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Prediction of Post Total Thyroidectomy Hypocalcemia Using Perioperative Parathyroid Hormone

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ABSTRACT

Background: hypocalcaemia, which is a major contributing factor for delayed hospital discharge, occurs in many patients following total thyroidectomy. Parathyroid hormone (PTH) measurement has been proposed as a marker of this condition.

Aim: the aim of this study was to evaluate the reliability of perioperative parathyroid hormone measurement to predict post-total thyroidectomy hypocalcaemia.

Patients and methods: a prospective randomized study was conducted in the period between July 2015 and September 2017 in Ain Shams University, General Surgery Department, Endocrine Surgery Unit, Cairo, Egypt. The study was conducted on sixty patients for whom total thyroidectomy was done. Parathyroid hormone was measured pre-operative and 6 hours postoperative, and serum Ca was measured daily to predict hypocalcaemia. Patients were evaluated for symptoms of hypocalcaemia and treated with calcium and vitamin D supplementation as necessary.

Results: the study included 60 patients, 12 males and 48 females with mean age 39.1± 16.52 (20-65). Co morbid conditions included HTN, DM, ISHD and COPD. Most patients had nodular goiter (48 patients) whether unilateral or bilateral. 63.3% of patients had follicular lesion by FNABC. All patients underwent total thyroidectomy. Hypocalcemia developed in 16.7% (10 of 60) of the patients. Best cut off was 66% reduction giving 77% Sensitivity and 91.4% Specificity. Positive predictive value was 85% and negative predictive value was 94%.

Conclusion: the evaluation of PTH and corrected calcium levels 6 hours after thyroidectomy allows for an accurate prediction of the trend of hypocalcemia. This study enables us to discharge most patients safely within 24 hours after total thyroidectomy.

Keywords: parathyroid hormone, total thyroidectomy, hypocalcaemia, parathyroid gland, serum CA.

INTRODUCTION

Total thyroidectomy is now accepted worldwide as the standard surgical procedure for the management of benign bilateral nodular thyroid disease. Hypocalcemia is a common complication of that procedure; the reported incidence varies from as low as 1% to as high as 50% for patients who underwent total thyroidectomy [(1)]. Symptoms range from mild paresthesia and tingling to more severe cramps, tetany, and convulsions. Hypocalcemia typically occurs at around 24–48 h postoperatively but may be as delayed as day 4, resulting in longer patient stays than is otherwise necessary. With the increasing preference for shorter hospital stay [(2, 3),] post-thyroidectomy hypocalcemia became a problem. The most commonly accepted reasons for hypocalcemia are hypoparathyroidism secondary to devascularization of the parathyroid glands, resection of the glands or both. Various strategies for diagnosing and managing post thyroidectomy hypocalcemia have been used. The traditional method of inpatient clinical assessment and monitoring of serum calcium levels is still used. The routine use of oral calcium and/or vitamin D supplements has been advocated by some endocrine surgeons to minimize the incidence of hypocalcemia and shorten hospital stays [(4, 5)]. More recently measurement of parathyroid hormone (PTH) after total thyroidectomy has been utilized to try to predict those patients at risk of developing post-thyroidectomy hypocalcemia.

The aim of this study is to evaluate the reliability of perioperative parathyroid hormone measurement to predict post-total thyroidectomy hypocalcaemia.

PATIENTS AND METHODS

A prospective randomized study was conducted in the period between July 2015 and September 2017 in Ain Shams University, General

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Surgery Department, Endocrine Surgery Unit, Cairo, Egypt. The study included 60 patients having thyroid disease for whom total thyroidectomy were done during the study period and were prospectively enrolled into this study.

Inclusion criteria included: Thyroid disease to which total thyroidectomy was indicated (e.g. Multinodular goiter with cosmetic or pressure symptoms, thyroiditis, Age: more than 18 years, No previous neck or thyroid surgery.

