

Original Article



Parathyroid hormone assay in total thyroidectomy

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Abstract

Background: Total thyroidectomy is commonly practice now-a-days for either malignant or benign multinodular goitre. And post-operative hypocalcaemia is a sequel in this operation. **Objectives:** To find out whether post-operative PTH level is a parameter to identify hypocalcaemia after total thyroidectomy. **Materials & Methods:** This study was carried out from July 2013 to July 2014 in department of Surgery Sir Salimullah Medical College & Mitford Hospital. Total 116 patients were selected. PTH assay was performed before and after thyroidectomy. 92 patients were undergoing total thyroidectomy and were selected as test group. Rest 24 patients were undergoing unilateral lobectomy and were selected as control group. Serum calcium levels were measured in 1st and 2nd post-operative day. **Results:** Out of 92 test group patients 31(26.7%) developed post-operative hypocalcemia. Hypocalcemic patients had significantly lower post-operative PTH 5.43 ± 5.32 (median 3.3) compared with that of normocalcemic patient 16.04 ± 11.96 (median 12.5). Serum calcium was significantly lower in hypocalcemic patients at 2nd post-operative day (median 9.8) than in 1st post-operative day (median 10.15). Linear regression curve estimation revealed significant association between post-operative PTH with 2nd post-operative serum calcium. **Conclusion:** PTH assay can identify patients at risk of clinically significant hypocalcemia much earlier than serum calcium monitoring. A single PTH level post-operatively can reflect early result and help to take necessary measure to avoid hypocalcaemic effect.

Keywords: Early post-operative period, Hypocalcaemia, PTH.

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Introduction

During the early half of the nineteenth century thyroid surgery had increased mortality rate and was performed only to confront with life-threatening situations. Kocher¹ was the first who achieved a significant reduction in the mortality rate. Since then continuous developments in surgical techniques, better understanding of thyroid anatomy and pathology and with the advent of general anaesthesia thyroidectomy become a safe operation and reduce the incidence of complications. Now a day total thyroidectomy is commonly practice; due to any types of thyroid malignancy, multinodular goitre when both lobes are involved and in Graves' disease. Second time thyroid surgery is more difficult and more chance to injury vital structures. As multinodular hyperplasia frequently involves the whole gland in endemic regions, so there is no normal tissue to leave behind. The rate of recurrence is high

after hemi or subtotal resections for multinodular goiter in long-term follow-up, despite post-operative thyroid hormone supplementation.² Hypocalcaemia after thyroid surgery usually occurs due to parathyroid insufficiency for a transient period. But there has also unfortunate risk of permanent hypo-parathyroidism. It may occur in 0.2% to 10% of patients³. The reason for this hypo-parathyroidism is de-vascularization of parathyroid glands during surgery or accidental removal of these glands. The effect of parathyroid injury causes disarrangement of calcium metabolism. The fluctuation of serum calcium after thyroid surgery may give a clue of possibility of parathyroid insufficiency. It is usually detected in the early post-operative period by means of serum calcium assessment. But the actual picture of parathyroid insufficiency from serum calcium level comes later than parathyroid hormone level measurement.

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The half-life of calcium is longer, and it takes time to lower serum calcium level after parathyroid injury. As the half-life of parathyroid hormone is 2 - 5 minutes⁴, that reflect parathyroid insufficiency earlier after total thyroidectomy and we can easily identify the patient who may be a victim of hypocalcaemia and can take necessary action to overcome the situation. The utility of post-operative PTH measurement can act as a prognostic indicator of short and long term of parathyroid function. And a normal post-operative PTH level can be a strong predictor of post-operative eucalcaemia.⁵ Many studies suggest, symptomatic hypocalcaemia after thyroid surgery. In this study we want to justify the measurement the parathyroid hormone level gives better outcome after thyroid surgery, to avoid post-operative hypocalcaemia. We also want to identify in which group of post-operative PTH patient have more chance to develop hypocalcaemia.

Material and Methods

This prospective observational study was designed from Sir Salimullah Medical College & Mitford Hospital, Dhaka from July 2013 to July 2014. Patients those came for total thyroidectomy for either thyroid malignancy or multinodular goitre and who had normal pre-operative calcium level were included in this study as test group. Exclusion criteria included patient with history of metabolic bone disease or renal failure, history of taking medication affecting thyroid or parathyroid status, those had pre-operative hypo or hyper parathyroidism or hypo-albuminemia and those had history of hyper ventilation symptoms. After fulfill all inclusion and exclusion criteria, 92 patients were selected as a sample or test group. 24 patients those who came for hemi-thyroidectomy was selected as control group. From all these patients pre-operative PTH, serum calcium and serum albumin were measured as a base line. Then again PTH level was measured within 6 hours after thyroid surgery. Serum calcium was measured in 24 hours (1st post-operative day) and 48 hours (2nd post-operative day) after thyroid surgery. The test patients (case) were divided into normocalcemic and hypocalcemic group. Another division was made by normal postoperative PTH level group, an intermediate post-operative PTH level group and a low post-operative PTH level group.

