Original Research Paper

General Surgery



HYPOCALCEMIA AND HYPOPARATHYROIDISM AFTER NEAR TOTAL THYROIDECTOMY:

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ABSTRACT

Background : Post-operative hypocalcemia is a common and usually a transient event after thyroidectomy due to iatrogenic injury to the parathyroid glands. Most of the studies had investigated the frequency of surgical complications in Total thyroidectomy patients. Unfortunately, very few studies had investigated about the hypocalcemia and hypoparathyroidism frequency in near total thyroidectomy patients post-surgically Aims: . We carried out this study to evaluate the hypothyroidism and hypoparathyroidism frequency in thyroid disorder patients who underwent near total thyroidectomy. Methods: We performed a retrospective analysis of 202 patients who underwent near-total thyroidectomy at our institution from May 2017 to April 2022. Institutional Ethical committee approval was taken and Waiver of consent was taken from the head of the surgery department before the data collection. Post near-thyroidectomy patients who were above 18 years old with normal preoperative serum calcium levels (i.e., 8.4-10.2µL) were included. The patients who underwent subtotal thyroidectomy, thyroidectomy with neck dissection, hemi-thyroidectomy, concurrent lymph nodes dissection, complete thyroidectomy following hemi-thyroidectomy, parathyroid auto transplantation and those who received calcium supplementation before surgery were excluded from the study. Therefore, medical records of 478 patients were reviewed and finally 202 patients were included in the study who fulfilled both the inclusion and exclusion criteria. Conclusion: The results obtained confirm that transient hypocalcemia can be observed after any operation; and particularly responsible is the decrease of the calcium concerning the proteins. We found that post-operative hypoparathyroidism is due to injury to the parathyroid glands (parathyroid ischaemia or surgical ablation of one or more glands). Here we see the delayed serum calcium level < or = 7.5 mg/dl or the delayed serum phosphorous level > 7.4 mg/dl. The results of our study, with 2 patients presenting transient post-operative hypoparathyroidism, contribute in confirming that the extracapsular total thyroidectomy aimed to reduce any injury to the parathyroid and to the recurrent nerves, represent the better operation also for the extended benignant thyroidopathies.

KEYWORDS : Hypocalcemia, hypoparathyroidism, low serum calcium, low serum PTH, near-total thyroidectomy, thyroid disorders, bethseda classification, normal calcium with low PTH levels

INTRODUCTION:

Hypocalcemia is the most severe surgical complication following thyroidectomy. The primary cause of hypocalcemia is secondary hypoparathyroidism, which is due to inadvertent removal or damage to parathyroid gland(PG) or inadvertent removal of PG during surgical removal of thyroid. Even a small thyroid swelling needs to be addressed by the physician and the treatment varies based on the disorder type. Thyroidectomy can be performed especially for Goiter which is arguably the commonest among the thyroid disorders. The analysis of both genders in post thyroidectomy patients showed that higher incidence of hypocalcemia is seen in female patients than males ^{1,2}. Patients with preoperative 25(OH) Vitamin D, postoperative hypomagnesemia and hypoparathyroidism would foresee the risk of postoperative hypocalcemia¹.

The single strong predictor of significant hypocalcemia is PTH level (≤ 8pg/mL)⁵. Patients with normal PTH levels doesn't "Parathyroid insufficiency". Devascularization of parathyroid glands during surgery, compromises parathyroid gland function, remaining parathyroid tissue gives maximum stimulus to maintain normal parathormone levels however that is not sufficient to maintain normal calcium levels². Posthyroidectomy PTH levels foretell postoperative hypocalcemia⁶. Hypocalcemia and hypoparathyroidism plays a vital role in increasing the length of stay in the hospital⁸.

Different surgical procedures can be performed for structural, functional and cosmetic reasons. Although in India, the ideal choice for the most common thyroid disorder is total thyroidectomy. After surgical removal of thyroid, surgeons generally investigate for pre and post-operative calcium and PTH values because Post-operative hypocalcemia has an incidence of 1.2-40% and permanent hyoparathyroidism is

registered in 3% of cases.¹

Hence, our study primarily focused to evaluate the hypothyroidism and hypoparathyroidism frequency in thyroid disorder patients who underwent near total thyroidectomy. Most of the studies had investigated the total thyroidectomy post-surgical complications. Unfortunately, very few studies had investigated about the hypocalcemia and hypoparathyroidism frequency in post-near total thyroidectomy (NTT) patients. Thus, it may guide the future researchers about the NTT complications and it guides them to pick the right choice of thyroidectomy with lesser complications that may minimize the surgical complications. Furthermore, it will also help the patients by decreasing morbidity and financial burden on patients by early detection of complications.

