Original Research Paper

Volume - 12 | Issue - 11 | November - 2022 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

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EARLY PARATHYROID HORMONE ASSAY AS A PREDICTOR OF HYPOCALCEMIA FOLLOWING TOTAL THYROIDECTOMY

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ABSTRACT **BACKGROUND :** Hypocalcemia following total thyroidectomy is a major contributing factor in prolonged length of hospital stay. We prospectively evaluated the utility of serum parathormone level after total thyroidectomy in predicting post operative hypocalcemia. **MATERIAL AND METHODS :** A non-randomized descriptive study which included 82 patients undergoing thyroidectomy for various thyroid disorders at Kidwai Cancer Hospital, Bengaluru from March 2016 to February 2017. Base line serum parathyroid hormone level, serum albumin and serum calcium were estimated. The investigations were repeated on post operative day 1, day 7 and 6 months after surgery. Calcium supplementation was started in patients with symptomatic hypocalcemia. **RESULTS :** The study included 82 patients amongst which 25% of patients were in the age group of 40-49 years. 81.7% were diagnosed with Papillary carcinoma of the thyroid, 11.0% had Follicular carcinoma of the thyroid, 6.1% had Medullary carcinoma of the thyroid, 1.2% had Hurthle cell carcinoma (HCC) of the thyroid. There was an association between 24hrs parathormone level and 7th post operative day calcium in patients undergoing surgeries for malignancy of thyroid. **CONCLUSION:** There was correlation between serum parathyroid hormone levels at 24 hour after surgery and serum calcium levels on the 7th day after surgery. Hence routine use of serum parathyroid hormone assay should be considered mandatory, especially with patients undergoing neck dissections along with total thyroidectomy as a treatment for malignancy of thyroid for early detection and treatment of hypocalcemia.

KEYWORDS : Parathyroid hormone assay, Total thyroidectomy, Hypocalcemia

Total thyroidectomy is considered as a standard surgical procedure for malignancy of thyroid. With a significant decrease in the rates of post operative hemorrhage, recurrent laryngeal nerve palsy and permanent hypocalcemia, there has been a subsequent reduction in the duration of length of hospital stay. However, temporary hypocalcaemia commonly occurring secondary to temporary hypoparathyroidism is one of the most frequent morbidities following thyroidectomy, with incidence ranging between 3 and 40%.[1,2]

With the increasing preference for shorter hospital stay, there has been renewed interest in post thyroidectomy hypocalcemia.[3-6] To safely manage postoperatively hypoparathyroidism/hypocalcaemia, various approaches have been adopted. The most common being serial calcium monitoring wherein calcium levels are typically drawn at 6-12 hr intervals until a normocalcaemic plateau or a stable upward trend is demonstrated but this involves patients staying for at least 1- 2 nights in the hospital.[7] Measuring the serum parathyroid hormone (PTH) immediately after surgery is a sensitive and specific method of assessing the function of the parathyroid glands and for identifying patients at risk for hypocalcemia. This study aims to determine the correlation between the measurement of parathyroid hormone after thyroidectomy and the subsequent occurrence of hypocalcemia.

OBJECTIVES

- To determine the occurrence of low serum parathyroid hormone 24 hours after total thyroidectomy surgery for thyroid cancer patients.
- To determine the occurrence of hypocalcemia in these patients.
- To determine the correlation between the levels of postoperative parathyroid hormone levels and occurrence of hypocalcemia.

METHODOLOGY

This hospital based prospective non-randomized descriptive study was conducted from March 2016 to February 2017 at Kidwai Cancer Hospital, Bengaluru. A total of 82 patients who underwent total thyroidectomy for thyroid cancer and gave informed consent to participate in the study were included as study subjects. Those patients with history of thyroid surgery / irradiation, concomitant parathyroid diseases and such comorbidities that creates bias were excluded from the study.