PTH concentrations were measured using automated electrochemo-luminescent immunoassay analyzer (IMMULITE 2000; SIMENS). The reference range of PTH was 11-65 pg/ml (according to the manufacturer's normative data). Serum calcium was measured by colorimetric method using semi auto colorimeter. The reference range was 9 to 11 mg/dl^{6,7}. Hypocalcaemia was defined when calcium < 9 mg/dl⁷ (according to the normal values of the assay). Hypoparathyroid defined when PTH < 11 pg/ml⁶. It was categorized as mild when levels were within 5 to 10.9 pg/ml and severe when < 5 pg/ml. Categorical variables are presented as frequencies and percentages and continuous variables as mean \pm SD. Student's t tests were used to compare differences between groups. To compare categorical variables, chi-square test was used with 95% confidence interval to make inference. For all analytical tests, p values less than 0.05 was considered statistically significant, less than 0.001 was considered as

highly significant. Pearson correlation test (Bivariate) was performed to assess the difference between first and second post-operative calcium with post-operative PTH. Linear Regression analysis was done to correlate postoperative PTH with first and second post-operative calcium values. Statistical analysis was performed using a commercially available software package (SPSS version 21).

Results

The mean (\pm SD) age of the patients was 40 ± 11.75 years with age range from 16 to 65 years. Males were 22% and females were 78%. Out of 92 test group patient, 31 (26.7%) patients developed hypocalcaemia.

Table I: Pre and post-operative PTH level at different time interval (n = 116).

S. PTH (pg/ml)	Mean \pm SD	Median	Min - Max	p value
Pre-operative PTH	26.67 \pm 13.43	23.65	10.60– 65.30	0.001
Post-operative PTH	12.68 \pm 10.24	10.40	3.08– 53.60	0.079

The result is expressed as number (%), mean SD and median.

In table I we found post-operative PTH values were less than pre-operative values. The post-operative median was 10.4 (3.08-53.6) and there was a significant difference.

Table II: S.PTH level in post-operative (6 hours after operation) period at different class interval (n=116), where normal PTH level consider 11-55 pg/ml.

S. PTH (pg/ml)	Frequency	Percentage	Mean \pm SD	Median	p-value
< 5	31	33.7	3.48 \pm 0.51	3.20	
5 - 10	30	23.9	8.02 \pm 1.92	8.29	0.001
> 10	55	42.4	20.41 \pm 9.99	16.50	

The result is expressed as number (%), mean SD and median.

Table II shows in post-operative period 31 (33.7%) had PTH level <5 pg/ml and 30 (23.9%) patients had PTH level in a range 5-10.9 pg/ml. In PTH <5 group mean value is significantly lower than other groups.

Table III: Pre and post-operative S. Calcium level of the study subject at different time interval (n = 116).

S. Calcium (mg/dl)	Mean \pm SD	Median	Min - Max	p-value
Pre-operative	10.67 \pm 0.84	10.60	9.00 – 12.80	
1st post-operative day (after 24 hours)	10.04 \pm 0.84	10.15	7.70 – 12.12	0.001
2nd post-operative day (after 48 hours)	9.44 \pm 1.11	9.80	6.62 – 11.30	

The result is expressed as mean \pm SD & median.

In table III we found fall of serum calcium level in 2nd post-operative day (median 9.8) than in 1st post-operative day (median 10.15). And the difference was significant with p-value 0.001

Table IV: Corresponding values of S. calcium in 1st and 2nd post-operative day in relation with post-operative PTH in defined class intervals.

PTH (pg/ml) Post-operative	S. Calcium(mg/dl) 1 st post-operative day		S. calcium (mg/dl) 2 nd post-operative day	
	Mean ± SD	Median	Mean ± SD	Median
< 5	9.83 ± 0.87	9.8	8.29 ± 1.03	8.0
5 - 10.9	9.81 ± 0.91	10.1	9.50 ± 0.88	9.7
11 - 55	10.27 ± 0.73	10.2	10.04 ± 0.71	10.1

The result is expressed as mean ± SD and median.

Table IV shows when S.PTH level fall then S.calcium level also fall down. But in 2nd post-operative day calcium level was significantly fall. In the second lower group when S.PTH level in a range between 5 and 10.9 pg/ml often need medical attention. And those S.PTH level lower than 5 pg/ml definitely need calcium supplement in post-operative period, if this group can identify early in post-operative period than we can easily prevent symptoms of hypo-calcaemia.

