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General Surgery

Effect of Parathyroid Hormone Level within One Hour of Total Thyroidectomy on Serum Calcium Level

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Abstract		Original Research Article

Background: Parathyroid dysfunction leading to symptomatic hypocalcemia is not uncommon following a total or completion thyroidectomy and is often associated with significant patient morbidity and a prolonged hospital stay. The current study is designed to evaluate the role of parathormone (PTH) levels detected in a standard time frame after total thyroidectomy as a predictor of post-thyroidectomy hypocalcemia. **Objectives:** To investigate whether postoperative parathyroid hormone level is a parameter to identify hypocalcemia after total thyroidectomy as well as to find out the optimum cut-off value of parathyroid hormone in early postoperative period. **Methodology:** This was a cross-sectional study. A total of 103 patients' male-female with a variety of thyroid disorders with an indication of total thyroidectomy attended the outpatient department and inpatient department of Surgery and Otolaryngology, BSMMU. This study was carried out from March 2018 to September 2019. The routine clinical assessment and the preoperative laboratory investigations were performed before operation. Preoperative levels of serum PTH were measured. Statistical analysis was carried out using SPSS version.22.0. **Results:** The levels of PTH in the immediate postoperative period showed that 17(16.50%) patients belonged to low PTH (<14). The mean PTH in immediate post-operative was 36.79±21.71 with a range from 0.2 to 111.3. Regarding the distribution of the study patients by serum calcium, it was observed that 20.39% of patients belonged to low (<8 mg/dl) serum calcium. The mean serum calcium level was 8.47±1.19 with ranging from 2.1 to 10.6. In the current study, the scatter diagram showed a positive significant correlation (r=0.310; p=0.001) between PTH and S. Calcium immediate post-operative period. ROC curve for finding the cut-off value of PTH in the immediate post-operative period to predict hypocalcemia among the study population. **Conclusion:** Hypocalcaemia after the total or completion of thyroidectomy is not uncommon. Calcium level is usually measured on the 1st postoperative day to see hypocalcemia and if symptoms produce then calcium level is checked frequently. But if we measure a single parathyroid hormone levels in the postoperative period that can reflect early results and help to take necessary measures to avoid the hypocalcaemic effect. Low intraoperative PTH levels during thyroid surgery are therefore a feasible predictor of postoperative hypocalcemia.
Keywords: Parathyroid dysfunction, Symptomatic hypocalcemia, Total thyroidectomy, Parathormone (PTH), Serum Calcium level.

INTRODUCTION

Post thyroidectomy hypocalcemia is a common complication that may be transient in 10-50% of patients or permanent occurring in 0.5-10.6% of patients.1 The nadir for hypocalcemia typically at around 24-48h postoperatively but may be as delayed as post-operative day 4.2 Patient have to be observed for this time period prior to discharge in order to prevent the development of clinically significant hypocalcemia and this significantly lengthen hospital stay.3 Despite the recent development of surgical techniques and every

effort of surgeons to preserve as many parathyroid glands as possible, early postoperative hypocalcemia and hypo parathyroidism still remain a great challenge so prediction of hypocalcemia after total thyroidectomy is important for early treatment in order to avoid troublesome symptoms to ensure safe discharge. Measuring plasma calcium level just after thyroid surgery is of little value in predicting the onset of subsequent hypocalcemia or symptoms, because of its relatively slow decline. The search for early risk factors predicting hypocalcemia has focused the interest on the post-operative monitoring of iPTH because of its short half-life ranging 2 to 5 minutes observed that Measurement of total serum calcium is less expensive but it may be inaccurate because of post-operative haemodilution and it poorly predicts symptomatic hypocalcemia.4-6 In most of the studies, to predict post thyroidectomy hypocalcemia, the use of post-operative serum PTH was recommended with a sensitivity ranging from 64% to 100% specificity ranging from 72% to 100%.7 One hour post-operative PTH drop to 70% or more had a negative predictive value of 97%.8 Comparing pre-operative to 10 minutes post-operative PTH percent change, patients with a greater than 75% decrease are likely to have hypocalcemia with a sensitivity of 100%.9 There is no consensus regarding what is considered the gold standard testing of hypocalcemia complicating thyroid surgery. The purpose of this study is to evaluate whether PTH level within one hour is a reliable marker to identify those patients with the risk of developing hypocalcemia. It may help in the identification, prevention, and treatment of hypocalcemia in patients after total thyroidectomy.

