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Parathyroid Hormone as a Predictor of Hypocalcaemia after Total Thyroidectomy

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Abstract: ***Background: Thyroidectomy has been established as the preferred operation for various thyroid disorders. Post-operative hypocalcaemia is one of the major concerns following total thyroidectomy. Our study aims to determine whether measurement of parathyroid hormone level in immediate postoperative period in total thyroidectomy patients could predict hypocalcaemia and to standardize the test levels to predict the hypocalcaemia postoperatively. Study design: A single institution, prospective study over a period of one year. Results: Hypocalcaemia was noted in 36% of patients at 24 hours post total thyroidectomy, out of which 12% of patients were symptomatic which required medical management. Post-operative hypocalcaemia developed 2.0±3.13 day after surgery. High incidence of hypocalcaemia in malignant disease who underwent total thyroidectomy with or without neck dissection, followed by surgery for graves disease. Postoperative serum calcium level was statistically lower than the preoperative serum calcium level irrespective of whether the patient is symptomatic or not, which was in correlation to the serum PTH levels post operatively, signifying that PTH levels drop is an early predictor of hypocalcaemia patients undergoing total thyroidectomy. Conclusion: Serum PTH hormone levels should be checked for all patients undergoing total thyroidectomy at 2 hours post operatively , which is a reliable early predictor for patients going in for hypocalcaemia even before serum calcium levels drop which takes at least 24-48 hours, and hence predicting patients in risk of developing hypocalcaemia and treat them prophylactically.***

Keywords: parathhormone, total thyroidectomy, hypocalacemia

1. Need for the Study

Thyroidectomy has been established as the preferred operation for various thyroid disorders in various forms ranging from hemi, subtotal to total thyroidectomy. Post-operative hypocalcaemia is one of the major concerns following total thyroidectomy. It often extends the duration of the hospital stay for biochemical tests. When severe it can lead to serious complications like laryngeal stridor and convulsions and requires intravenous therapy with calcium.

Transient hypocalcaemia has been reported in up to 50% of cases, which is more likely in patients who undergo concomitant total thyroidectomy with central and lateral neck dissections and in patients with Graves' disease1. Rates of post thyroidectomy hypocalcaemia are approximately 5%; it resolves in 80% of cases in approximately 12 months2. A postoperative decrease of serum calcium is frequently observed within 2 to 5 days after a total or subtotal thyroidectomy, requiring exogenous replacement therapy to alleviate clinical symptoms.

Variety of strategies for diagnosis and management of post thyroidectomy hypocalcaemia has been advocated. Measurement of serum calcium after 24 hours has been the most commonly followed. But studies suggest that symptoms can appear as early as 6 hours, by predicting early the chances of a patient having postoperative hypocalcaemia will benefit the patient. In the absence of reliable indicators for predicting hypocalcaemia, prolonged hospitalization has been the standard care.
To minimize the postoperative complications and to minimize hospital stay and early discharge, it's important to predict patients at risk of developing hypocalcaemia. Measurements of parathyroid hormone in the immediate postoperative period along with serum calcium are useful and reliable methods. Even though many current studies suggest the use of parathyroid hormone as early predictor of hypocalcaemia, due to variation in test standards and difference in the duration post operatively when to measure the parathyroid hormone, It has not been followed universally. Our study aims to determine whether measurement of parathyroid hormone level in immediate postoperative period in total thyroidectomy patients could predict hypocalcaemia and to standardise the test levels to predict the hypocalcaemia postoperatively.

Objectives of the study

- To measure parathyroid hormone at 2nd hour post total thyroidectomy.
- To measure serum calcium levels pre and post total thyroidectomy.
- To correlate both parathyroid hormone and serum calcium values.

2. Materials and Methods

Source of data
Patients more than 18yrs admitted to Vydehi Institute of Medical Sciences and Research Centre, Bangalore undergoing total thyroidectomy, from December 2015 to June 2016.

Method of collection of data
Sample Size: 50
Type of study: Prospective observational study

Inclusion criteria:
- Patients more than 18years of age, admitted and diagnosed with a thyroid disorder and requiring total thyroidectomy.

- Patients who have given written informed consent for the study.

Exclusion criteria:
- Previously thyroid operation or irradiation
- Renal dysfunction
- Concomitant parathyroid disease
- Patents already on calcium supplementation

Sample Size: minimum 50 patients

Methods of Data Collection
- Patients undergoing total thyroidectomy in Vydehi Institute of Medical Sciences and Research Centre, Bengaluru.