A semistructured questionnaire was used to interview the patients regarding their sociodemographic details and a detailed medical history. A thorough clinical examination was done. Pre-operative investigations like base line serum parathyroid hormone level, serum albumin and serum calcium was done. The same investigations were done on post-operative day 1, day 7 and 6 months after surgery. The patients were monitored for the signs and symptoms of hypocalcemia during this period.

The diagnostic criteria for diagnosis of hypoparathyroidism was set to serum parathyroid hormone level was less than 10 pg/mL. Serum calcium level of less than 8mg/dL at 24 hours after surgery was taken as post-operative hypocalcemia. Corrected calcium level was calculated using the formula [{0.8 X (normal albumin- patient's albumin)} + serum Calcium level]. Data was entered in Microsoft excel spreadsheet and analysed using SPSS (statistical package for social sciences) version 20. For descriptive statistics, numericals and percentages were used. For measures of central tendencies of continuous quantitative data, mean and standard deviation were used. Cochran Armitage test was used to test for linear trend. Chi square test was used as a tool of analytical statistics to determine the association between two or more discrete groups. Yates correction was used when the number of subjects in any cell was less than 5. For statistical significance probability (p) value was taken as less than 0.05. Student t test was used for comparing the difference between two groups with continuous quantitative data. For more than two groups, Analysis of Variance (ANOVA) / F test was used. For statistical significance probability (p) value was taken as less than 0.05. Correlation test was used to corelate the values of series of two different variables, that is 24 hour serum PTH levels and 7th day serum calcium levels.

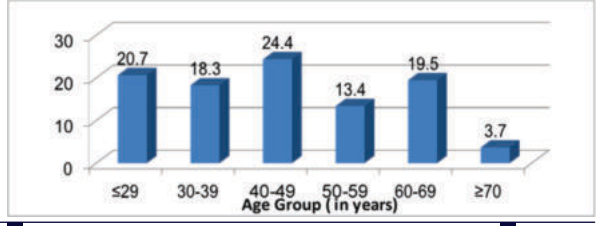
RESULTS

A total of 82 subjects were included in the prospective non randomized descriptive study.

1. Distribution Of Subject According To Age Group:-

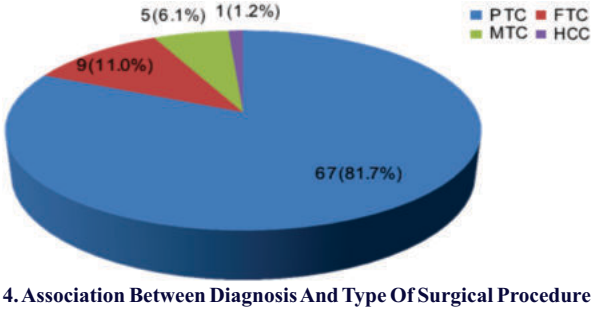
20 patients (24.4%) were aged 40-49 years and 17 patients were aged 20-29 years, 16 (19.5 %), 15 (18.3%), 11 (13.4%) & 3 (4.5%), patients belonged to 6th, 3rd, 4th & 7th decade respectively.

Chi square test value of 15.48 giving a p value of 0.417 showed that there was no significant difference in the occurrence of thyroid malignancy in the different age groups



2. Distribution Of Subject According To Gender:-
Amongst the 82 subjects, 65 patients were females (79.3%) and 17 patients were male (20.7%)

3. Distribution Of Subjects According To Diagnosis:-
Out of the 82 patients, 67 patients (81.7%) were diagnosed with papillary thyroid cancer (PTC), 9 patients (11.0%) with Follicular thyroid cancer (FTC), 5 patients (6.1%) with Medullary thyroid cancer (MTC) and one patient (1.2%) with Hurthle cell thyroid cancer (HCC).