OBJECTIVES
General Objective
- To determine the level of PTH within one hour of the total thyroiedectomy as a predictor of post operative hypocalcemia.

Specific Objectives
- To determine the frequency of hypoparathyroidism.
- To determine the frequency of hypocalcemia.
- To measure the validity of postoperative PTH level as a predictor of postoperative hypocalcemia.
- To determine diagnostic accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).

MATERIAL AND METHODS
This was a cross-sectional study, was carried out at the General Surgery and Otolaryngology, Department of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka from 3rd March 2018 to September 2019. After obtaining the approval of the IRB a total of 103 patients who were undergone total thyroidectomy were enrolled in this study following the inclusion and exclusion criteria. Purposive Sampling was done. The routine clinical assessment and the preoperative laboratory investigations of the study population were performed. All the relevant particulars of the patients in relation to the study were recorded in a predesigned datasheet. The informed written consent signed by the patients was also collected. The preoperative level of PTH was measured using a chemiluminescent immunometric assay (Dade Behring, Dimension RxL-Max, Eschborn, Germany). The reference interval for PTH in the laboratory is 14 to 74 pg/mL (1.5-7.8 pmol/L). In the postoperative phase, serum PTH levels were measured in the recovery room within 1 hour of the procedure and 24 hours after thyroidectomy. The serum calcium level was measured preoperative, immediate postoperative, 24 hours, 48 hours, 72 hours after surgery using a colorimetric assay with endpoint determination and sample blank in the Modular Hitachi analyzer. The reference interval for calcium in the laboratory is 8.6-10.0 mg/dL (2.15-2.50 mmol/L). It was hypothesized that immediate postoperative PTH level may predict postoperative hypocalcemia with a sensitivity of 80% or greater. The sample size was calculated for a power level of greater than 80%, an error of 0.05, and a sensitivity of 71%6 or greater based on previous reports. Patients with a history of previous neck surgery, taking exogenous calcium or Vitamin-D before their operation, underlying parathyroid disorder, and renal impairment in addition to their thyroid condition was excluded from the study. Blood samples were dawned from a peripheral vein in the preoperative period, immediate post-operative, 24 hours, 48 hours, and 72 hours after surgery. All the samples were sent to the laboratory for further processing. In the laboratory, the blood samples were allowed to clot and were centrifuged at 3,500 rpm for 5 minutes for separation of serum. Then the serum was frozen at -40°C until assessment. However, during the study, the surgeon followed assessed and managed the patients. The eventual discharge of the patients was based on regular calcium level measurement at 24 hours, 48 hours, and 72 hours after surgery and observation for clinical symptoms of hypocalcemia. Statistical analysis was carried out by using SPSS version 22.0. Quantitative variables were presented as means ± standard deviations and qualitative observations were indicated by frequencies and percentages. For comparison of repeated assessments (preoperative immediate post-operative and 24 hours after operation), the paired t-test was used an unpaired t-test was performed between hypocalcemia and normocalcemia. Correlations between variables were evaluated by Pearson's correlation and explore the role of PTH to develop hypocalcemia after total thyroidectomy by using the receiver operating characteristic (ROC) curve. A P value less than 0.05 was considered significant. Signed informed consent from the patient convinced that the privacy of the patient was maintained. That was taken free of duress and was not exploiting any weakness of the participants.