Study Period
- Period of study is from December 2015 to June 2016

Procedure
- Detailed history and clinical examination of patient.
- Confirmative preoperative diagnosis of thyroid disorder, serum albumin, calcium levels, with all the other routine investigations.
- With a prior informed consent from patient
- Postoperative measurement of parathormoneby chemiluminescent immunoassay method within 2 hours of surgery.
- Postoperative investigations including serum calcium, albumin levels and calculation of serum corrected calcium levels after 24 hours of surgery.

Statistical Analysis: To analyze sensitivity, specificity, positive predictive value and negative predictive value for 2nd hour post-operative parathyroid hormone with serum calcium levels as reference. Chi square test will be used to find the association.

3. Results

Table 1: Distribution of subject according to age group

Age group (in years)	No of subjects (n)	Percentage (%)
21-30yrs	12	24
31-40yrs	16	32
41-50yrs	14	28
>50yrs	8	16

The above table shows the age distribution of the patients in the study with age ranging from 21 to 60 years, with majority of patients falling in the category of 31 to 40years range(32%) .

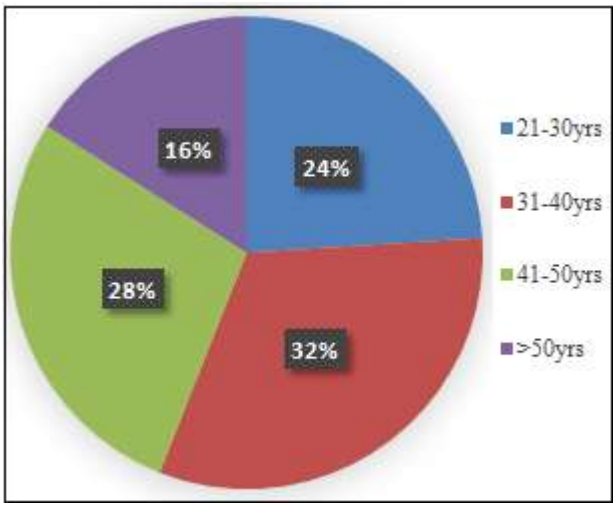

Figure 1: Graph showing Distribution of subject according to age group

Table 2: Distribution of subject according to sex

Sex	*No of subjects (n)*	*Percentage (%)*
Male	17	34
Female	33	66

Among the 50 patients, 17 were male (34%) and 33 were female (33%), with prevalence of thyroid disease more in females.

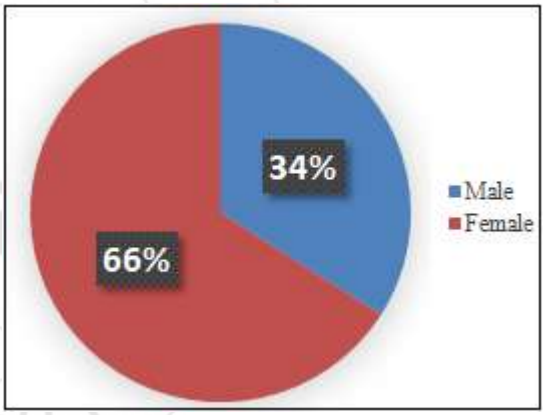

Figure 2: Graph showing Distribution of subject according to sex

Table 3: Distribution of subject according to Diagnosis

Diagnosis	*No of subjects (n)*	*Percentage (%)*
Follicular ca	2	4
Graves disease	1	2
MNG	40	80
Papillary ca	7	14

The above table depicts total no. of cases with preoperative diagnosis majority being 80% of them with multi nodular goiter, 14% being papillary Ca, 4% being follicular Ca, 2% being graves disease,.

