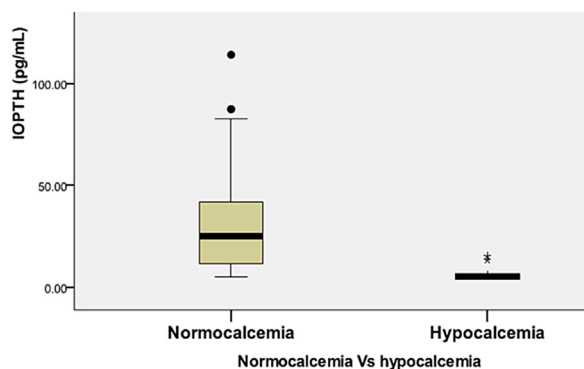


Fig. 1. Comparison of ioPTH @ 20 min between Group I (Normocalcaemia) and Group II (Clinical hypocalcaemia).

groups, Group I (Normocalcaemia and biochemical hypocalcaemia) and Group II (Clinically relevant hypocalcaemia), there was no sig-

and specificity 83.1%).

Tables 4 and 5 compares ioPTH-20 min post thyroidectomy ≤ 9.0 pg/ml or ≥ 9 pg/ml between group-I and group-II. Of the 23 patients in group II, 21 patients had ioPTH ≤ 9 pg/ml and 2 patients had ioPTH ≥ 9 pg/ml whereas 15 patients with PTH ≤ 9 pg/ml did not develop any symptoms of hypocalcaemia and were discharged without any calcium supplements.

4. Discussion

In our study, test sensitivity and specificity of quick ioPTH @20 min for predicting post thyroidectomy hypocalcaemia were 91% and 83% respectively, and were consistent with those reported by other authors [15]. The group with ioPTH @20 min < 9 pg/ml would need closer monitoring and oral calcium and/or calcitriol supplements to maintain normocalcaemia. It would be advisable to keep this group of patients overnight post-surgery for serial calcium monitoring.

Table 3

Factors predicting Post-Operative Hypocalcaemia (binary logistic regression analysis).

| Covariates | Beta - coefficients | Odd's ratio (95% CI) | P |
|---|---------------------|----------------------|-------|
| Preoperative total calcium (mg/dL) | -1.67 | 0.18 (0.02–1.24) | 0.08 |
| Preoperative Ionic calcium (mg/dL) | 0.54 | 1.72 (0.02–76.65) | 0.77 |
| Type of thyroid surgery (TT/CT) | -17.8 | 0.00 | 0.98 |
| Lymph node dissection | -0.58 | 0.56 (0.05–5.57) | 0.62 |
| No. of parathyroid glands identified & preserved | -0.66 | 0.51 (0.076–3.52) | 0.51 |
| No. parathyroid glands auto transplanted | -0.913 | 0.40 (0.02–5.78) | 0.50 |
| Malignant lesion | -0.48 | 0.619 (0.03–10.40) | 0.73 |
| Intra-operative PTH-20 min post thyroidectomy (pg/mL) | -0.46 | 0.63 (0.47–0.83) | 0.001 |

nificant difference in sex distribution ($p=0.94$), age of the patients ($p=0.14$), pathological nature of the lesion ($p=0.58$), presence or absence of thyroiditis ($p=0.26$), hyperthyroidism ($p=0.7$) and associated lymph node dissection ($p=0.36$). There was no difference in pre-operative TSH value ($p=0.7$). There was no difference in the number of parathyroid glands auto-transplanted between 2 groups ($p=0.64$), but number of parathyroid glands identified and preserved during surgery significantly correlated to the development of postoperative hypocalcaemia ($p=0.04$). Preoperative total calcium level (9.17 ± 0.53 vs 8.91 ± 0.51 mg/dL; $p=0.04$) and intra-operative PTH level, 20 min after thyroidectomy (30.61 ± 28.06 Vs 5.88 ± 2.64 pg/ml; $p < 0.001$) were significantly lower in Group II compared to Group I. (Table 2, Fig. 1).

On multivariate logistic regression analysis; ioPTH @ 20 min post thyroidectomy was the only independent predictor ($p=0.001$) of post operative hypocalcaemia (Table 3). In predicting hypocalcaemia, the best cutoff values for ioPTH @20 min post thyroidectomy was ≤ 9.0 pg/ml (Youden's index = 0.925; sensitivity 92.3%

Transient hypoparathyroidism is one of the most frequent morbidities following thyroidectomy and is a major reason for delayed hospital discharges, as potentially life threatening hypocalcaemic symptoms may not develop for 24–48 h following surgery [12,13]. To safely manage postoperative hypoparathyroidism/hypocalcaemia with a shortened hospital stay, various approaches have been proposed. The mechanism of transient post-thyroidectomy hypoparathyroidism is possibly related to brief intraoperative ischemia of the parathyroid glands [16], [17–20]. Physiologically active iPTH (84 amino acids) has a short in vivo half-life of 2–4 min [21], because of rapid hepatic and renal clearance. Therefore, measurement of PTH levels after thyroidectomy, offers a promising means for identifying those individuals at an increased risk of developing hypocalcaemia and PTH-directed selective supplementation is being considered a safe and effective approach [6,7].