4. Association Between Diagnosis And Type Of Surgical Procedure Conducted:-
Of the 67 surgeries for Papillary Thyroid Cancer, 34 (50.7%) underwent total thyroidectomy (TT) and 33 (49.3%) underwent total thyroidectomy with functional neck dissection (TT+FND). All the nine Follicular carcinoma patients underwent total thyroidectomy. All the 5 medullary carcinoma patients underwent total thyroidectomy with central neck dissection (TT+CND). The only Hurthle cell cancer patient underwent total thyroidectomy with functional neck dissection (TT+FND).

5. Serum Calcium Levels Of Subjects Before Surgery, 24 Hours After Surgery And 7th Day After Surgery:-
Out of the 82 subjects, 10 (12.20%) subjects had serum calcium level of 8 to 8.9 mg/dL which increased to 12 (14.63%) 24 hour after surgery and decreased to 06 (7.32%) on the 7th day after surgery.

Table 1:- Patients with Serum Calcium levels before and after surgery

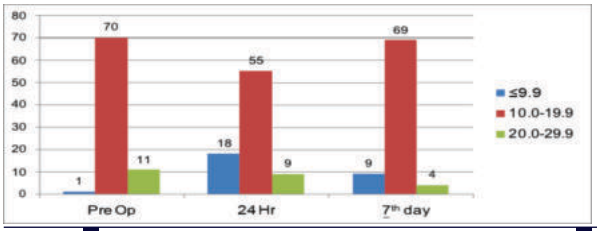
Serum Calcium level(mg/dL)	No. of patients in Pre operative period	No. of patients 24 hours after surgery	No. of patients 7th day after surgery	Chi square value = 28.72 P-value = <0.001
≤7.9	0	10 (12.2%)	9(11.0)	
8-8.9	10 (12.2%)	12 (14.6%)	06 (7.3%)	
9-9.9	30 (36.6%)	29 (35.4%)	31 (37.8%)	
10-10.9	34 (41.5%)	27 (32.9%)	31 (37.8%)	
≥11	8 (9.8%)	04 (4.9%)	14 (17.1%)	
Total	82	82	82	

6. Distribution Of Subjects According To Pre Operative Serum Parathyroid Hormone (pth) Level Before Surgery, 24 Hours After Surgery And 7th Day After Surgery:-
Out of the 82 subjects, one (1.22%) subject had serum PTH level of ≤9.9 which increased to 18 patients (21.95%) 24 hour after surgery, and decreased to 9 patients (10.97%) on the 7th day after surgery.

PTH of 10.0-19.9 was found in 70 (85.37%) patients before operation, 55 patients (67.07%) 24 hours after surgery and 69 patients (84.15%) on the 7th day after surgery.

PTH of 20.0-29.9 was found in 11 (13.41%) patients before operation, 9 patients (10.98%) 24 hours after surgery and 4 patients (4.88%) on the 7th day after surgery.The 24 hour PTH levels had significantly decreased compared to preoperative levels and progressively increased after 7 days after surgery but not coming to the baseline value.

Serum Pth Levels Of Subjects Before Surgery, 24 Hours After Surgery And 7th Day After Surgery:-



