ORIGINAL ARTICLE

Parathyroid Hormone Measurement in Prediction of Hypocalcaemia following Thyroidectomy

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ABSTRACT

Objective: To determine the risk of postthyroidectomy hypocalcaemia by measuring parathyroid hormone (PTH) level after thyroidectomy.

Study Design: Cross-sectional study.

Place and Duration of Study: Baqiyatallah Hospital, Tehran, Iran, from March 2008 to July 2010.

Methodology: All included patients were referred for total or near bilateral thyroidectomy. Serum Calcium (Ca) and PTH levels were measured before and 24 hours after surgery. In low Ca cases or development of hypocalcaemia symptoms, daily monitoring of Ca levels were continued. Data were analyzed using SPSS 20 software (SPSS, Chicago, IL, USA). A p-value less than 0.05 were considered statistically significant. To assess the standard value of useful predictive factors, we used receiver operating characteristic (ROC) curves.

Results: Of total 99 patients who underwent bilateral thyroidectomy, 47 patients (47.5%) developed hypocalcaemia, out of them, 12 (25.5%) became symptomatic while 2 patients developed permanent hypoparathyroidism. After surgery, mean rank of PTH level within the normocalcaemic and hypocalcaemic patients was 55.34 and 44.1 respectively, p=0.052. Twenty four hours after surgery, 62% drop in PTH was associated with 83.3% of symptomatic hypocalcaemic. For diagnosis of symptomatic hypocalcaemia, 62% PTH drop had sensitivity and specificity were 83.3% and 90.80%. The area under the ROC curve for the PTH postoperative and PTH drop for diagnostic symptomatic hypocalcaemia were 0.835 and 0.873 respectively.

Conclusion: Measuring PTH levels after 24 hours postthyroidectomy is not reliable factor for predicting hypocalcaemia itself. For predicting the risk of hypocalcaemia after thyroidectomy it is more reliable to measure the serum PTH level before and after operation and compare the reduction level of percentage of PTH drop for predicting the risk of hypocalcaemia.

Key Words: *Hypocalcaemia. Hyperparathyroidism. Parathyroid hormone (PTH). Thyroidectomy.*

INTRODUCTION

Transient hypocalcaemia is the most common post-operative complication following thyroidectomy with an incidence ranging from 0.5% to 30% or even 50%. Direct injury, devascularization, or accidental removal of parathyroid glands is mainly contributed to occurrence of this condition. Permanent hypocalcaemia, however, occurs upto 2%.[1-3] The most prevalent cause of hypoparathyroidism in adults is trauma to parathyroid glands during thyroid surgery especially in total thyroidectomies. In acute hypocalcaemia, decreased ionized calcium level causes neuromuscular hypersensitivity. The earliest symptom is tingling or 'pins and needles' sensation in around the lips, and in extremities. On physical examination of patients, Chvostek's sign becomes positive and subsequently carpopedal spasms and seizure occurs. Life threatening complications include tetany and laryngospasm.[4] Early detection and managing post-thyroidectomy hypocalcaemia still remains a challenge.[2] Highest incidence of hypocalcaemia occurs after bilateral thyroidectomy, and it is the reason of delayed discharge from hospital.

Many recent studies have focused for detection of reliable predictors to make earlier diagnosis of post-operative hypocalcaemia. Monitoring the level of serum total calcium (Ca) or ionized calcium (iCa^{++}), calculating slopes in the change of Ca or iCa^{++} levels, measuring intraoperative or standard intact parathyroid hormone (iPTH) level, and ultimately making a new algorithm by combining more than two of these values, all have been reported as useful predictors.[5]

Some studies have demonstrated that measuring calcium and PTH levels alone is not reliable for predicting the risk of hypocalcaemia.[6] Viewing the fact that PTH increases rapidly in response to hypocalcaemia, it is suggested that PTH should be measured immediately after the surgery.[7-10] Post-operative PTH level can be used to stratify the risk of patients developing hypocalcaemia after thyroidectomy.[2,11]

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Nevertheless, this practice has not been widely adopted, nor has it been incorporated into a standardized system of care for patients undergoing total thyroidectomy.[2]

Comparison of serum PTH levels before and after the operation with different techniques has been an area of high interest for researchers to yield promising results for predicting the risk of postoperative hypocalcaemia.[6,12,13]

The aim of this study was to determine whether measuring the PTH level before and after surgery can predict the risk of hypocalcaemia occurrence and to prevent the related complications and obviate the need of prolonged hospitalization.

