ORIGINAL RESEARCH PAPER

ENT

KEY WORDS: Thyroidectomy, Hypocalcemia, Risk factors, Kashmir

RISK FACTORS OF POST-OPERATIVE HYPOCALCEMIA AMONG PATIENTS UNDERGOING TOTAL THYROIDECTOMY IN A TERTIARY CARE HOSPITAL IN KASHMIR- A LONGITUDINAL STUDY

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ABSTRACT

Introduction: The parathyroid glands produce parathyroid hormone (PTH), which regulates blood calcium levels. Hypocalcemia secondary to hypoparathyroidism is one of the common complications after total thyroidectomy, which may cause uncomfortable symptoms that result in longer hospital stays. Post-operative hypocalcemia is reported with an incidence of 1.2% to 40%. **Objectives:** 1. To determine the risk factors of postoperative Hypocalcemia among patient undergoing total thyroidectomy. 2. To study the effect of site of ligation of inferior thyroid artery in total thyroidectomy patients on postoperative Hypocalcemia. **Methods:** A Hospital-based Prospective Observational Study was conducted in the Department of Otorhinolaryngology and Head and Neck surgery, Government SMHS Hospital Srinagar, among the patients undergoing total thyroidectomy. **Results:** A total of 37 eligible participants were included & followed in the study. More than fourth-fifths (81%) of study participants were females with majority of patients being Papillary Carcinoma Thyroid (78.4%). The mean age of study participants was 36.35 years with a standard deviation of 15.37 (26.43±7.44 for males & 38.67±15.89 for females). The mean serum Calcium level was lesser in case of patients undergoing neck dissection on all the three post-operative days, with statistically significant difference on Day 2 & Day 3. 54 % patients developed symptoms of hypocalcemia within first three postoperative days. Development of hypocalcemic symptoms was significantly associated with age of subjects, pre-operative Calcium level, pre-operative PTH level, post-operative Calcium level and post-operative PTH level. There was a significant strong positive correlation between postoperative Ca at day 3 & post-operative PTH level.

INTRODUCTION

The thyroid gland is an essential organ of our body which manages multiple metabolic processes in the body.There are usually four parathyroid glands two on each side, one superior and another inferior. The parathyroid glands are located on the posterior & medial aspect of each lobe of thyroid gland. The parathyroid glands produce parathyroid hormone (PTH), which regulates blood calcium levels. Low blood calcium levels cause the production and secretion of PTH. Parathyroid hormone (PTH) has three main actions, all of which act to **increase calcium** levels in the body. These include 1.**Increased bone resorption**, 2.**Increased reabsorption in the kidney & 3.Vitamin D synthesis.**

The most common indications for total thyroidectomy are the following:
1. Thyroid cancer; Cancer is the most common reason for thyroidectomy.
2. Noncancerous enlargement of the thyroid (goiter).
3. Overactive thyroid (hyperthyroidism).
4. Indeterminate or suspicious thyroid nodules.

Hypocalcemia secondary to hypoparathyroidism is one of the common complications after total thyroidectomy, which may cause uncomfortable symptoms that result in longer hospital stays. Post-operative hypocalcemia is reported with an incidence of 1.2% to 40%.[1,2,3]

Usually the decrease in the function of Parathyroids and the resulting hypocalcemic features are transitory, however at times (less than 3 %) there might be permanent damage to them.[5,6,7] The pathophysiology behind transient hypoparathyroidism and hypocalcemia is not well understood but is thought to be related to a transient ischemia to the parathyroid glands or perhaps an increased release of the acute phase reactant endothelin-1.[4]

The classic presenting symptoms of hypocalcemia include numbness and tingling of the digits or perioral area, carpopedal spasm, or the presence of a Chvostek sign or a Trousseau sign. In severe cases, patients may also experience tetany, EKG changes (QT prolongation), seizures, mental status changes, or cardiac arrest secondary to hypocalcemia. Intra-venous replacement is recommended in symptomatic or severe hypocalcemia with cardiac arrhythmias or tetany . Doses of 100- 300 mg of elemental calcium in 50-100ml of 5% dextrose should be given over 5-10 minutes.