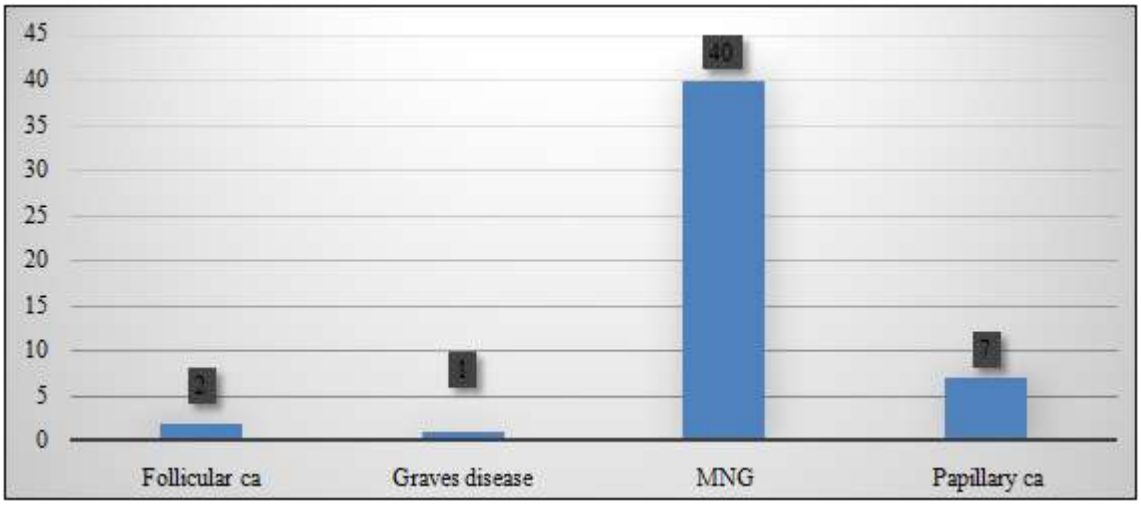

Figure 3: Graph Distribution of subject according to Diagnosis

Table 4: Distribution of subject according to Thyroid profile

Thyroid profile	*No of subjects (n)*	*Percentage (%)*
Euthyroid	44	88
hyperthyroid	3	6
hypothyroid	3	6

The above table shows preoperative thyroid profile, of which 44 patients(88%) were euthyroid, 3 patients were hyperthyroid(6%), and 3 patients were hypothyroid(6%)

Table 5: Comparison of pre-Op calcium and Post-op calcium at 24hrs

	Mean	*Standard Deviation*	*P value*
Pre-Op calcium	9.026531	0.3946388	< 0.001
Post-op calcium at 24hrs	8.257143	0.5024938	

There was statistically significant difference was found between pre-Op calcium with mean of 9.026531 and Post-op calcium at 24hrs with mean of 8.257143.

Table 6: Comparison of pre-Op calcium and Post-op PTH

	Mean	*Standard Deviation*	*P value*
Pre-Op calcium	9.026531	.3946388	< 0.001
Post-op PTH	9.404082	3.9190219	

There was statistically significant difference was found between pre-Op calcium with mean of 9.026531 and Post-op PTH with mean of 9.404082.

Table 8: Comparison of Post-op calcium at 24hrs and Post-op calcium at 72hrs

	Mean	*Standard Deviation*	*P value*
Post-op calcium at 24hrs	8.257143	.5024938	0.002
Post-op calcium at 72hrs	7.820408	.9736058	

There was statistically significant difference was found between post-Op calcium at 24hrswith mean of 8.257143 and Post-op calcium at 72hrs with mean of 7.820408.

Table 9: Comparison of Post-op PTH and Post-op calcium at 24hrs

	Mean	*Standard Deviation*	***P value***
Post-op PTH	9.404082	3.9190219	**0.04**
Post-op calcium at 24hrs	8.257143	.5024938	

There was statistically significant difference was found between post-Op PTH with mean of 9.404082 and Post-op calcium at 24hrs with mean of 8.257143

Table 10: Comparison of Post-op PTH and Post-op calcium at 72hrs

	Mean	*Standard Deviation*	*P value*
Post-op PTH	9.404082	3.9190219	0.003
Post-op calcium at 72hrs	7.820408	.9736058	

There was statistically significant difference was found between post-Op PTH with mean of 9.404082 and Post-op calcium at 72hrs with mean of 7.820408

Table 11: Comparison of Post-op calcium at 24hrs with respect to sex

	Mean	*Standard Deviation*	*P value*
Male	0.50	0.444	0.727
Female	0.45	0.376	

There was no statistically significant difference was found between post-Op calcium at 24hrs and sex

Table 12: Comparison of Post-op calcium at 72hrs with respect to sex

	Mean	*Standard Deviation*	*P value*
Male	1.281250	1.2324603	0.708
Female	1.169697	.8210073	

There was no statistically significant difference was found between post-Op calcium at 72hrs and sex

Table 13: Comparison of Post-op calcium at 24hrs with respect to age

Age group (in years)	*Mean*	*Standard Deviation*	*P value*
21-30yrs	.458333	.3872005	0.912
31-40yrs	.418750	.4069705	
41-50yrs	.507143	.3812213	
>50yrs	.528571	.4855042	

There was no statistically significant difference was found between post-Op calcium at 24hrs and Age group