RESULTS

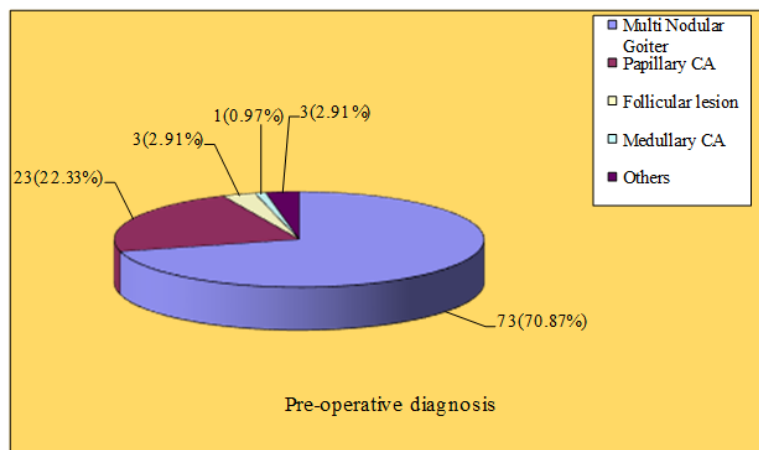**Table-1: Distribution of the study populations by age (N=103)**

Age (in years)	Frequency (n)	Percentage (%)
≤30 yrs.	24	23.30
31-40 yrs.	25	24.28
41-50 yrs.	38	36.89
51-60 yrs.	10	9.71
61-70 yrs.	5	4.85
>70 yrs.	1	0.97
Mean ±SD	41.72	±12.12
Range (min-max)	7	-80

Table 1 showed the distribution of the study patients by age. It was observed that more than one third (36.89%) patients belonged to age 41-50 years. The mean age was 41.72±12.12 years with ranged from 7 to 80 years.
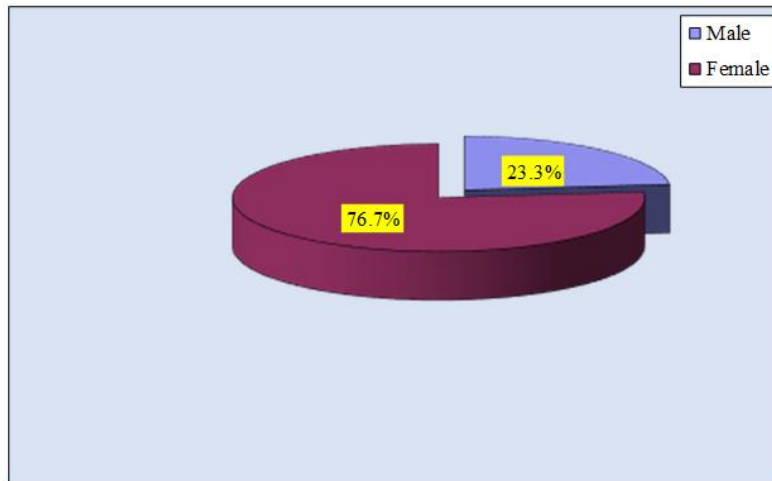
Fig-I: Pic Chart Showing Gender Distribution of Participants

Fig-II: Pie chart showing pre-operative diagnosis of the study populations

Figure II showed the distribution of the study patients by pre-operative diagnosis. It was observed that almost three fourth 73(70.87%) patients had multi nodular goiter followed by 23(22.33%) in papillary CA, 3(2.91%) in follicular lesion, 1(0.97%) Medullary CA, 3(2.91%) in others.

Table-2: Comparison of PTH Between Pre-Operative and immediate post operative

PTH Level	Pre-Operative	immediate post operative	p- value
Mean ±SD	45.41±15.56	37.63±20.22	0.001[s]

p-Value reached from paired t-test.

The mean PTH level was 45.41±15.56 pg/ml in pre-operative and 37.63±20.22 pg/ml was immediate post-operative period. The difference was statistically significant (p<0.05) between pre-operative and immediate post-operative period.