Aim of the study:

The primary aim of the study was to evaluate the frequencies of post NTT hypocalcemia and hypoparathyroidism by comparing preoperative and postoperative values and also to determine hypoparathyroidism in postoperative normocalcemic and hypocalcemic patients.

MATERIALS AND METHODS:

We performed a retrospective analysis of 201 patients who underwent near-total thyroidectomy at Father Muller Medical College, Kankandy, Mangalore, Karnataka, India from May 2017 to April 2022. Our Institutional Ethical committee approval was obtained before commencement of the study. Waiver of consent was taken from the head of the surgery department before the data collection. We included patients of both sexes (>18 years old) who underwent NTT with normal preoperative serum calcium levels (i.e., $8.4-10.2/\mu$ L) in Father Muller Medical College, Kankanady, Mangalore, Karnataka,

India. The patients who underwent subtotal thyroidectomy, thyroidectomy with neck dissection, hemi-thyroidectomy, concurrent lymph nodes dissection, complete thyroidectomy following hemi-thyroidectomy, parathyroid auto transplantation and those who received calcium supplementation before surgery were excluded from the study. Therefore, medical records of 478 patients were retrospectively reviewed and finally 201 patients were included in the study who fulfilled both the inclusion and exclusion criteria.

All surgeries were performed by an experienced general surgeon or a resident under supervision. NTT is the removal of both thyroid lobes except the thyroid tissue (approximately <1 gram) which is located adjacent to recurrent laryngeal nerve near ligament of berry. Adequate aseptic precautions were made throughout the surgery. Antibiotics were administered within 30 minutes from the beginning of surgery and one dose given after 8 hours from the last dose administered. Standard Technique of NTT was performed in all the surgeries. After the surgical removal of the thyroid gland, tissue samples were sent for the pathological investigation. Based on the cytopathological diagnosis, patients were categorized into 6 categories with the help of Bethseda Classification.

Table 1: Bethseda Classification

Bethseda Category	Cytopathologic category	Malignancy risk (%)
Ι	Non-diagnostic	1-4
II	Benign	0-3
III	Atypia/ follicular lesion of undetermined significance	5-15
IV	Follicular neoplasm or suspicious for follicular neoplasm	15-30
V	Suspicious for malignancy	60-75
VI	Malignant	97-99

Study protocol:

Serum calcium levels was measured immediate preoperative and early postoperative days 1 and 2 in the morning times and the date of discharge. Normal serum calcium levels in our laboratory range between 8.4 and 10.2 mg/dL. Intact PTH was measured post operatively day 2 and on the day of discharge after the end of the operation by electrochemilumescence method using the automatic analyzer COBAS 6000 (in Father Muller Lab Diagnostics, Kankanady, Karnataka, India). Normal serum intact PTH concentrations in our laboratory range between 15 and 65 pg/mL. Hypocalcemia was defined as that the patient had low calcium levels than our laboratory range. Hypoparathyroidism was defined as the postoperative serum PTH levels of <15pg/ml along with persistent calcium need in order to maintain normal calcium levels.

For all of the patients, clinical, biochemical and surgical data were collected retrospectively for individual patient using a commercially available software package (Microsoft Word and Microsoft Excel, Microsoft Corporation, Redmond, WA). As this is a retrospective study, the patients were not followed after the discharge.

The parameters such as age, sex, final pathological diagnosis, bethseda classification based on diagnosis, surgical procedure, preoperative and postoperative serum calcium levels and postoperative PTH levels were recorded in the proforma created.

Statistical analysis:

Data were analyzed with SPSS software (IBM, SPSS Inc., Chicago, United States) to find out the frequency of hypocalcemia and hypoparathyroidism in the patients who underwent NTT. Associations between variables were analyzed via cross-tabulations. There was no missing data in the study population.

The primary clinical end points including hypocalcemia and hypoparathormone were evaluated with chi-square test and fisher's exact test.

RESULTS:

A total of 201 cases were selected from May 2017 to April 2022 (5 years). The mean age of the patients was 46.4 years (standard deviation [SD] of 13) and 85.07% of them were women. In accordance with age, patients were categorized into 3 groups- <40 years which included 65 patients (32.33%), 40-50 years which included 61 patients (30.34%) and >50years which included 75 patients (37.31%). On the basis of cytopathological analysis, patients were categorized into 6 categories with the help of Bethseda Classification: I had 7 (3.48%) patients, II had 159 (79.10%) patients, III had 8 (3.98%) patients, IV had 10 (4.97%) patients, V had 13 (6.46%) patients and VI had 4 (1.99%) patients. Overall, hypocalcemia was reported in 115 out of 201 patients (57.21%), overall hypoparathormone was reported in 72 out of 201 patients (35.82%). Hypocalcemia and hypoparathyroidism were more common in patients with the following variables such as age >50 years, female sex and in Bethseda classification I patients who underwent NTT. (Table 1)