METHODOLOGY

This cross-sectional study was conducted from March 2008 to July 2010. The study was approved by the Medical Research Ethics Committee of the Baqiyatallah University of Medical Sciences. A total of 112 patients entered the study. Informed consent was obtained from the participants before the start of study. Thirteen cases were excluded from the study because either they did not participate in this study or did not co-operate with researchers in follow-up period.

At the time of admission, serum PTH (PTH1) and Ca along with other laboratory tests were measured. Normal limit for serum PTH was 17-73 pg/ml and its serum concentration was measured using chemiluminescence technique. Normal limit of blood serum Ca was taken as 8.5-10.5 mg/dl. Surgeons were asked to report viewing of parathyroid glands and number of saved glands during surgery in their surgical report sheets.

On the first day after surgery, serum Ca and PTH (PTH2) concentrations were measured and percentage of PTH drop was calculated as [PTH1-PTH2/PTH1] x 100. If Ca dropped to less than normal ranges or if the patients became symptomatic, they would be kept in hospital. If the patient has symptomatic hypocalcaemia, Ca would be administered. In cases with asymptomatic hypocalcaemia, signs of hypocalcaemia would be taught to patients at the time of discharge. Patients would also be provided with a phone number to contact in case of emergency by their physicians. If patients developed any symptoms of hypocalcaemia, they would be asked to return to hospital for future evaluations. Subsequently their serum Ca level would be monitored and more calcium and vitamin D derivatives would be administered, if necessary. Serum Ca level was controlled weekly for a month and if hypocalcaemia continued, Ca monitoring would be continued monthly for a period of 6 months. Ca monitoring would be discontinued whenever serum Ca levels reached normal limits. Patients' data including age, gender, type of disease, serum PTH and Ca levels before and after operation, development of permanent hypoparathyroidism, and other complications were collected. Final diagnosis was based on permanent pathology report.

PTH, calcium and PTH drop values between groups were compared using Mann-Whitney test. Calcium and PTH, before and after surgery compared using paired t-test. To examine correlation, we used a Spearman correlation coefficient age. For assessing qualitative data frequency and percentage, chi-square test was used. Data were analyzed using SPSS 20 software (Chicago, IL, USA). We estimated the areas under the corresponding receiver operating characteristic (ROC) curves to calculate and compare the predictive power of the PTH values and percentages of PTH drop. To assess the standard value of useful predictive factors, we used receiver operating characteristic (ROC) curves using Stata 11.2 software. A p-value less than 0.05 were considered statistically significant.

RESULTS

In these 99 patients, there were 17 (17.2%) males who underwent total or near total thyroidectomy. The mean age of males was 48.76 ± 14.65 years (ranging from 26 to 85 years) and of females was 48.64 ± 12.04 years (ranging from 20 to 77 years). Among the 99 patients, 76 patients (76.8%) had the diagnosis of multinodular goiter, 20 patients (20.2%) had papillary thyroid cancer, 2 patients (2%) had Graves' disease, and 1 patient (1%) had medullary thyroid cancer, all of them underwent bilateral thyroidectomy. Difference between mean age of males and females was not statistically significant ($p = 0.97$). After operation, 47 patients (47.5%) developed hypocalcaemia, 12 (25.5%) out of them became symptomatic and underwent treatment with Ca and some with or without vitamin D supplement and 35 (74.4%) patients became asymptomatic. Finally 2 patients (2%) developed permanent hypoparathyroidism diagnosed as papillary thyroid cancer.

In classification of postoperative serum PTH levels in three categories; below the normal limits (PTH < 17 pg/ml), within the normal limits (17-73 pg/ml) and over the normal limits, in 99 patients, 9 patients became hypocalcaemic (9.1%) with PTH < 17 pg/ml, 28 hypocalcaemic patients (59.6%) had normal PTH levels and 10 hypocalcaemic cases (21.3%) had PTH levels over the normal limits (Table I).