AIMS AND OBJECTIVES

This prospective hospital based study was conducted with the following aims and objectives:

Aim:

- To study the post-operative hypocalcemia after total thyroidectomy.

Objectives:

- To determine the risk factors of postoperative Hypocalcemia among patient undergoing total thyroidectomy.
- To study the effect of site of ligation of inferior thyroid artery in total thyroidectomy patients on postoperative Hypocalcemia.

MATERIALS AND METHODS

Study Design:
Hospital-based Prospective Observational Study.

Study Period:
The study was done for a period of 18 months from May 2019 up to October 2020. Study area: Study was conducted in the Department of Otorhinolaryngology and Head and Neck surgery, Government SMHS Hospital Srinagar, which caters patients from whole of Kashmir division.

Study Participants:
All the patients undergoing total thyroidectomy in the

Department during the period.

Inclusion Criteria:

- All the patients undergoing total thyroidectomy for various causes with or without neck dissection.

Exclusion Criteria:

- Patients having hypocalcemia prior to thyroidectomy.
- Patient with such co-morbidities which might influence the serum calcium level.

Sample Size Estimation:

No specific number of participants were planned to be included in the study. All the participants who fulfilled the inclusion & exclusion criteria and underwent total thyroidectomy within the said period were included.

Selection Of Sample And Data Collection:

All the patients dated for total thyroidectomy during the data collection period were assessed for inclusion & exclusion criteria and those found eligible were included in the study. Written and Informed consent in local language was obtained from patients before enrolling them into the study. A clearance from the ethical committee of Government Medical College Srinagar was obtained prior to the start of study. After enrolling the participants into the study they were assessed at base-line before surgery, during surgery and during first 3 days of post-operative period. A pretested semi-structured questionnaire was used to record the information at the base-line and on different follow-ups. This questionnaire included information regarding age, gender, diagnosis of the patient, pre-operative TSH, Preoperative Ca, Preoperative PTH, type of surgery, site of ligation of Inferior Thyroid Artery, Post-operative Ca on Day1, Day2&Day3, Post-operative PTH and hypocalcemic symptom development on post-operative day1, day2 & day3. This data was collected through interviews, patient examinations, from operative notes, patient's file records & laboratory reports.

Statistical Analysis:

The data was entered in the Microsoft excel 2007 and analyzed using SPSS v23. Categorical variables were described as Frequencies & Percentages while as continuous variables were described as Mean & Standard Deviation. Appropriate statistical tests were used when required. A p Value of less than 0.05 % was considered to be statistically significant.

OBSERVATIONS & RESULTS

Table-1. Baseline Characteristics Of Participants:

Characteristics	Sub-Group	Frequency	Percentage
Gender	Males	7	19%
	Females	30	81%
Type of Thyroid Cancer	Pappilary Carcinoma	29	78.4%
	Medullary Carcinoma	5	13.5%
	Follicular Carcinoma	3	8.1%
Type of surgery	Total thyroidectomy	14	37.8
	Total thyroidectomy with Neck dissection	23	62.2
Site of ligation of Inf Thyroid Artery	Distal	36	97.3
	Truncal	1	2.7
Symptoms of Hypocalcemia	No symptom	17	45.9
	Symptoms developed	20	54.1

Table-2. Distribution Of Various Continuous Variables Among Study Subjects:

Variable	Minimum	Maximum	Mean	Std. Deviation
Age in yrs	14.0	65.0	36.35	15.37
Preoperative TSH	.06	12.28	3.88	3.01
Preoperative Ca	8.20	10.40	9.07	0.50
Postoperative Ca at Day1	6.31	9.41	8.18	0.84
Postoperative Ca at Day 2	5.68	9.68	7.88	1.03
Postoperative Ca at Day 3	5.40	9.46	7.97	0.95
Preoperative PTH	31.70	192.80	72.26	38.76
Postoperative PTH	.40	111.00	38.96	38.05