Table 14: Comparison of Post-op calcium at 72hrs with respect to age

Age group (in years)	*Mean*	*Standard Deviation*	*P value*
21-30yrs	1.191667	.9605475	0.834
31-40yrs	1.118750	.9311060	
41-50yrs	1.400000	1.1176899	
>50yrs	1.206122	.9627236	

There was no statistically significant difference was found between post-Op calcium at 72hrs and Age group

Table 15: Comparison of Post-op calcium at 24hrs with respect to diagnosis

Diagnosis	*Mean*	*Standard Deviation*	*P value*
Follicular ca	.800000	.7071068	0.013
Graves disease	.200000		
MNG	.389744	.3647601	
Papillary ca	.857143	.2507133	

There was statistically significant difference was found between post-Op calcium at 24hrs and Diagnosis.

Table 16: Comparison of Post-op calcium at 72hrs with respect to diagnosis

Diagnosis	*Mean*	*Standard Deviation*	*P value*
Follicular ca	2.000000	.7071068	0.023
Graves disease	1.500000		
MNG	1.000000	.9075705	
Papillary ca	2.085714	.8434623	

There was statistically significant difference was found between post-Op calcium at 24hrs and Diagnosis

Table 17: Comparison of Post-op PTH with respect to sex

SEX	*Decreased*	*Normal*	*P value*
Female	30	3	0.377
Male	14	3	

There was no statistically significant difference was found between post-Op PTH and Sex

Table 18: Comparison of Post-op PTH with respect to age

Age group (in years)	*Decreased*	*Normal*	*P value*
21-30yrs	10	2	0.5329
31-40yrs	13	3	
41-50yrs	13	1	
>50yrs	8	0	

There was no statistically significant difference was found between post-Op PTH and age group

Table 19: Comparison of Post-op PTH with respect to diagnosis

Diagnosis	*Decreased*	*Normal*	*P value*
Follicular ca	2	0	0.038
Graves disease	0	1	
MNG	35	5	
Papillary ca	7	0	

There was statistically significant difference was found between post-Op PTH and diagnosis

4. Discussion

Thyroidectomy has been established as the preferred operation for various thyroid disorders in various forms ranging from hemi, subtotal to total thyroidectomy. Post-operative hypocalcaemia is one of the major concerns following total thyroidectomy. It often extends the duration of the hospital stay for biochemical tests. When severe it can lead to serious complications like laryngeal stridor and convulsions and requires intravenous therapy with calcium. In our study hypocalcaemia was noted in 36% of patients at 24hours post total thyroidectomy, out of which 12% of patients were symptomatic which required medical management. Hypocalcaemia was noted in 68% of patients at 72hours post-surgery.

The severe symptoms of hypocalcaemia like cardiac arrhythmias, spasm, and stridor were not reported in our study.

Study done by Nair from the year 2005 to 2006 analysed 806 patients, an observational study found incidence of hypocalcaemia in patients undergoing total thyroidectomy was 23.6% and that of permanent hypocalcaemia was 1.61%. Onset was delayed up to third postoperative day in thirteen patients. Hypocalcaemia was significantly associated with thyroidectomy for Grave's Disease, Hashimoto's thyroiditis, and with incidental Parathyroidectomy.[3]

Another study was done by Graff from 2004 to 2005 with study population of 69 suggested single early postoperative intact PTH measurement 6-18 hours after surgery was found to be the most cost effective screening tool for hypocalcaemia. But even greater specificity can be achieved by combining those findings with a serum calcium measurement taken 6 hours postoperatively[6].

A recent prospective study by Puzziello on75 patients showed the relative decrease in i PTH determined 2 hours after total thyroidectomy together with the serum calcium concentration 24 hours after thyroidectomy proved to be useful predictors of sustained hypocalcaemia and might change the clinical management of these patients after thyroid surgery requiring a longer hospitalization[7].

Temporary hypocalcaemia has been reported to occur in 1.6-50% of the patients after bilateral thyroidectomy. Permanent hypoparathyroidism results in 0-13 % of patients after bilateral thyroid surgery.10Early postoperative calcium monitoring, although important, is a poor predictor of subsequent symptomatic hypocalcaemia. Even though postoperative serum calcium levels usually correlates with the development of symptomatic hypocalcaemia, its use has been limited as the results are not available until 24–48 hours post total thyroidectomy.