Exclusion criteria included: Patients with hypo or hyperparathyroidism, Patients with hypo or hypercalcemia due to any cause. Patients with abnormally low or high serum magnesium due to any cause, Patients with proved malignant disease, Patients with acute or chronic kidney disease needing treatment and Patients receiving any of the following medications: Vitamin D, Thiazide diuretics, Estrogens and antiestrogens, Androgens, Vitamin A and Lithium.

Ethical consideration: All the patients signed the informed consent. **The study was approved by the Ethics Board of Ain Shams University.**

Preoperative workup: included History taking; Personal habits (smoking, heavy exercise …), History of previous operations, other systems review (urological, cardio-vascular system, respiratory, liver diseases, or history of DM), current medications and Presenting indication for total thyroidectomy. General Examination and Local full Neck examination. Endocrinal assessment. Laboratory investigations for all the patients include HB level, Coagulation profile, Liver function tests, renal function tests, Random blood sugar, thyroid function tests and blood samples were taken from every patient pre-operatively for Serum calcium (total and ionized) (not more than 12 hours before surgery), Serum phosphorus, Serum magnesium and parathyroid hormone level (not more than 12 hours before surgery). Other investigations when needed. Radiological investigations included Chest X-Ray and neck us.

Operative workup: Prophylactic antibiotic with induction of anesthesia was used. All patients received standard general anesthesia with endotracheal intubation, the operation was done by an endocrinal surgeons, after anesthesia patient was put in supine position with hyperextended neck, skin preparation and draping. Transverse collar incision of skin, opening of subcutaneous tissue including platysma muscle, opening of investing layer of deep cervical fascia, dissection of the gland with ligation of middle thyroid veins then ligation of superior and inferior thyroid vessels (only terminal branches) followed by separation of the gland from recurrent laryngeal nerve, trachea and surrounding structures, hemostasis and closure in layers with drain.

Postoperative work up: Close observation for vital signs. Blood samples were taken from every patient postoperatively for parathyroid hormone level (six hours post operatively) Parathyroid hormone was measured by chemoillumeniscence using ADVIA centaur (N: 10-69). Serum calcium (total and ionized) was measured 24 and 48 hours post-operatively. The presence and the type of symptoms of hypocalcaemia were registered together with evaluation of chvostek's sign twice a day from the day of surgery to postoperative day three. Symptomatic hypocalcaemic patients received Intravenous calcium gluconate till symptoms disappeared then oral calcium and vitamin D were recieved. Asymptomatic hypocalcaemic patients received oral calcium and vitamin D. Supplementation therapy were tapered subsequently on the basis of serum calcium measurements which were measured daily till normalization.

Follow up of cases: Follow up visits were planed 1, 2 and 4 weeks after discharge for removal of stitches and examination to detect any complication.

Statistical methodology: Analysis of data was done by IBM computer using SPSS (statistical program for social science version 21) as follows:

- **Description** of quantitative variables as mean, SD and range
- **Description** of qualitative variables as number and percentage
- **Chi-square** test was used to compare qualitative variables between groups.
- **Unpaired t-test** was used to compare quantitative variables, in parametric data (SD <50% mean)'
- **Paired t-test** was used to compare quantitative variable within the same group before and after in parametric data (SD<50%mean)
- **ROC Curve** (receiver operator characteristic curve was used to find out the best cut off value, and validity of certain variable.)
- **Sensitivity** (ability of the test to detect +ve cases) = true +ve /true +ve + false –ve
- **specificity** (ability of the test to exclude negative cases) = true -ve/true-ve+ false +ve

- **PPV** (positive predictive value) = true+/true +ve +false +ve = % of true +ve cases to all positive
- **NPV** = true-/true-ve + false –ve = % of the true –ve to all negative cases

P value >0.05 insignificant

P <0.05 significant – P <0.001 highly significant [6].

RESULTS

This study was conducted on sixty patients for whom total thyroidectomy was done.