Several PTH criteria have been proposed by various studies to predict which patients are at risk for developing clinically relevant postoperative hypocalcaemia [4–7]. These PTH criteria can be categorized into two main approaches -firstly, focusing on the percentage drop in PTH level from the preoperative to the post-operative period, and the other being measuring a single intra operative or postoperative PTH level some time after surgery with a cutoff value [4–7].

We selected the latter approach as there was no need for drawing blood samples multiple times and importantly the overall cost of PTH testing was reduced. In our study, test sensitivity and

Table 4

Comparison of ioPTH@20 min between Group I (Normocalcaemia) and Group II (Clinical hypocalcaemia).

| Variable | Group I | Group II | Total number |
|----------------------------|---------|----------|--------------|
| IOPTH @ 20 min > 9 pg/mL | 62(TN) | 2(FN) | 64 |
| IOPTH @ 20 min < 9 pg/mL | 15(FP) | 21(TP) | 36 |
| Total number | 77 | 23 | 100 |

Table 5

Comparison of Test Sensitivity and Specificity of Quick ioPTH @20 min for Postoperative Clinical Hypocalcaemia.

| IOPTH cut off | Test sensitivity (%) | Test specificity (%) | Positive predictive value | Negative predictive value | Accuracy |
|------------------------------|----------------------|----------------------|---------------------------|---------------------------|----------|
| ioPTH @20 min ≤ 9 pg/ml | 92.3% | 83.1% | 60% | 96% | 83% |

specificity are 91% and 83%, respectively, and were consistent with those reported by other authors [15],22–25. With regards to the timing of PTH sampling, recent reviews have suggested that a single PTH measurement taken any time from 10 min to upto 6 h after surgery seemed to provide equally accurate predictive results [6,7,14]. Therefore, in our study with the advantages of reduced pain, logistic simplicity, and quicker PTH results, the utility of PTH assay 20 min post thyroidectomy was evaluated.

However, despite these encouraging results, ioPTH @20 min was not 100% accurate. Most concerning was that 2 out of 64 patients with PTH at 20 min post thyroidectomy >9 pg/ml still required calcium supplements on discharge. If oral calcium and calcitriol requirements were analyzed more closely, none of the two patients with ioPTH >9 pg/ml required both oral calcium and calcitriol on discharge, suggesting that they suffered from only mild hypocalcaemia. In contrast, 21 of 36 patients with ioPTH <9 pg/ml required both oral calcium and calcitriol and 1 patient eventually developed permanent hypoparathyroidism. Hence, in the future, patients with ioPTH >9 pg/ml could be discharged on the same day of surgery and be instructed to take oral calcium when symptoms of hypocalcaemia develop as the chance of a life-threatening episode of severe hypocalcaemia would seem unlikely in this group of patients.

The group with PTH <9 pg/ml would need closer monitoring because even though 15 out of 36 patients never developed clinically relevant hypocalcaemia, the other 21 patients required oral calcium and/or calcitriol supplements to maintain normocalcaemia. Perhaps, the best strategy would be to keep this group of patients overnight post-surgery for Serial Calcium monitoring. One important point worth discussing is that although the turbo quick iPTH assay used in our present study may cost more than the conventional PTH assay, the quick PTH assay is able to produce results more quickly and this helps to facilitate early hospital discharge and day care surgery, reducing the overall medical cost of the operation. Thus, quick iPTH assay is an extremely useful tool for stratifying patients as low and high risk for post-thyroidectomy hypocalcaemia. The present study had a limitation of small sample size and was an observational study, a further randomized interventional study may be more helpful.

5. Conclusion

The criterion of ioPTH serum level below 9 pg/ml at 20 min post thyroidectomy in a single measurement has the highest accuracy in predicting post thyroidectomy clinically relevant hypocalcaemia. It would seem a reasonable approach to discharge patients with ioPTH greater than 9 pg/ml on the same day of surgery as the risk of a life threatening hypocalcaemic episode is unlikely.

However, we suggest that those with ioPTH below 9 pg/ml should receive early calcium prophylaxis and have at least one overnight hospital stay for calcium monitoring.

Ethical approval

Ethical approval was taken by the Institutional Ethical Committee.

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Author contribution

Ashwini C Reddy, MS- one of the investigators and data

collector.

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Sabaretnam M, Mch- one of the investigators and data collector.

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Conflicts of interest

No conflict of interest.

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Guarantor

DR Gyan Chand.

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