Various factors account for these differences in the literature, such as the definition of hypocalcaemia, the type of disease, and the surgical technique. Among potential factors causing this decrease in serum calcium, there are post-operative hemodilution and calcitonin release.[19]

Elevation of serum calcitonin (calcitonin leak), secondary to manipulation of the thyroid, was suspected to participate in this calcium decrease, but this was not confirmed in further studies.[10]

Preoperative hyperthyroid status is associated with decreased gastrointestinal calcium absorption and increased osteoclast activity, with increased bone resorption to maintain serum calcium levels10.Wingert and colleagues found that risk for transient hypocalcaemia after thyroid operation for Graves' disease is 20 times higher than in other groups.[08] However, in this study no difference was found statistically between patients with hyperthyroidism and post-operative hypocalcaemia.

The serum calcium generally reaches its lowest within 48 hours of surgery.[10] In this study post-operativehypocalcaemia developed 2.0±3.13 day after surgery.

It is clear that impaired parathyroid function is the major contributing factor in determining hypocalcaemia. Proper surgical technique is of important in preserving viable parathyroid glands and several factors have been associated with impaired post-operative function. Susceptibility of parathyroid glands to injury during neck dissection mainly resides in their widely variable anatomical position, and their relationship with the thyroid gland, and in their very delicate vascular supply.

A higher incidence of postoperative hypocalcaemia is seen after total thyroidectomy. Other factors associated include central neck dissection, surgery for carcinoma and surgery for Grave's disease.[10] In the present study, there was high incidence of hypocalcaemiain malignant disease whounderwent total thyroidectomy with or without neck dissection, followed by surgery for graves disease. There was no difference in post op calcium levels with respect to age and sex of the patients. This, emphasizes the need for careful identification parathyroid gland with its vascular supply during total thyroidectomy to prevent post-operativehypocalcaemia.

In the absence of any reliable predictors of hypocalcaemia after total thyroidectomy, prolonged hospitalization to monitor calcium levels has been considered the standard of care. Conversely current health-care practices encourage shorter hospitalization to reduce costs. For this reason there has been a great deal of interest in identifying peri-operative factors that can predict the development of post thyroidectomy hypocalcaemia, allowing for early treatment of patients at risk and safe early discharge of patients not at risk.

In this study, the postoperative serum calcium level was statistically lower than the preoperative serum calcium level irrespective of whether the patient is symptomatic or not, which was in correlation to the serum PTH levels post operatively, signifying that PTH levels drop is an early predictor of hypocalcaemia patients undergoing total thyroidectomy .

A study done by Cayo AK et al DB, October 13, 2012 including 112 patients concluded that, onmultivariate analysis, postoperative PTH were independent predictors of postoperative hypocalcemia.[11]

Another study done by AwadAlQahtani, et al in the year august 2014 included 149 patients found that PTH-1 levels were predictive of symptomatic hypocalcaemia 24 hours after thyroidectomy. Routine measurement of PTH should be considered, as it could prompt the early administration of calcitriol to patients at risk of developinghypocalcaemia and allow for the safe and early discharge of patients who are expected to remain eucalcemic.[(9)]

In the current study two of the 50 patients whose serum PTH value post operatively was within the normal range developed hypocalcaemia. The data showed the high sensitivity of the serum PTH value two hours post-surgery to predict hypocalcaemia. A combined measurement of PTH 2 hourspost-surgery and serum calcium levels at 24 hours is recommended to identify patients at risk for developing hypocalcaemia. Severe, progressive hypocalcaemia is unlikely with a normal PTH level, and thus PTH can be used cautiously to facilitate early discharge for many patients.

A recent prospective study by Puzziello on75 patients showed the relative decrease in i PTH determined 2 hours after total thyroidectomy together with the serum calcium concentration 24 hours after thyroidectomy proved to be useful predictors of sustained hypocalcaemia and might change the clinical management of these patients after thyroid surgery requiring a longer hospitalization[7].

5. Conclusion

In our study we found that incidence of hypocalcaemia is higher in patients undergoing for total thyroidectomy, for malignant thyroid conditions, no statistically significant results were found with respect to age or sex in our study .Patients who had drop in the post-operative serum parathyroid hormone levels had high incidence of hypocalcaemia which was proved by serum calcium levels on post-operative day 3.

Hence serum PTH hormone levels should be checked for all patients undergoing total thyroidectomy at 2 hours post operatively, which is a reliable early predictor for patients going in for hypocalcaemia even before serum calcium levels drop which takes at least 24-48 hours, and hence predicting patients in risk of developing hypocalcaemia and treat them prophylactically

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