Table (1): Distribution of the studied cases as regard general data:

Variables	**Mean± SD**	**Range**
Age (years)	39.1± 16.52	20-65
Swelling duration (months)	4±3	1-7
Gender	No.	%
Female	48	80%
Male	12	20%
Co morbid conditions		
HTN	9	15%
DM	6	10%
IHD	3	5%
Others (CLD, COPD, MR).	4	6.6%

Table (1) shows that 80% of the studied cases were females and the average age of the studied cases was 39.1 years.

Table (2): Ultrasound findings of patients:

Ultrasound findings of patients	**Number**	**Percentage %**
Multi nodular goiter	48	80%
Solitary solid mass	10	16.7%
Lymph node enlargement	4	6.6 %
Solitary cystic mass	2	3.3%

Table (2) shows that most patients had multinodular goiter.

Table (3): Distribution of the studied cases as regard fine needle results

Variables	**No**	**%**
Follicular lesion	38	63.3%
Colloid goiter	13	21.7%
Hemorrhagic smear (inadequate sample)	6	10%
Hashimoto's thyroiditis	3	5%

Table (3) shows that 63.3% of the studied cases had follicular lesion.

Table (4): Changes in serum Ca and serum PTH before and after the operation

Variables	**Mean± SD**	**Range**
Ca before	9.1 ± 1.1mg/dL	8.0-10.5 mg/dL
Ca *24 h postoperative*	8.5 ± 1.6 mg/dL	6.8-10.4 mg/dL
Ca 48 h postoperative	8.6 ± 1.3mg/dL	7.2-10.4 mg/dL
PTH before	41.1 ± 25.2 pg/ml	12.5-69.8 pg/ml
h postoperative	26.4 pg/ml	0 pg/ml

Table (4) shows that average ca before was 9.1 mg/dL, and declined to be 8.5 mg/dL 24h postoperative and 8.6 mg/dL 48 h postoperative. And average PTH before was 41.1pg/ml, and declined to be 36.7 pg/ml 6 h postoperative.

Table (5): Prevalence of hypocalcaemia in our studied patients:

	Number	Percentage
Hypocalcaemia (laboratory)	10	16.7%
Manifest	6	10%
Asymptomatic	4	6.7%

Table (5) shows hypocalcaemia was founded in 10 (16.7%) of our patients after total thyroidectomy it was manifested in 6 (10%) patients and asymptomatic in 4 (6.7%) patients.

Table (6): Comparison between patients with and without postoperative hypocalcaemia as regards to demographic findings, clinical presentation, ultrasonographic findings and number of identified parathyroid glands:

Demographic findings	Normocalcaemia (N = 50)		Hypocalcaemia (N = 10)		P
Age (years)					
Mean ± SD	38.2 ± 15.8		44.7 ± 8.3		0.15
	Number	%	Number	%	
Gender					
Male	10	20.0	2	20.0	0.31
Female	40	80.0	8	80.0	
Clinical presentation					
Swelling	41	82.0	9	90.0	0.95
Toxic symptoms	15	30.0	0	0.0	0.13
Pain	4	8.0	2	20.0	0.59
Pressure symptoms	3	6.0	2	20.0	0.82
Ultrasound findings					
Multi nodular goiter	40	80.0	8	80.0	0.06
Solid	8	16.0	2	20.0	0.09
Lymph node enlargement	3	6.0	1	10.0	1.0
Cystic	2	4.0	0	0.0	0.72
Number of identified parathyroid glands					
Identification of 4 parathyroid glands	45	90.0	9	90.0	0.16
Identification of 3 parathyroid	5	10.0	1	10.0	0.16

Table (6) shows there was no statistically significant difference between normocalcaemic and hypocalcaemic groups as regards demographic findings, clinical presentation, preoperative ultrasonographic finding or number of identified parathyroid glands.