Table-3: Comparison of PTH Between Pre-Operative and 24H after thyroidectomy

PTH Level	Pre-Operative	24 H after thyroidectomy	p- Value
Mean ±SD	45.41±15.56	38.27±18.71	0.001[s]

p-Value reached from paired t-test.

The mean PTH level was 45.41±15.56 pg/ml in pre-operative and 38.27±18.71 pg/ml was 24H after thyroidectomy. The difference was statistically significant (p<0.05) between pre-operative and 24H after thyroidectomy.

Table-4: Comparison of PTH Between Pre-Operative and 48H after thyroidectomy(N=103)

PTH Level	Pre-Operative	48 H after thyroidectomy	p- Value
Mean ±SD	45.41±15.56	41.41±17.6	0.001[s]

p-Value reached from paired t-test.

The mean PTH level was 45.41±15.56 pg/ml in pre-operative and 41.41±17.6 pg/ml was 48 H after thyroidectomy. The difference was statistically significant (p<0.05) between pre-operative and 48H after thyroidectomy.

Table-5: Distribution of the study population by Pre-operative serum calcium level (N=103)

Serum Calcium (mg/dl)	Frequency (n)	Percentage (%)
Low <8	0	0.0
Normal 8-10	103	99.03
High >10	1	1.0
Mean±SD	8.87±0.56	
Range (min-max)	5.8-10.4	

Table 5 showed the distribution of the study patients by serum calcium. It was observed that 103(99.03%) patients belonged to low normal (8-10 mg/dl) serum calcium. The mean serum calcium level was 8.87±0.56 (mg/dl) with ranged from 5.8 to 10.4 (mg/dl).

Table-6: Distribution of the study populations by immediate post-operative serum calcium (N=103)

Serum Calcium (mg/dl)	Frequency (n)	Percentage (%)
Low <8	21	20.39
Normal 8-10	81	78.64
High >10	1	0.97
Mean ±SD	8.47	±1.193
Range (min-max)	2.1	-10.6

Table 6 showed the distribution of the study patients by serum calcium. It was observed that 21(20.39%) patients belonged to low (<8 mg/dl) serum calcium, 81(78.64%) was normal and 1(0.97%) was high serum calcium level. The mean serum calcium level was 8.47±1.19 (mg/dl) with ranged from 2.1 to 10.6 (mg/dl).

Table-7: Distribution of the study populations by clinical diagnosis (N=103)

Clinical diagnosis	Frequency (n)	Percentage (%)
Euthyroid	91	88.34
Hyper thyroid	6	5.83
Hypo thyroid	6	5.83