Table-3. Relationship Between Type Of Surgical Procedure And Serum Calcium Level At Different Post-operative Days:

Parameter	Surgical Procedure	Mean	Std. Deviation	Mean Difference	p Value
Postoperative Ca Day1	Thyroidectomy	8.44	1.01	.431	.173
	Thyroidectomy with Neck Dissection	8.01	0.69		
Postoperative Ca Day 2	Thyroidectomy	8.52	0.87	1.027	.002
	Thyroidectomy with Neck Dissection	7.49	0.94		
Postoperative Ca Day 3	Thyroidectomy	8.66	0.53	1.110	.000
	Thyroidectomy with Neck Dissection	7.55	0.91		

The mean serum Calcium level was lesser in case of patients undergoing neck dissection on all the three post-operative days, with statistically significant difference on Day 2 & Day 3.

Table-4. Relationship Between Baseline Characteristics And Hypocalcemic Symptom Development:

Characteristics	Sub-Group	Frequency of Hypocalcemic Symptoms	Percentage	p Value
Gender	Males	5	71.4	0.42
	Females	15	50.0	
Type of Thyroid Cancer	Pappilary Carcinoma	17	58.6	0.6
	Medullary Carcinoma	2	40.0	
	Follicular Carcinoma	1	33.3	
Type of surgery	Total thyroidectomy	6	42.9	0.33
	Total thyroidectomy with Neck dissection	14	60.9	
Site of ligation of Inf Thyroid Artery	Distal	19	52.8	0.54
	Truncal	1	100.0	

Table-5. Relationship Of Hypocalcemic Symptoms With Various Continuous Variables:

Variable	Symptom development	N	Mean	Std. Deviation	Mean Difference	p Value
Age in yrs	Asymptomatic	17	43.35	17.15	12.95	.012
	Symptomatic	20	30.40	10.90		
Preoperative TSH	Asymptomatic	17	3.39	4.06	-0.91	.368
	Symptomatic	20	4.30	1.71		
Preoperative Ca	Asymptomatic	17	8.86	0.41	-0.40	.013
	Symptomatic	20	9.26	0.51		
Postoperative Ca at Day1	Asymptomatic	17	8.53	0.69	0.65	.014
	Symptomatic	20	7.88	0.85		
Postoperative Ca at Day 2	Asymptomatic	17	8.23	0.78	0.65	.055
	Symptomatic	20	7.58	1.14		
Postoperative Ca at Day 3	Asymptomatic	17	8.38	0.80	0.75	.014
	Symptomatic	20	7.63	0.95		
Preoperative PTH	Asymptomatic	17	86.58	45.36	26.49	.046
	Symptomatic	20	60.09	27.83		
Postoperative PTH	Asymptomatic	17	60.40	31.62	39.66	.001
	Symptomatic	20	20.74	33.78		

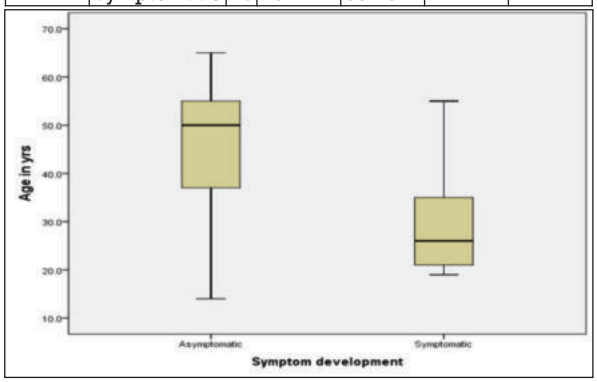

Figure-1. Box Plot Depicting Age Variation Among Asymptomatic & Symptomatic Cases.