Table (7): Serum calcium in patients with and without hypocalcaemia

	Normocalcaemia		Hypocalcaemia		P
Serum calcium	*Mean* ± SD	Range	*Mean* ± SD	Range	
Preoperative	9.1 ± 0.8 mg/dL	8.2-10.5 mg/dL	9.0 ± 1.0 mg/dL	8.0-10.2 mg/dL	
24 hours postoperative	9.0 ± 0.9 mg/dL	8.1-10.4 mg/dL	7.3± 0.5 mg/dL	6.8-7.8 mg/dL	< 0.001
48 hours postoperative	9.1 ± 0.9 mg/dL	8.2-10.4 mg/dL	± 0.4 mg/dL	7.2-8.1 mg/dL	< 0.001

Table (7) shows serum calcium in patients with and without hypocalcaemia.

Table (8): Parathyroid hormone level in patients with and without hypocalcaemia:

	Normocalcaemia		Hypocalcaemia		P
Parathyroid hormone	*Mean* ± SD	Range	*Mean* ± SD	Range	
Preoperative	42.3± 24.6 pg/ml	16.7-69.8 pg/ml	39.8 ± 19.1 pg/ml	12.5-60.2 pg/ml	
6 hours postoperative	40.2 ±21.2 pg/ml	14.5-64 pg/ml	12.9 ± 8.5 pg/ml	4.4-23.1 pg/ml	< 0.001

Table (8) shows serum parathyroid hormone in patients with and without hypocalcaemia.

Tables (7) and (8) show there was statistically significant difference between normocalcaemic and hypocalcaemic groups as regards the mean serum calcium levels 24, 28 hours postoperatively and as regard the mean parathyroid hormone level 6 hours postoperatively.

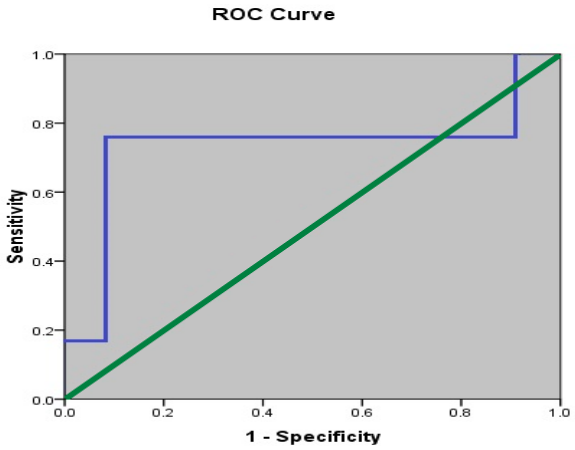
Table (9): Relative decline of serum calcium and parathyroid hormone in patients with and without hypocalcaemia:

	Normocalcaemia	Hypocalcaemia	P
Relative decline in calcium			
24 hours	1.1%	18.8%	0.001
48 hours	0.81%	15.5%	0.001
elative decline in parathyroid hormone			
6 hours	4.9%	67.6%	0.001

Table (10): Validity of PTH % of reduction in prediction of hypocalcaemia:

Variables	%
Best cut off	66%
Area under the curve (AUC)	0.71
Sensitivity	77%
Specificity	91.4%
Positive predictive value (PPV)	85%
Negative predictive value (NPV)	94%

Table (10) shows that PTH % of reduction was considered better negative than positive predictor for hypocalcemia with higher specificity.



ROC curve

DISCUSSION

Hypoparathyroidism is a common cause of hypocalcemia after total thyroidectomy whether transient or permanent [7, 8]. It occurs in about 30% of patients and can be attributed to many factors including injury, removal, or devascularization of the parathyroid glands [7, 9]. Because parathyroid hormone (PTH) has short half-life of only 1 to 4 minutes, any insult leading to impairment in its secretion will lead to immediate decrease in its serum level [10, 11]. This results in a reduction in serum calcium levels, because PTH is the major regulator of serum calcium level.

The aim of this study was to determine accuracy and reliability of monitoring (PTH) to predict patients with increased risk of developing hypocalcaemia following total thyroidectomy.