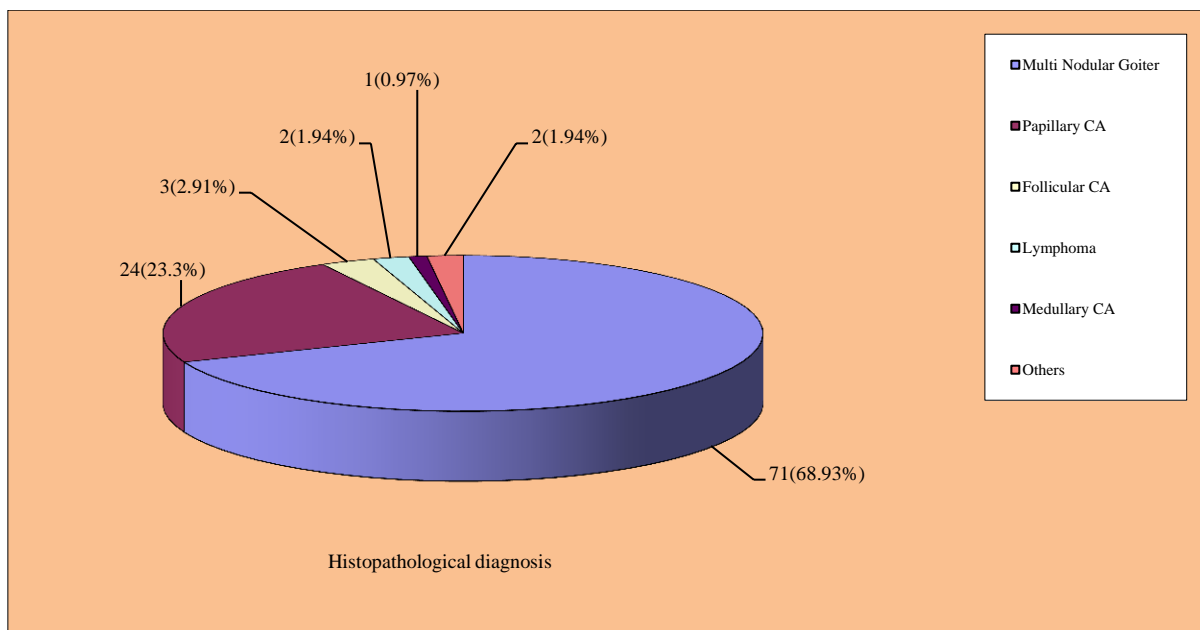Table 7 shows the distribution of the study patients by clinical diagnosis. It was observed that majority 91(88.34) patients had euthyroid and 6(5.83%) in hyper/ hypo thyroid.

Table-8: Distribution of the study populations by FNAC (N=103)

FNAC	Frequency (n)	Percentage (%)
Multi Nodular Goiter	72	69.9
Papillary CA	21	20.39
Follicular lesion	5	4.86
Medullary CA	1	0.97
Others	4	3.88

Table 8 distribution of the study patients by FNAC. It was observed that more than two third (69.90%) patients had multi nodular goiter followed by 21(20.39%) in papillary CA, 5(4.86%) in follicular lesion, 1(0.97%) medullary CA and 4(3.88%) in others.

Fig-III: Pie chart showing histopathological diagnosis of the study population

Figure 3 shows the distribution of the study patients by histopathological diagnosis. It was observed that more than two third (68.93%) patients had multi nodular goiter followed by 24(23.30%) in papillary CA, 3(2.91%) in follicular CA, 2(1.94%) in lymphoma, 1(0.97%) in medullary CA and 2(1.94%) in others.

Table-9: Comparison between features of hypocalcemia with PTH with level in immediate post operative period of the study populations (N=103).

PTH within 1 hour of operation	Hypocalcemia (n=11)		Normal (n=92)		p- Value
	n	%	n	%	
Low <14	11	100.0	6	6.5	
Normal 14-74	0	0.0	78	84.8	
High >74	0	0.0	8	8.7	
Mean ±SD	8.10±4.80		40.12±20.36		0.001[s]
Range (min-max)	0.6-14.30		0.2-111.3		

s=significant, p value reached from Unpaired t-test

Table 9 showed the comparison between features of hypocalcemia with PTH with **level** in immediate post-operative period of the study patients. It was observed that all (100.0%) patients had PTH with in 1 hour of operation low <14 pg/ml in hypocalcemia and 6(6.5%) in normal. The mean PTH with in 1 hour of operation was 8.10±4.80 pg/ml in hypocalcemia and 40.12±20.36 pg/ml in normal. The difference was statistically significant (p<0.05).
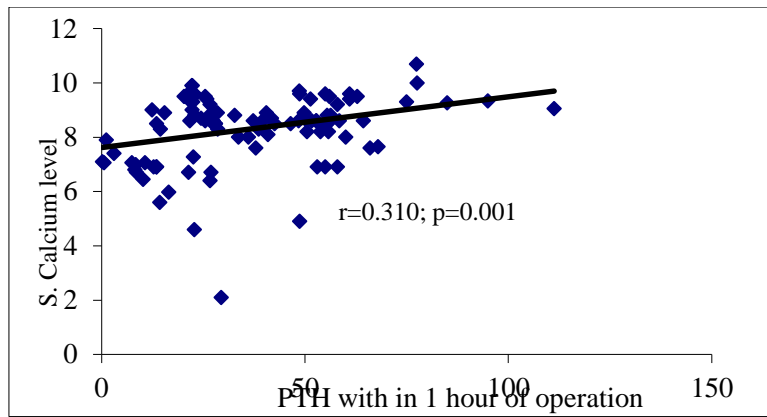
Fig-IV: Scatter diagram showing positive significant correlation (r=0.310; p=0.001) between PTH and serum Calcium in immediate post operative period.