Sl. No			Frequency	Percentage (%)
1	Age	<40 years	65	32.33
		40-50 years	61	30.34
		>50 years	75	37.31
2	Sex	Male	30	14.92
		Female	171	85.07
3	Calcium	Normal	86	42.78
		Hypocalcemia	115	57.21
4	PTH	Normal	129	64.17
		Hypopara-	72	35.82
		thyroidism		
5	Bethseda	Class I	7	3.48
	Classifi-	Class II	159	79.10
	cation	Class III	8	3.98
		Class IV	10	4.97
		Class V	13	6.46
		Class VI	4	1.99

Table 1: Frequency and percentage

Hypocalcemia in association with age: patients with age <40 years had the incidence of 35 hypocalcemic cases out of 65 patients, patients with age 40-50 years had the incidence of 34 hypocalcemic cases out of 61 patients and patients with age >50 years had the incidence of 46 hypocalcemic cases out of 75 patients. Chi-square test of independent variables such as age was not significantly associated with hypocalcemia and the p value was 0.646, non-significant [NS]. (Table 2)

Table 2: Occurrence of Hypocalcemia in relation to Age,	Sex
and Bethseda Classification	

S1.			Serum Calcium		Р
No			Normal	Нуро-	Value
				calcemia	
1	Age	<40 years	30	35	Chi-square
		40-50 years	27	34	test, p= 0.646,
		>50 years	29	46	NS
2	Sex	Male	13	17	Chi-square
		Female	63	108	test, $p = 0.303$,
					NS
3 Bethseda Classifi- cation	Class I	1	6	Fisher's exact test, p= 0.808, NS	
	Class II	62	97		
	Class III	3	5		
	Class IV	3	7		
		Class V	6	7	
		Class VI	1	3	

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Hypoparathyroidism in association with age: patients with age <40 years had the low PTH levels in 25 cases out of 65 patients, patients with age 40-50 years had the low PTH levels in 18 cases out of 61 patients and patients with age >50 years had the low PTH levels in 29 cases out of 75 patients. Chisquare test of independent variables such as age was not significantly associated with hypoparathyroidism and the p value was 0.468, NS. (Table 3)

Table 3: Occurrence of Hypoparathormone in relation to Age, Sex and Bethseda Classification

S1.			Serum PTH		Р
No			Normal	Hypopara	Value
				-thormone	
1	Age	<40 years	40	25	Chi-square
		40-50 years	43	18	test, p=
		>50 years	46	29	0.468, NS
2	Sex	Male	19	11	Chi-square
		Female	107	64	test, p=
					0.937, NS
3	Bethseda	Class I	3	4	Fisher's exact
	Classifi-	Class II	104	55	test, p=
	cation	Class III	6	2	0.303, NS
		Class IV	6	4	
		Class V	5	8	
		Class VI	2	2	

Hypocalcemia and hypoparathyroidism in association with gender: Among 30 males, 17 were hypocalcemic and 11 patients found to have low PTH levels. Among 171 females, 108 were hypocalcemic and 64 patients found to have low PTH levels. Chi-square test of independent variables such as gender was not significantly associated with hypocalcemia and hypoparathyroidism and the p value was 0.303, NS and 0.937, NS. (Table 2, 3)

By the whole of Bethseda classification with hypocalcemia and hypoparathyroidism: in class I- 6 out of 7 had hypocalcemia, 4 out of 7 had hypoparathyroidism, in class II-97 out of 159 had hypocalcemia, 55 out of 159 had hypoparathyroidism, in class III- 5 out of 8 had hypocalcemia, 2 out of 8 had hypoparathyroidism, in class IV- 7 out of 10 had hypocalcemia, 4 out of 10 had hypoparathyroidism, in class V-7 out of 13 had hypocalcemia, 8 out of 13 had hypoparathyroidism and in class VI- 3 out of 4 had hypocalcemia, 2 out of 4 had hypoparathyroidism. Fisher's exact test of independent variables such as bethseda classification was not significantly associated with hypocalcemia and hypoparathyroidism and the p value was 0.808, NS and 0.303, NS. (Table 2, 3)

Calcium and PTH co-relation showed that both the calcium and PTH were normal in 71 patients, normal PTH with low calcium levels were noted in 55 patients, normal calcium levels with low PTH levels were noted in 5 patients. Furthermore, both calcium and PTH were in lower ranges in 70 patients. (Table 4)

Table 4: Calcium and PTH co-relation

		Serum Calcium	
		Normal	Hypocalcemia
Serum PTH	Normal	71	55
intact	Hypoparathormone	5	70