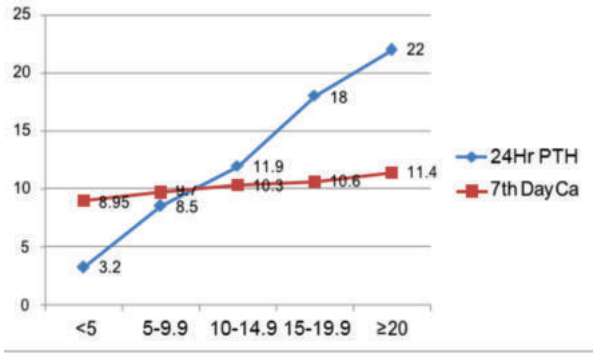
7. Correlation Between Serum Parathyroid Hormone Level At 24 Hour After Surgery And Serum Calcium Levels On The 7th Day After Surgery:-
On comparing the serum parathyroid hormone level at 24 hour after surgery and serum calcium levels on the 7th day after surgery, it was found that 4 patients had PTH levels less than 5 pg/ml. The average PTH level was 3.2 pg/ml and the average 7th day serum calcium of these patients was 8.95 ± 0.369 mg/dl. Fourteen patients had PTH levels 5-9.9 pg/ml, the average PTH level was 8.5 pg/ml and the average 7th day serum calcium of these patients was 9.7 ± 0.661 mg/dl. Thirty nine patients had PTH levels 10-14.9 pg/ml, the average PTH level was 11.9 pg/ml and the average 7th day serum calcium of these patients was 10.29 ± 0.765 mg/dl. Sixteen patients had PTH levels 15-19.9 pg/ml, the average PTH level was 18.0 pg/ml and the average 7th day serum calcium of these patients was 10.65 ± 0.681 mg/dl. Nine patients had PTH levels ≥20 pg/ml, the average PTH level was 22.0 pg/ml and the average 7th day serum calcium of these patients was 11.4 ± 0.975 mg/dl.

Statistical analysis showed that there was significant correlation between serum parathyroid hormone levels at 24 hour after surgery and serum calcium levels on the 7th day after surgery.

Table 2:- Correlation between serum parathyroid hormone level at 24 hour after surgery and serum calcium levels on 7th day after surgery

PTH	No.of patients (%)	Avg 24Hr PTH in pg/ml	Avg 7th day Serum Calcium in mg/dl	
<5	4 (4.9)	3.2 ± 1.5	8.95 ± 0.369	Correlation = 0.98
5 – 9.9	14 (17.1)	8.5 ± 1.5	9.7 ± 0.661	
10-14.9	39 (47.6)	11.9 ± 1.4	10.29 ± 0.765	
15-19.9	16 (19.5)	18.0 ± 1.2	10.65 ± 0.681	P value <0.01
≥20	9 (10.9)	22.0± 2.1	11.4 ± 0.975	
Total	82 (100)	12.72	10.2	

Association between serum parathyroid hormone level at 24 hours after surgery and serum calcium levels on 7th day after surgery



DISCUSSION

Postoperative hypocalcemia remains the single greatest predictor of length of stay after total or completion thyroidectomy. Transient hypocalcemia has been reported to occur in up to 30% of patients.[8-10] The mechanism of transient hypocalcemia remains elusive. Hemodilution secondary to intraoperative fluid administration,[9] calcitonin release after manipulation of the thyroid,[11] "hungry bone syndrome" secondary to skeletal uptake of calcium in patients with thyrotoxic osteodystrophy[12] and, ultimately the earliest proposed mechanism, after injury/removal or devascularization of the parathyroid glands.[13] The extent of surgery to central and/or lateral neck lymph nodes is responsible for a high rate of transient hypoparathyroidism owing to a high probability of unplanned parathyroidectomy or parathyroid gland devascularisation[14]. Parathyroid Hormone achieves calcium homeostasis through a number of physiologic mechanisms including renal distal tubule calcium re-absorption, vitamin D mediated intestinal calcium absorption, and bone resorption.[15] In the absence of the reliable predictors of hypocalcemia, prolonged hospitalization has been considered the standard of care. Routine supplementation therapy with oral calcium or vitamin D effectively prevents symptomatic hypocalcaemia after total thyroidectomy and may allow for a safe early discharge. The combination of oral calcium and vitamin D may further reduce the rate of post operative hypocalcaemia,[16] without inhibiting parathyroid hormone secretion. Oral administration of 1 µg of calcitriol twice per day and 500 mg of calcium salts 3 times per day after total thyroidectomy significantly decreases the risk of severe

postoperative hypocalcemia.[17]

Since the current health care strategy encourages a shorter duration of hospital stay there is a great zeal of interest in identifying the peri-operative risk factors that can predict the development of post thyroidectomy hypocalcemia allowing for early treatment of patients at risk. In the present study all patients were normocalcemic (>8mg/dl) preoperatively and 10 patients (12%) were hypocalcemic 24 hours after the surgery and 9 patients (11)% were hypocalcemic 7 days after surgery which were much lower than the standard studies. This can be attributed to the injury to the parathyroid glands during surgery[18].