Figure IV scatter diagram shows correlation between PTH and serum Calcium in immediate post operative period in all 103 patients. The value Pearson's correlation 0.310 and, which is statistically significant (p<0.05).

Table-10: Receiver operating characteristic (ROC) curve of PTH in immediate post-operative period to predict the hypocalcemia of the study patients. (N=103)

	Cut of value	Sensitivity	Specificity	Area under the ROC curve	P value	95% Confidence interval (CI)	
						Lower bound	Upper bound
PTH within 1 hour of operation	≤14.4	94.6	100.0	0.987	0.001[s]	0.952	1.000

The area under the receiver-operating characteristic (ROC) curve for finding the cut off value of PTH in immediate post operative period to predict the hypocalcemia among the study population is depicted in the table.
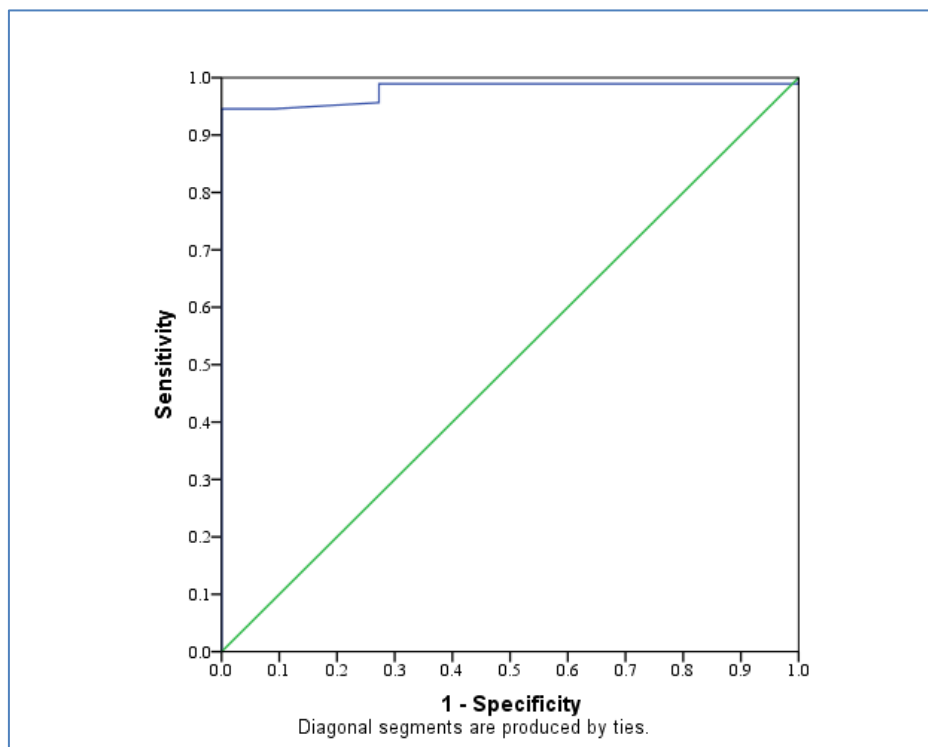
Fig-5: Receiver- operating characteristic (ROC) curve of PTH in immediate post operative period to predict post operative hypocalcemia.