Mean ± SD serum Ca level of patients before operation was 9.06 ± 0.47 mg/dl and after operation became 8.35 ± 0.61 mg/dl ($p < 0.001$). Also, mean ± SD PTH was 96.23 ± 53.54 before surgery and 63.82 ± 37.13 after surgery, difference was statistically significant ($p < 0.001$). Pre-operative PTH and calcium values for patients who remained normocalcaemic after surgery were not significantly different from those patients who became hypocalcaemic ($p = 0.079$ for PTH, $p = 0.246$ for calcium) [Table II]. Calcium level after surgery in hypocalcaemic in comparison to normocalcaemic patients was statistically significant ($p < 0.001$). However, there was no significant differences in calcium levels among the normocalcaemic and hypocalcaemic patients ($p < 0.052$, Table II). The difference of PTH drop between the hypocalcaemic and normocalcaemic patients was statistically significant ($p < 0.0001$, Table II). The mean percentage of calcium was 7.90 ± 0.35 mg/dl in asymptomatic hypocalcaemic and 7.53 ± 0.41 mg/dl in symptomatic hypocalcaemic patients. The difference of PTH drop between the asymptomatic and symptomatic hypocalcaemic patients was statistically significant ($p = 0.018$).

The mean rank of PTH was 27.83 pg/mL in asymptomatic hypocalcaemic and 12.82 pg/mL in symptomatic hypocalcaemic patients. The difference of PTH drop between the asymptomatic and symptomatic hypocalcaemic patients was statistically significant ($p < 0.001$).

A significant difference was found in PTH percentage drop between symptomatic and asymptomatic hypocalcaemic patients (36.17 vs. 19.83, $p < 0.001$). Also, a significant correlation was found between calcium level after surgery and percentage of PTH drop, ($r = -0.31$, $p = 0.002$, Figure 1).

The area under the ROC curve for the PTH postoperative and PTH drop for diagnostic hypocalcaemia (symptomatic and asymptomatic) were 0.613 and 0.692 respectively (Figure 2). Also, for PTH postoperative and PTH drop for diagnostic symptomatic hypocalcaemia were 0.835 and 0.873 (Figure 3), so the ROC curves show that both PTH postoperative value and PTH drop are reliable predictors of hypocalcaemia and symptomatic hypocalcaemia. Consequently, the PTH drop is more reliable. A summary of diagnostic hypocalcaemia and symptomatic hypocalcaemia characteristics for the best cut off point (corresponding to the maximum sensitivity, specificity, positive and negative predictive values, accuracy and likelihood ratio) is given in Table III and Table IV, in which each test is considered independently.

When the level of PTH was lower than 17 pg/mL, the sensitivity in predicting hypocalcaemic was 19.15%, the specificity was 100%, and the positive predictive value (PPV) was 100%. When PTH was lower than 19 pg/mL, the sensitivity was 23.4%, the specificity was 100%, and the PPV was 100%. When measured, PTH was lower than 20 pg/mL, the sensitivity was 23.4%, the specificity was 98.8%, and the PPV was 91.7% (Table III).

For percentage of PTH drop, when the level of PTH was greater than 61 pg/mL, the sensitivity in predicting hypocalcaemic was 34.04%, the specificity was 94.23%, and the positive predictive value (PPV) was 76.9%. When PTH was greater than 62 pg/mL, the sensitivity was 34.04%, the specificity was 96.15%, and the PPV was 88.9%. When measured, PTH was greater than 69 pg/mL, the sensitivity was 25.5%, the specificity was 98.1%, and the PPV was 92.3% (Table III). Therefore, considering the sensitivity, specificity, and positive predictive value, a PTH concentration of 19 pg/mL and PTH drop 62 were found to be the most useful predictor of hypocalcaemic (Table III).

Table I: Calcium and PTH levels and their relations in patients after operation.

Items	PTH grouping postoperative (pg/ml)		
	Below normal < 17	Normal 17 – 73	Above normal > 73
Hypocalcaemia (n = 47)	9 (9.1%)	28 (59.6%)	10 (21.3%)
No hypocalcaemia (n = 52)	0 (0%)	34 (65.4%)	18 (34.6%)

Table II: Means ± SD of PTH and calcium alternation before and after surgery between normal and hypocalcaemic patients.