Table-6. Relationship Of Postoperative Ca At Day 3 With Other Variables:

Correlation between Postoperative Ca at Day 3 &	Correlation Co-efficient	p Value
1.Pre-operative TSH	- 0.406	.013
2. Postoperative PTH	0.649	< 0.001

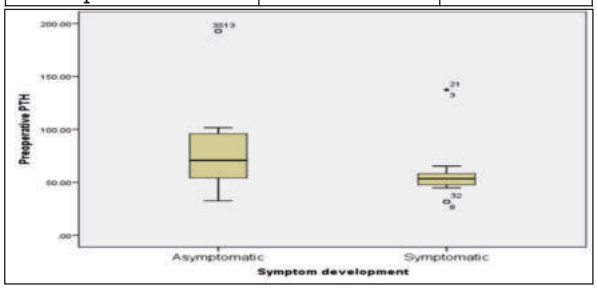

Figure-2. Box Plot Depicting Variation In Pre-operative PTH Among Asymptomatic & Symptomatic Cases.

DISCUSSION

A total of 37 eligible participants were included & followed in the study. More than fourth-fifths (81%) of study participants were females. Majority of patients had Papillary Carcinoma Thyroid (78.4%) followed by Medullary Carcinoma Thyroid (13.5%). Neck dissection was performed in 62% of cases. In all but one cases (36 cases) Inferior Thyroid Artery was at distal end. The mean age of study participants was 36.35 years with a standard deviation of 15.37 (26.43±7.44 for males & 38.67±15.89 for females). The Serum Calcium level at first, second & third post-operative day was 8.18±0.84, 7.88±1.03 & 7.97±0.95 mg/dl respectively. The mean serum Calcium level was lesser in case of patients undergoing neck dissection on all the three post-operative days, with statistically significant difference on Day 2 & Day 3. 54 % patients developed symptoms of hypocalcemia within first three postoperative days with majority of them developing it on first postoperative day. There was no statistically significant difference in the development of hypocalcemic symptoms during the first three post-operative days between males & females, between different types of diagnosis, between types of surgery & site of ligation of Inferior thyroid artery. Development of hypocalcemic symptoms during the first three post-operative days was significantly associated with age of subjects, pre-operative Calcium level, pre-operative PTH level, post-operative Calcium level and post-operative PTH level. There was a significant strong positive correlation between postoperative Ca at day 3 & post-operative PTH level.

In our study 81% of study participants were females. Many similar studies showed similar female preponderance among patients undergoing total thyroidectomy. 5,6

The most common indication for total thyroidectomy among the study participants was Pappilary Carcinoma Thyroid (78.4%) followed by Medullary Carcinoma Thyroid (13.5%). It is quite expected as the Papillary Carcinoma Thyroid is the most common thyroid malignancy. The incidence of hypocalcemic symptoms during first three post-operative days of total thyroidectomy was estimated to be 54%. It is proposed that during surgeries of thyroid gland there is partial compromise in the blood supply to parathyroid glands resulting into transient hypoparathyroidism & subsequent transient hypocalcemia. Immediate postoperative rates of transient hypocalcemia vary in the literature from between 5-50%.[7,8,9,10,11,12,13]

The serum Calcium levels at first, second & third post-operative days were 8.18±0.84, 7.88±1.03 & 7.97±0.95 mg/dl respectively. As evident the mean serum Calcium level was less than the normal range during all the three days. The patients undergoing neck dissection in addition to total thyroidectomy had a lesser mean serum calcium levels on all the three post-operative days as compared to patients undergoing only total thyroidectomy. This difference was statistically significant on second & third post-operative days. Jong-LyelRoh etal[14] found in their study titled "Prevention of Postoperative Hypocalcemia With Routine Oral Calcium and Vitamin d Supplements in Patients With Differentiated Papillary Thyroid Carcinoma Undergoing Total Thyroidectomy Plus Central Neck Dissection" that patients undergoing neck dissection with total thyroidectomy had a higher incidence of post-operative hypocalcemia as compared with patients undergoing total thyroidectomy alone. This is expected to be due to more extensive exploration in the neck compartment, which may cause a high probability of unplanned parathyroidectomy or parathyroid gland devascularization.[15]

Development of hypocalcemic symptoms during the first three post-operative days was significantly associated with age of subjects, pre-operative Calcium level, pre-operative PTH level, post-operative Calcium level and post-operative PTH level.