Based on the ROC curves PTH in immediate post operative period had the best area under the curve 0.987, showing cut off value of ≤14.4 pg/ml with 94.6% sensitivity and 100.0% for prediction of hypocalcemia.

DISCUSSION

Le *et al*. (2014)1 showed post thyroidectomy hypocalcemia is a common complication that may be transient in 10-50% of patients or permanent occurring in 0.5-10.6% of patients. Roh and Park, (2009)2 found that the nadir for hypocalcemia typically at around 24-48h postoperatively but may be as delayed as postoperative day 4. Sarkar et al. (2014)3 observed that patients have to be observed for this time period prior to discharge in order to prevent the development of clinically significant hypocalcemia which would significantly lengthen hospital stay. Despite the recent development of surgical techniques and every effort of surgeons to preserve as many parathyroid glands as possible, early postoperative hypocalcemia and hypo parathyroidism still remain a great challenge so prediction of hypocalcemia after total thyroidectomy is imperative for early management in order to avoid devastating symptoms to ensure safe discharge. AlQahtani *et al*. (2014)10 found that parathyroid dysfunction leading to symptomatic hypocalcemia is not uncommon following a total or completion thyroidectomy and is often associated with significant patient morbidity and a prolonged hospital stay. A simple, reliable indicator to identify patients at risk would permit earlier pharmacologic prophylaxis to avoid these adverse outcomes. In this study, a total of 103 cases were evaluated the mean age by the study population was 41.72±12.12 yrs. Ranging from 13-18 yrs. In another study by Christopher RM *et al*. (1994)11 mean age of the study was 45.5±11.8 which is some extent higher than this study. Lo, *et al*. (2002)9 reported that the median age was 42 yrs which is closer to this study. Islam *et al*. (2012)12 reported mean age was 39±13.18 with a range of 15 to 75 yrs which is similar to our study. In this study group, 103 of which male was (23.30%) and 79(76.70%) were female, with a ratio male: female, = 1:3.3. Glinoer *et al*. (2010)13 reported that the male, the female ratio was 1:3.3. Didivitis RA et al. (2010)14 reported that female was a major victim of thyroid diseases. So our observation is consistent with the others. Among the study population 73(70.78%) patients were found benign (MNG) and 30 (29.22%) patients were treated for malignant disease. The result similar to Quiros Ruet *et al*. (2005)15. In the study group out of 103 patients, the preoperative mean value of PTH was 45.41±15.56 pg/ml and the immediate post-operative mean PTH level was 36.79±21.70 pg/ml. So there found a significant difference (p=0.001). The post-operative sample was taken 1-hour offer after total thyroidectomy. Mehrvarz *et al*. (2017)16 found that the mean PTH was 96.23±53.54 pg/ml before surgery, the difference was significant which is consistent with the current study. In this present study, it was observed that below normal (<14 pg/ml) PTH level was found 17 (16.50%) at immediate postoperative period and not found in the preoperative period. Islam *et al*. (2012)12 found intraoperative PTH was <15 pg/lm in 27 cases and >15 pg/ml in 38 cases. The total study population was 103, where biochemical hypocalcemia was found in 21 (20.39%) and normocalcaemia 81 (78.64%) of the study populations. The incidence of hypocalcemia was 20.39% after total thyroidectomy. Post portative hypocalcemia after total thyroidectomy has been reported to range from 1.3 to 50% (Rechards *et al*. 2003; Mehanna *et al*. 2010)17,18 Incidence of hypocalcemia was within the international norms. So the incidence of hypocalcemia in our study is consistent with the others. In the present study, total hypocalcemia patients were 21. Asymptomatic hypocalcemia was found in 10 (47.6%) and symptomatic hypocalcemia was found in 11 (52.4%) Le *et al*. (2014)1 reported that transient hypocalcemia was found in 10-50% patients which is consistent with one study. Our study showed that immediate postoperative PTH level is a predictor of post thyroidectomy hypocalcemia which is statistically significant. Our study was supported by AL Qahtani *et al*. (2014).19 They showed that PTH level after one-hour assay alone is predictive of the development of postoperative hypocalcemia with a sensitivity of 89%. By Markuszewska *et al*. (2010)20 PTH levels were assessed and a strong correlation was found between PTH level measured in the immediate post-operative period and development of hypocalcemia (r= 0.73, P<0.05), In the present study, PTH was statistically significant (P<0.05) in the post-operative group but not statistically significant (P>0.05) in preoperative period PTH levels. Immediate postoperative PTH levels were assessed and a significant correlation was found between immediate postoperative PTH levels and development of hypocalcemia after 24 hours and 48 hours of total thyroidectomy. Lam and Kerr (2003)21 showed that the incidence of post thyroidectomy hypocalcemia is 1 to 50%. In our study, the percentage of hypocalcemia reached 20.4% which is consistent with Lam and Kerr's study.21 It is almost nearer to similar in our study (≤14.4pg/ml). In our study post-operative hypocalcemia was found in 24 hours, 48 hours, and 72 hours after surgery. Maximum 8 out of eleven was found 48 hours after total thyroidectomy. It is similar to the study of Roh and Park (2006).22 In the current study it was observed that regarding clinical diagnosis majority of the patients had euthyroid (88.35%) and the rest are hyper or hypothyroid (5.83%). It was almost similar to Amouzeger *et al*.'s (2017) study.23 Noureldine *et al*. (2014)24 reported that the presence of malignant neoplasm carried out a 30.09% risk of mild hypocalcemia. It is similar to our study. The area under the receiver operating characteristic curve (ROC) for finding the cut-off value, sensitivity, specificity of PTH in the immediate post-operative period to predict the postoperative hypocalcemia was ≤14.4 pg/ml, 94.6%, 100% respectively. It was statistically significant. Lumbardi *et*