The average serum calcium levels at 24hrs among those who underwent total thyroidectomy was 10.34 mg/dl; those who underwent total thyroidectomy with central neck dissection was 9.66mg/dl and who underwent total thyroidectomy with functional neck dissection was 9.81 mg/dl; which is nearly similar levels of serum calcium in all types of surgery. However at the 7th day post operatively, the serum calcium levels were found to be low (i.e., average of 7.8mg/dl) which indicates the injury to the parathyroid glands. A study conducted by Richard et al showed that the serum calcium levels reduced drastically from first day post operatively to day 7 post operatively.[19]

In a comparative study conducted by Avi Khafif et al , and AJ Cherian demonstrated that total thyroidectomy with neck dissections were associated with higher incidence of hypoparathyroidism compared to only total thyroidectomy. [20,21]This can be attributed more injury and accidental removal of parathyroid gland and also more tissue inflammation leading to loss of function of the gland. This also explains the recovery of the gland after 7 days.

On obtaining serum PTH levels of these patients, it was found that amongst the 82 patients, the serum PTH level was found to be low in one patient pre operatively(<9 pg/dl), the etiology of which could not be explained. However, the serum calcium level was within the normal limits.

However, when the serum PTH level was obtained after 24hrs of surgery, it was reduced in 21% of the patients (<10pg/dl) and also out of these individuals 11% did continue to have decreased levels at 7th day post operatively which was significant.

A study conducted by Vescan A et al which showed similar results with 30% of individuals suffering from hypoparathyroidism 24hrs after surgery and in 80% of patients the serum PTH levels remained low after 7 days of surgery. This gives a trend path showing the damage done during surgery to parathyroid continue to have hypo secretions of hormone even at 7 days after surgery.[7]

A study by Celestino Pio Lombardi et al which was very similar to our study showed PTH level <10pg/ml 24hrs after surgery had a specificity of 100% and sensitivity of 94% and an overall accuracy of 98% as predictor of postoperative hypocalcemia after 24 hrs after surgery.[22]

100% correlation was found between the 24hrs PTH level and 24 hours calcium level. There is also significant association between 24hours PTH level and the serum calcium measured on post operative day 7 in patients undergoing surgeries for malignancy of thyroid. This was also correlated with the type of surgery performed for malignancy of thyroid and with their respective parathyroid hormone levels.

A study by conducted by Bhattacharyya N also showed an absolute correlation between the 24 hrs parathyroid levels to the calcium levels of the 7th day postoperative which was directly proportional with value levels[23]. These studies also concluded that 24 hrs parathyroid levels was a sensitive predictor of hypocalcemia which could be developed either 24hrs or 7th day post operatively. Hence routine use of serum parathyroid hormone assay should be considered mandatory, especially with patients undergoing neck dissections along with total thyroidectomy as a treatment for malignancy of thyroid. This PTH assay is an extremely useful tool for early detection of hypocalcemia, as it could prompt the early administration of calcitriol in patients at risk of hypocalcemia.

CONCLUSION

There was correlation between serum parathyroid hormone levels at 24 hours after surgery and serum calcium levels at 24 hours after surgery. Similarly there was correlation between serum parathyroid hormone levels at 24 hour after surgery and serum calcium levels on the 7th day after surgery. Hence routine use of serum parathyroid hormone assay should be considered mandatory, especially with patients undergoing neck dissections along with total thyroidectomy as a treatment for malignancy of thyroid. This PTH assay is an extremely useful tool for early detection of hypocalcemia, as it could prompt the early administration of calcitriol in patients at risk of hypocalcemia.

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