Table V: Correlation between post-operative PTH with first and second post-operative calcium values (n=116).

Post-operative PTH (6 hours after operation)	1 st post-operative day	2 nd post-operative day
	S.Calcium r/p	S.Calcium r/p
	0.243/ 0.008**	0.486/0.001**

r = Correlation coefficient, p = level of significance (2-tailed).
 * Correlation is significant at the 0.05 level (2-tailed).
 ** Correlation is significant at the 0.01 level (2-tailed).

Table V shows correlation between post-operative PTH with 1st and 2nd post-operative calcium level both are significant. But more significant with 2nd post-operative calcium level. It reflects post-operative PTH more correspond with 2nd post-operative calcium level. So, hypocalcaemic group determined with those had fall calcium level in 2nd post-operative day.

Table VI: Corresponding post-operative PTH value in different groups according to calcium status.

	Mean ± SD	Median	p- value
Post-operative PTH in control group	13.51 ± 3.63	12.6	0.001
Post-operative PTH in normocalcaemic test group	16.04 ± 11.96	12.5	0.001
Post-operative PTH in hypocalcaemic test group	5.43 ± 5.32	3.3	0.001

The result is expressed as mean ± SD and median.

Table VI revealed post-operative PTH significantly fall in hypocalcaemic group patients, in relation with normocalcaemic group patients.

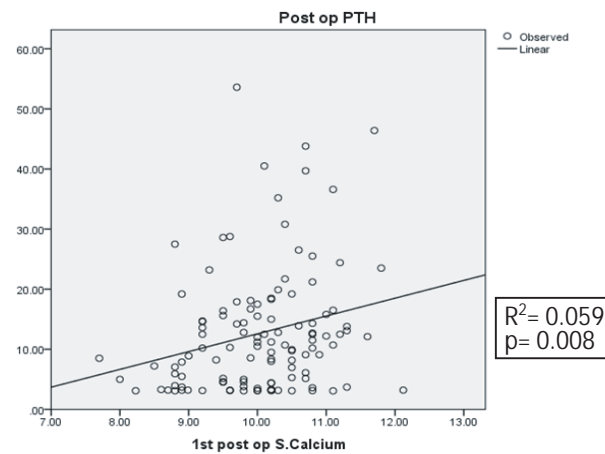
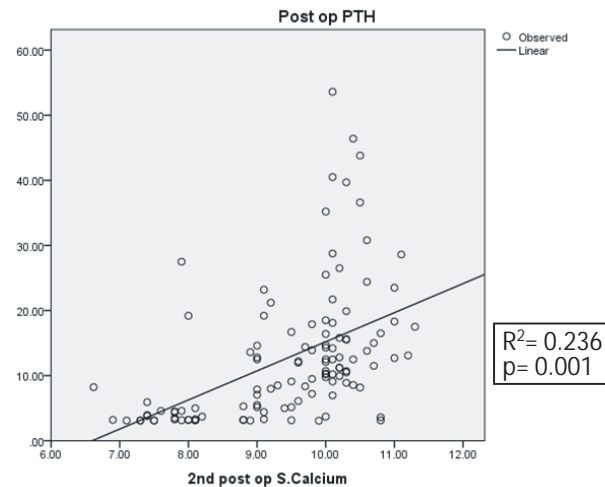


Figure 1: Relation between post-operative PTH with 1st post-operative calcium status by linear regression analysis, where 1st post-operative day calcium is independent variable and post-operative PTH is dependent variable.

This figure shows there is significant association between post-operative PTH and 1st post-operative calcium level (p<0.05).

Figure 2: Relation between post-operative PTH with 2nd post-operative calcium status by linear regression analysis, where 2nd post-operative day calcium is independent variable and post-operative PTH is dependent variable.



This figure shows there is highly significant association between post-operative PTH and 2nd post-operative calcium level (p<0.001).

Discussion

In most of the case of multinodular goitre involving both lobes and thyroid malignancy are the selection criteria for total thyroidectomy. In some cases, near total thyroidectomy is also performed. Completion thyroidectomy is needed most of the recurrent cases like multinodular goitre when hemithyroidectomy was previously performed or in malignant cases when FNAC was reported as benign but histopathology conformed as malignant. The second time thyroid surgery is more difficult because of more adhesion, normal anatomy become jeopardize and more chance to injury to vital structures like laryngeal nerves and parathyroid glands. Despite advances in surgical techniques and surgeons' efforts to identify and preserve all parathyroid glands during thyroid surgery, early post-operative hypocalcaemia and PHPP remain challenging clinical problems even in the most experienced hands.³ Accurate identification of potential causes for transient postsurgical hypocalcemia is necessary to allow safe early discharge.^{3,8} The mechanism of transient hypocalcaemia remains elusive and the aetiology of hypocalcaemia is multifactorial.⁸ Numerous theories have been described in the literature. Hemodilution secondary to intra-operative fluid administration, calcitonin release after manipulation of the thyroid, 'hungry bone syndrome' secondary to skeletal uptake of calcium in patients with thyrotoxicosis osteodystrophy, and after injury/removal or de-vascularization of the parathyroid glands.^{8,12}