al. (2004)25 reported that early prediction of post-operative hypocalcemia by single intra-operative PTH measurement with 98% accuracy. In our study, the scatter diagram showed a positive significant correlation between PTH and serum calcium in the immediate post-operative period. It was supported by Markuszawska *et al*. (2010).20

CONCLUSION

Concomitant parathyroid hormone (PTH) and serum calcium measurement are evaluated in predicting hypocalcemia after completion of total thyroidectomy. It can be inferred that postoperative hypocalcemia is a common complication of total thyroidectomy resulting from manipulation, resection, or devascularization of the parathyroid glands. Parathyroid hormone (PTH) levels were assessed in pre-operative, immediate post-operative, and 24 hours after total thyroidectomy to predict the development of hypocalcemia. Therefore, it could be speculated that the generation of hard data in a large series of study patients for PTH levels detection after thyroidectomy and correlation with serum calcium levels would supplant much of the foregoing issues and controversies in this growing field of medical research.

LIMITATIONS

Purposive sampling was done. For realistic evidence, random sampling should be needed. The biochemical value of total calcium was measured but if ionized calcium value could be detected that would be more authentic. It was one center study. If the multi centric study was done, it was a more representative population-based study.

RECOMMENDATIONS

A standard PTH protocol for the prevention of hypocalcemia following total or completion thyroidectomy is highly efficacious. By using a PTH cut-off point ≤14.4 pg/mL to determine which patients should be treated with calcium and/or calcitriol, can minimize the number of postoperative symptomatic hypocalcemia. The measurement of serum PTH level in the immediate post-operative period can accurately identify the patients likely to develop hypocalcemia. It allows more timely initiation of calcium supplement (instead of waiting to become symptomatic) and potentiates for early discharge. Because of high sensitivity, specificity, accuracy, positive and negative predictive value, postoperative serum PTH can be used as a predictor of hypocalcemia after total thyroidectomy.

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