Items	Pre-operative Ca, mg/dL	post-operative Ca, mg/dL	Pre-operative PTH, pg/mL	Post-operative PTH, pg/mL	Percentage of PTH drop
Hypocalcaemic (symptomatic and asymptomatic) (n = 47)	53.51	24.01	55.33	44.1	60.0
Normocalcaemic (n = 52)	46.83	73.50	45.18	55.34	40.96
p-value*	0.246	< 0.001	0.079	0.052	0.001

Difference between two groups, using Mann-Whitney U-test.
Parenthesis values are mean rank.

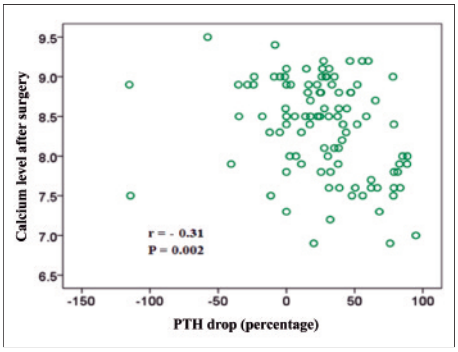

Figure 1: Pearson's correlation for PTH drop and calcium level after surgery.

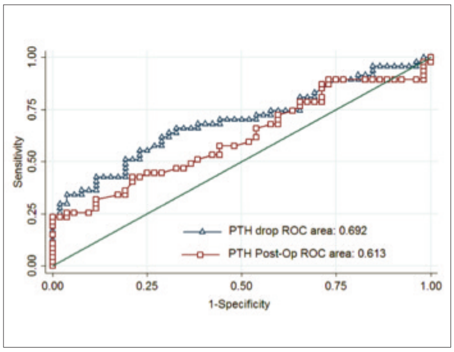

Figure 2: Receiver operating characteristic curves demonstrating the accuracy of thresholds PTH postoperative and PTH drop (in prediction whether patients will become hypocalcaemic (symptomatic and asymptomatic).

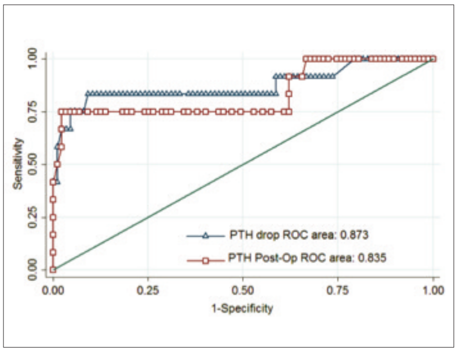

Figure 3: Receiver operating characteristic curves demonstrating the accuracy of thresholds PTH postoperative and PTH drop (in prediction whether patients will become symptomatic hypocalcaemia).

Table III: Comparison of diagnostic characteristics for hypocalcaemia (symptomatic and asymptomatic).

Items	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	Positive LR	Negative LR
PTH ≤ 17 pg/ml	19.15	100.00	100.00	57.80	61.62	–	0.80
PTH ≤ 19 pg/ml	23.40	100.00	100.00	59.10	63.70	–	0.76
PTH ≤ 20 pg/ml	23.40	98.80	91.70	58.60	62.63	12.17	0.78
PTH drop ≥ 61	34.04	94.23	76.90	63.00	65.66	3.16	0.66
PTHdrop ≥ 62	34.04	96.15	88.90	61.70	66.67	8.85	0.68
PTH drop ≥ 69	25.5%	98.1%	92.3%	59.3%	64.70	14.38	0.73

LR = likelihood ratio; NPV = Negative predictive value; PPV = Positive predictive value; PTH = Parathyroid hormone.
These values correspond to the cutoff values showing the maximum sum for sensitivity and specificity in predicting clinical hypocalcaemia.

Table IV: Comparison of diagnostic characteristics for symptomatic hypocalcaemia.