We conducted a prospective randomized study in the period between July 2015 and September 2017 in Ain shams university, general surgery department, endocrine surgery unit, Cairo, Egypt. The study was conducted on sixty patients for whom total thyroidectomy was done.

In our study, age ranged from 20 to 65 with mean of 39.1± 16.52. Eighty percent of patients were females and only 20% were males. Other studies showed similar data (Pyne et al., 2005; age 49.3 (21-76), 19 male and 51 females [12], Alia et al., 2007; age 44.5 (13-88), 12 male and 40 females [15]. Disease duration ranged from 1 to 7 months and co-morbid conditions included hypertension, diabetes mellitus and Ischemic heart disease.

In this study, most patients had multinodular goiter whether unilateral or bilateral then secondry toxic goiter, solitary solid nodule finally solitary cystic nodule respectively. Avi Khafif et al., 2006 had most of their patients having papillary carcinoma of thyroid gland 62.5% then multinodular and toxic goiter [13].

Pre- operative fine needle aspiration biopsy cytology in our study was follicular lesion for 63.3% of cases, colloid goiter in 21.7%, haemorrhagic smear in 10% and less commonly Hashimoto's thyroiditis.

Laboratory investigations were done routinely for all patients including creatinine, lever function tests, serum albumin and serum hemoglobin level. Serum calcium was done before operation and was followed up post operatively at 24 and 48 hours. PTH was measured the day before operation and six hours post operatively. The presence and the type of symptoms of hypocalcaemia were registered together with evaluation of chvostek's sign twice a day from the day of surgery to postoperative day three. Symptomatic hypocalcaemic patients received Intravenous calcium gluconate till symptoms disappeared then oral calcium and vitamin D were recieved. Asymptomatic hypocalcaemic patients received oral calcium and vitamin D. Supplementation therapy were tapered subsequently on the basis of serum calcium measurements which were measured daily till normalization. **Avi khafif *et al.*** measured PTH preoperative and 30 minutes postoperative [13] and **Vanderlei *et al.*** measured it with induction of anesthesia, one hour and one day after surgery [14].

Correlation between percent of reduction of PTH versus other variables showed no statistically significant relation. Changes in the PTH and Ca before and after the operation showed statistically significant decline in Ca and PTH after surgery by using paired t-test and by using ROC curve

Patients were considered hypocalcemic on either clinical or laboratory bases (serum calcium level below 8mg/dl. or the development of signs and symptoms of hypocalcemia, such as perioral numbness, paresthesias of the upper extremity digits, and a positive Trousseau's sign). In our study, hypocalcemia developed in 10/60 patients (16.7%) which is similar to other studies [12, 13, 14, 15]. In our study, the lower incidence of hypocalcaemia could be explained by the difference in type of selected patients (we excluded patient with proved malignant disease) and the study was done in specialized endocrine surgical department.

Different cutoff values for postoperative PTH have been proposed in different works. In our study, the best cut off was 66% drop of PTH level compared to preoperative level giving 77% Sensitivity , 91.4% Specificity, PPV 85%, NPV 94% and 92% overall accuracy. Avi khafif et al. 2006 found that 50% as cut off gives 92% sensitivity and 66% specificity while 75% gives 23%sensitivity and 75% specificity. Venderlei et al. 2012 found that 73.5% as cut off gives 91.6% sensitivity and 87.5% specificity. Alia et al. 2007, found that 62.5% as cut off gives 93.3% sensitivity.

CONCLUSION

In conclusion, a drop in intraoperative PTH levels by more than 66% may serve as a sensitive and specific indicator of hypocalcemia and this will help in selecting patients for early discharge after total thyroidectomy. Correlation between percent of reduction of PTH versus the number of preserved parathyroid glands showed no statistically significant relation. All patients are sent home with specific instructions describing the signs and symptoms of hypocalcemia along with appropriate course of action.

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