The age of participants was inversely related to the development of hypocalcemic symptoms during post-operative days, lesser the age more the chances of hypocalcemic symptoms. The mean age of patients who developed post-operative hypocalcemic symptoms was 30.4 years against the 43.4 years among those who did not develop hypocalcemic symptoms, & this difference was statistically significant. In literature, contrary opinions have been asserted about correlation between development of postoperative hypocalcemia and patient age. Some studies, found transient hypocalcemia to be associated with advanced age, whereas others reported an association with younger age. A systematic review performed by Edafe et al. Observed no significant difference in mean age between patients who had transient hypocalcemia and those who did not.[16,17]

The pre-operative serum calcium level of participants was related to the development of hypocalcemic symptoms during post-operative days, more the pre-operative serum calcium level more the chances of post-operative hypocalcemic symptoms. The mean serum calcium level of patients who developed post-operative hypocalcemic symptoms was 9.26 mg/dl against the 8.86 mg/dl among those who did not develop hypocalcemic symptoms, & this difference was statistically significant. There have been different observations in different studies conducted so far with majority of them showing no relationship between pre-operative serum calcium level & postoperative hypocalcemia.[17]

The pre-operative PTH level of participants was associated with the development of hypocalcemic symptoms during post-operative days, lesser the pre-operative PTH level more the chances of post-operative hypocalcemic symptoms. The mean PTH level of patients who developed post-operative hypocalcemic symptoms was 60.09 mg/dl against the 86.58 mg/dl among those who did not develop hypocalcemic symptoms, & this difference was statistically significant. Thus pre-operative PTH levels can be utilized as an important modifiable predictor for postoperative hypocalcemia & the patients having very lesser levels of PTH should be properly managed for low PTH before undertaking total thyroidectomy.

The hypocalemic symptoms were also associated with post-operative Calcium levels and post-operative PTH level & the association was statistically significant; lesser the post-operative levels of Calcium/PTH higher the incidence of hypocalcemic symptoms. This is quite expected as the PTH manages the serum calcium levels & lesser PTH means lesser calcium level resulting in hypocalcemic symptoms. Also there was a significant strong positive correlation between postoperative Ca at day 3 & post-operative PTH level, which too is quite plausible and expected result.

Out of total 37 patients, the site of ligation of inferior thyroid artery was distal in 36 patients & truncal in only one patient. Though the patient in whom the said artery was ligated at truncal site developed symptoms of hypocalcemia in postoperative

Strengths and Limitations of the study:

- Our study is a prospective cohort study rather than a retrospective cohort study. This eliminates the chance of recal bias and also increases the validity of measurements, thus giving a more accurate estimation of incidence of hypocalcemic symptoms.
- There is no chance of selection bias in our study because we had no role in the admission of patients to the SMHS Hospital for thyroidectomy, and patients belonging to all strata of socio-economic status from all over the Kashmir get thyroidectomy at Department of Otorhinolaryngology and Head and Neck surgery, Government SMHS Hospital Srinagar.
- All the investigations were carried out in the same laboratory of SMHS Hospital and following the same protocol every time. This decreases the chances of inter-instrument, intra-observer and inter-observer variations thus minimizing the chances of errors in the investigations.
- Our study could not study the effect of site of ligation of inferior thyroid artery in total thyroidectomy patients on postoperative serum calcium levels and also could not determine the association of some of the factors factors on the development of hypocalcemic symptoms after total thyroidectomy because of small sample size of the study. Due to the pandemic of Covid-19 very less number of patients were admitted & operated at Department of Otorhinolaryngology and Head and Neck surgery, Government SMHS Hospital Srinagar; as compared to what was expected at the start of study.

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