Items	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	Positive LR	Negative LR
PTH ≤ 17 pg/ml	58.33	97.70	77.70	94.40	92.93	25.37	42.26
PTH ≤ 18 pg/ml	75.00	97.70	81.80	96.60	94.95	32.62	25.59
PTH ≤ 20 pg/ml	75.00	96.55	75.00	96.60	93.94	21.75	25.89
PTH drop ≥ 60	83.33	89.66	97.50	52.60	88.89	8.05	0.18
PTH drop ≥ 62	83.33	90.80	55.60	97.50	90.00	9.06	0.18
PTH drop ≥ 69	75.00	95.40	69.20	96.50	92.93	16.31	0.26

LR = Likelihood ratio; NPV = Negative predictive value; PPV = Positive predictive value; PTH = Parathyroid hormone.
These values correspond to the cutoff values showing the maximum sum for sensitivity and specificity in predicting clinical symptomatic hypocalcaemia.

Table V: Contingency table for asymptomatic hypocalcaemia using the cut-off points of PTH drop ≥ 62.

Items	Symptomatic hypocalcaemia	Normal or asymptomatic hypocalcaemia	Total
PTH drop < 62	2 (FP)	79 (TN)	81
PTH drop ≥ 62	10 (TP)	8 (FN)	18
Total	12	87	99

FN = False negative; FP = False positive; TN = True negative; TP = True positive.

Similarly, for diagnosis symptomatic hypocalcaemia, 62% PTH drop had sensitivity and specificity is 83.33% and 90.80% respectively and 55.6% PPV and 97.5% negative predictive value (NPV), Table V. PTH ≤ 18 had 75% sensitivity, 97.7% specificity, 81.8% PPV and 59.3% NPV (Table IV). The contingency table for the stratification of patients using the 62% PTH drop of cut-off points is shown in Table V. The percentage of PTH drop has a significant association with development of hypocalcaemia. With these data, we calculated the sensitivity, specificity, predictive values and accuracy of this issue.

DISCUSSION

Total or near total thyroidectomy can lead to hypocalcaemia due to transient hypoparathyroidism, although depends on the type of procedure.[14] It is important to screen patients who are at risk of hypocalcaemia. In some articles, the determination of parathyroid hormone has suggested evaluation of hypocalcaemia.[7-9] Toniato demonstrated that the PTH measurement on the first postoperative day may be considered a useful method to predict post thyroidectomy, hypocalcaemia prone patients avoiding prolonged hospitalization.[12]

Several studies have found that PTH levels cannot reliably predict postoperative hypocalcaemia.[2] In this study, no significant linear correlation was found between serum PTH levels 24 hours after the operation and development of hypocalcaemia postoperatively, however, serum PTH in majority of symptomatic patients was ≤ 19 pg/ml (normal ranges from 17 to 73 pg/ml) with 23.4% sensitivity and 100% specificity. In another study, PTH level of 9.6 pg/ml was associated with a greater risk of hypocalcaemia in which the normal limit of PTH was 10-55 pg/ml.[12] In a study by Lim, the PTH level < 23 pg/ml had 100% sensitivity for prediction of hypocalcaemia.[15]

Another evaluation was performed based on the serum level of PTH after the operation in 3 levels of normal, lower and upper than normal limit. Hypocalcaemia developed in all lower level of PTH values (100%) and 85% of them became symptomatic. Therefore, we can conclude that if PTH level is below the normal limit, the patient will most probably become hypocalcaemic and symptomatic and the relative risk of hypocalcaemia is high ($p = 0.004$, RR = 0.851, 95%; CI = 0.755-0.959). Whereas those with serum PTH level within or above normal range will be normocalcaemic or will develop asymptomatic hypocalcaemia. Progressive and severe hypocalcaemia is unlikely in the setting of a normal PTH level and hence PTH measuring can be cautiously used to facilitate discharge within 24 hours for many patients.[11]

The percentage of PTH drop is an important predictor for hypocalcaemia. In this study, the percentage of PTH drop has a significant relation with development of hypocalcaemia, 83.3% of symptomatic hypocalcaemic cases had 62% PTH drops. This percentage of drop had 34.04% sensitivity and 96.15% specificityfor diagnosis of hypocalcaemia. The area under the ROC curve for the PTH postoperative and PTH drop for diagnostic hypocalcaemia (symptomatic and asymptomatic) were