This study was carried out based on pre-operative and post-operative serum calcium and parathormone (PTH) level who were under gone total or completion of thyroidectomy. After fulfil all inclusion and exclusion criteria total 92 patients were taken as a sample; and 24 patients were taken as control group those are went for hemithyroidectomy. Out of 92 samples male were 20 (22%) and female were 72 (78%) with a ratio Male: Female = 1:3.6. The mean age of patients was 40 ± 11.75 years, ranged from 16 to 65 years. Similar sex distribution had been reported by Toniato A.¹⁷ where male was 35 (22%) and female 125 (78%), the mean age was 49.4 ± 14 years, ranged 18 to 86 years. Islam⁹ reported mean age was 39 ± 13.18 with ranged 15 to 75 years and in his study also found female predominant; with male 22.5% and female 77.5%. In a review of the literature, there are different definitions of post-operative hypo-parathyroidism after thyroidectomy, mostly based on serum calcium levels. More recently, the PTH levels measured intraoperatively, perioperatively, or in the immediate post-operative period are recommended to classify and predict post-operative hypo-parathyroidism more clearly. According to different definitions, the rates of developing hypocalcaemia after thyroidectomy range from 1.6% to 50%¹⁰, which should not occur in specialized endocrine surgical units. In this study group, out of 116 patients, pre-operative median value of PTH was 23.65 pg/ml. (Table I) Post-operative sample was taken 6 hours after operation. The median value of post-operative PTH in control group was 12.6 pg/ml (Table VI) and in normocalcaemic test group was 12.5 pg/ml. (Table VI). But in hypocalcaemic test group post-operative PTH was 3.3 pg/ml

(Table VI); which is significant ($p < 0.001$). From total 116 patients, 55 (42.4%) had normal PTH (Table II), 30 (23.9%) had intermediate PTH (5 to 10.9 pg/ml) and 31 (33.7%) had PTH level less than 5 pg/ml (Table II) and was the high-risk group. Simon Grodski and Stephen Farrel⁸ in their study took post-operative PTH at 4 to 12 hours, in their study over 76 patients, there were 58 patients with normal PTH (76%), 6 patients had intermediate PTH and 12 patients had an undetectable PTH. In this study linear regression analysis between post-operative PTH with 1st and 2nd post-operative serum calcium found association between post-operative PTH with serum calcium. But the association with 2nd post-operative calcium was highly significant with $p < 0.001$. (Figure 1 & 2). So we can say that reflection of hypocalcemia is much more earlier by measurement of PTH than measurement of serum calcium. And we can assume which patient will go hypocalcemia after operation.

The incidence of hypocalcaemia was 26.7% in this study. Post-operative hypocalcaemia developed in 61 cases. Among them 16 hypocalcaemia were developed after 24 hours and 45 were developed after 48 hours of total thyroidectomy. Islam et al⁹ in their study, the incidence of hypocalcaemia found 38.5% and post-operative hypocalcaemia found in 25 cases. Simon Grodski⁸ found 26% hypocalcaemia in his study. Jin Pyeong Kim et al¹¹ found 46% hypocalcaemia in their study. Many different studies show, temporary hypocalcaemia occurs in 1% to more than 50% of patients after undergoing total thyroidectomy or completion thyroidectomy.⁵ Cayo et al⁵ mentioned in his study, symptomatic hypocalcaemia developed in only 10% of patient those have PTH > 10 pg/ml and 48% of patient those have PTH < 10 pg/ml. And all can be treated successfully with calcium supplement.⁵ That study concluded as PTH > 10 pg/ml on 1st post-operative day is a strong predictor of post-operative eucalcaemia and have limited use of routine calcium supplementation.

Conclusion

The measurement of serum PTH level within 6 hours after total thyroidectomy can accurately identify the patients those likely to develop hypocalcaemia. It allows more timely initiation of calcium supplement (instead for waiting to become symptomatic) and potentiate for early discharge. Because of high sensitivity, specificity, accuracy positive and negative predictive value, post-operative serum PTH can be used as a predictor of hypocalcaemia after total thyroidectomy. By using a PTH cut-off point <8.02 pg/mL to determine which patients should be treated with calcium and/or calcitriol, we can minimize the number of post-operative symptomatic hypocalcaemia.

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