DISCUSSION:

The most common endocrine disorder worldwide is thyroid disorders. Thyroid disorders are highly prevalent which was reported in 110 countries of the world with 1.6 billion people association. In India, the prevalence estimated about 42 million people. Most of the patients are asymptomatic as the size of the swelling is small. Mostly the patients present with the symptoms of nocturnal dyspnea followed by dysphagia, hoarseness of voice and dilated veins over anterior chest wall. For the symptomatic patients, thyroidectomy is the ideal option. Four types of thyroidectomy are total thyroidectomy, hemithyroidectomy, subtotal thyroidectomy and NTT. The complications following thyroidectomy are hemorrhage, respiratory obstruction, recurrent laryngeal nerve injury, thyroid insufficiency, thyrotoxic crisis and parathyroid insufficiency (mostly seen during 2nd to 5th postoperative day following surgery). Hypocalcemia is secondary to hypoparathyroidism which causes severe symptoms that results in increase the hospital stay. Secondary hypoparathyroism happens due to damage or injury to ≥ 1 parathyroid gland or inadvertent removal of the PG during surgery. So, our retrospective study is entirely focused on the patients who underwent NTT. This study aimed to determine the frequencies of post NTT hypocalcemia and hypoparathyroidism at an early stage by comparing preoperative and postoperative values and also to determine hypoparathyroidism in postoperative normocalcemic and hypocalcemic patients.

Prior studies recommended intraoperative and perioperative intact PTH (iPTH) monitoring for early detection even so the high cost. However, in consideration of financial burden on patients; iPTH has as a limitation for clinical use. In several centers, calcium levels were repeated till the normal trends achieved. Yet in some centers, patients were discharged early with calcium supplementation without further investigations. P Tredici et al study supported., hypocalcemia found at the maximum of 36 hours. Thus, by monitoring the trends of day 1 and day 2 calcium, hypoparathyroidism was addressed.

As per the studies of Regina Promberger et al., 3 out of 8 patients with hypocalcemia post thyroidectomy had normal PTH levels. However, in our studies also, out of 201 patients 55 patients had hypocalcemia and normal PTH. Thus, it reveals that normal PTH values doesn't keep out "Parathyroid insufficiency" because devascularization of parathyroid glands during surgery, compromises parathyroid gland function, remaining parathyroid tissue gives maximum stimulus to maintain normal parathormone levels however that is not sufficient to maintain normal calcium levels².

Hypocalcemia and hypoparathyroidism were more frequently noticed in female gender, age >50 years, 115 patients were hypocalcemic (57.21%) and 72 patients were found to have hypoparathyroidism (35.82%). The higher incidences of hypocalcemia may be ascribed to hemodilution too.

Our study demonstrated a significant relationship between hypocalcemia and low PTH levels after thyroid surgery (Table 4). We found that postoperative hypoparathyroidism was significantly more likely in patients with hypocalcemia than in those without. Our data also suggests that hypocalcemia is an independent predictor for hypoparathyroidism after thyroid surgery.

Meter A., included 31 out of 40 patients had cancer (papillary or follicular type), remaining patients underwent surgery for benign thyroid disease; majority of patients underwent total thyroidectomy. Results revealed that 12 patients (30%) developed hypocalcemia⁶. Whereas in our study, the patients with malignancy (Bethseda classification VI) 3 out of 4 patients (75%) had hypocalcemia and 2 (50%) of them had hypoparathyroidism. Higher the cytopathological category, higher chances of malignancy and the complications also.

As this is a retrospective study, this study was limited to collect the data. Patient was not be able to follow-up after discharge and then not able to collect data such as vitamin D, magnesium and phosphate deficiencies, perioperative PTH levels and other associated co-morbidities, menopause.

Hence, our study guides the future researchers about the NTT

complications and it guides them to pick the right choice of thyroidectomy with lesser complications for the appropriate age of the patient that may minimize the surgical complications. Association of hypocalcemia and hypoparathyroidism frequency in Bethseda classification will help the future researchers to have a basic idea about the associated malignancy risk and its complications. Furthermore, it will also help the patients by decreasing morbidity and financial burden on patients by early detection of complications.

CONCLUSION:

Based on our assessment, here we support that the postoperative levels drop in comparison with preoperative levels helps to predict hypocalcemia and hypoparathyroidism . The higher the bethseda classification, higher complications might happen. These data suggest a need for further study the relationship between calcium and PTH to determine if preoperative correction of calcium can reduce the morbidity and length of hospital stay associated with metabolic complications of thyroid surgery by early treatment.

Conflicts of interest:

There are no conflicts of interest

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