0.613 and 0.692 respectively (Figure 2). The difference between the mean value was statistically significant. Therefore, the percentage of drop can be a more appropriate index for determining the risk of hypocalcaemia. Also, for diagnosis symptomatic hypocalcaemia, 62% PTH drop had sensitivity and specificity 83.33% and 90.80% respectively. The area under the ROC curve for the PTH postoperative and PTH drop for diagnostic symptomatic hypocalcaemia were 0.835 and 0.873 (Figure 3). On the other hand, the measurement of PTH drop in our work proved to be a good marker to rule out hypocalcaemia and symptomatic hypocalcaemia. In a study by Toniato, 68.7% drop in PTH level was associated with risk of hypocalcaemia development in 93.3% of cases.[12] The cutoff for percentage decline of ioPTH and 6hPTH (55.7% and 37.9%, respectively) was more accurate than an absolute value.[13] In another study, 65% PTH drop was associated with the highest risk of symptomatic hypocalcaemia (80% sensitivity and 74.3% specificity).[10] In Del Rio study, an 80% or higher decrease in delayed parathyroid hormone levels had 100% sensitivity (95% CI: 77.2 - 100%) and 87% specificity (95% CI: 77 - 93%) for selecting patients for early discharge. Using this test, 73.2% of the patients could have been discharged 24 hours after surgery.[16] Also, a decrease in PTH of 60%, 5 - 6 hours postoperatively resulted in a sensitivity and specificity of 100%.[17]

The time of blood sampling and PTH level measurement is controversial. Gentileschi in a study, suggested one hour after operation is a good predictor of early hypocalcaemia.[7] In another study also a significant correlation between the iPTH level one hour after operation with the calcium level 24 hours after the operation was demonstrated.[1] In Sywak survey, parathyroid hormone assay in early postoperative period has been recommended, also Grodski suggested that early postoperative PTH levels between 4 - 12 hours are a predictor of hypocalcaemia and facilitating safe early discharge after total thyroidectomy.[8,9] PTH measurement 6 hours after surgery was the more accurate measurement for early prediction of patients at risk of hypocalcaemia and helped in discharging patients within the first 24 hours.[18]

In another survey by reviewing 27 articles, it is concluded that a single PTH measurement taken any time from 10 minutes to several hours postoperative will provide equally accurate results for predicting post-thyroidectomy hypocalcaemia and anticipate the need for calcium replacement.[11] Changes in PTH levels checked 1 - 6 hours after thyroidectomy were excellent in predicting postoperative hypocalcaemia.[17] In Youngwirth study, PTH levels were tested on these patients 3 hours after surgery and the morning after surgery.[3] In Cote survey, 1-hour PTH measurement and prediction of cut-off point of 15 ng/L for prophylactic supplementation should allow the prevention of the majority of cases of hypocalcaemia, leading to significant cost savings by shortening hospital stay.[19]

Noordzij with an analysis of pooled individual patient's data from nine observational studies concluded that early prediction of hypocalcaemia is available by using parathyroid hormone in 1 - 6 hours after thyroidectomy.[10] In Cavicchi survey, determining of ioPTH decline in relation with 16-hour corrected calcium, was possible to distinguish early normocalcaemic patients from hypocalcaemic ones in most cases.[13] Using both iPTH level at 1 hour after surgery and postoperative iCa^{++} levels will increase the diagnostic accuracy for the early and reliable prediction of postoperative hypocalcaemia.[5] As another opinion, PTH dosage at first postoperative day is more reliable and less expensive than intraoperative quick PTH assay.[12]

Another important issue was the role of exploration, observations and saving of parathyroid glands by the surgeon during the surgery, which had a significant correlation with hypocalcaemia. Thus further attention should be paid during the operation to save the parathyroid glands and decrease the risk of hypocalcaemia.

CONCLUSION

Measurement of serum PTH level 24 hours after the operation as an independent factor can not appropriately predict the development of hypocalcaemia. It is more reliable to measure the serum PTH level before and after the operation and compare the percentage of drop of PTH level for predicting the risk of hypocalcaemia after total or near total thyroidectomy.

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