

Retrospective Analysis of Postoperative Hypocalcemia in Total Thyroidectomy Patients and the Role of 24 Hour Intact Parathyroid Hormone as a Predictor

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ABSTRACT

Background

Postoperative hypocalcemia, a common complication after total thyroidectomy is multifactorial. The management of early hypocalcemia lack uniformity. Universal or selective supplementation of calcium with or without vitamin D is carried out. The predictors for postoperative hypocalcemia is widely studied in literature with some factors described as independent predictors.

Objective

To explore occurrence of post-thyroidectomy hypocalcemia along with analysis of factors for predicting early and late hypocalcemia. The efficacy of selective supplementation of calcium with or without vitamin D was studied.

Method

The retrospective analysis of charts of total thyroidectomy patients above 18 years within a period of four years in a tertiary institute was carried out. The occurrence of early and late hypocalcemia and their relation with several preoperative and intraoperative factors were studied. The rates of readmissions for hypocalcemia symptoms were evaluated. Detailed analysis for relation of 24 hour serum parathyroid hormone with early and late hypocalcemia was done.

Result

Among 51 patients, 68.62% had early hypocalcemia and 11.76% had late hypocalcemia. Among other factors, 24 hour intact parathormone level showed significant relationship with early hypocalcemia with level less than 15 pg/ml associated with symptomatic status. Out of total patients, 58.8% of patients were treated for early hypocalcemia. None of the patients not supplemented with calcium required readmission for early hypocalcemia symptoms.

Conclusion

The symptom based treatment of post thyroidectomy hypocalcemia is shown to be effective with intact parathyroid hormone at 24 hours having significant role of predicting symptomatic early hypocalcemia requiring supplementation.

KEY WORDS

Hypocalcemia, Parathormone, Thyroidectomy

INTRODUCTION

Hypocalcemia is defined as serum calcium level less than lower limit of center-specific reference range.^{1,2} Post thyroidectomy hypocalcemia (PTHc) occurs due to altered calcium regulation resulting from hypoparathyroidism caused by parathyroid vascularity disruption owing to mechanical or thermal trauma, accidental or unintentional parathyroid excision. Female sex, vitamin D deficiency, Grave's disease, central neck dissection are identified as risk factors for PTHc.^{1,3}

British Association of Endocrine and Thyroid Surgeons (BAETS) has defined PTHc as early and late. Early hypocalcemia is defined as serum adjusted calcium (SAC) of below 8.4 mg/dl within 24 hours of surgery and late hypocalcemia is defined as need for calcium $\pm$ vitamin D supplementation even after 6 months follow up.⁴ Post-thyroidectomy hypoparathyroidism is categorized as temporary and permanent based on cut off time of 6 months by American thyroid association.¹ Whereas, it is categorized as transient (resolving within 4 to 6 weeks after surgery), protracted (persisting beyond 6 weeks) and permanent (occurring for more than 6 months) by European society.⁵ PTHc is also classified as temporary and permanent.⁶ The variations in definitions and in laboratory ranges have led to underestimation of true prevalence of PTHc.⁷ Universal supplementation with oral calcium $\pm$ vitamin D in all patients is advocated by some where as some prefer selective approach for the management of early hypocalcemia.^{1,2,8}

In our center, authors practice selective supplementation. This study aims to determine occurrence of PTHc along with evaluation of relation of risk factors with early and late hypocalcemia in our center. The study also explores the efficacy of selective supplementation.

METHODS

This is a retrospective cohort study based on review of past medical records of patients who underwent total thyroidectomy from June 2020 to June 2024 in the otolaryngology department of a tertiary hospital. Convenience sampling technique was used with inclusion of the available records of patients operated within four years duration and fulfilling the inclusion criteria. Ethical approval was taken from the Institutional Review Committee of the institute and waiver of consent was applicable due to retrospective analysis of data.

All the patients above 18 years of age with total thyroidectomy with or without neck dissection including completion thyroid surgery with follow-up period of at least a year, were included. In patient-chart confirmed the absence of diseases or conditions affecting calcium absorption like celiac disease, irritable bowel disease, prior gastric bypass surgery. In-patient and follow up

data present in the medical records were reviewed. Data on demography (age, sex), preoperative status of thyroid function and vitamin D, diagnosis, type of surgery, intraoperative status of parathyroid gland, number of parathyroid gland preservation, postoperative (POD) day one serum PTH level, POD 2 serum calcium level, supplementation of oral calcium with or without vitamin D along with duration were collected using Microsoft Excel spreadsheet.

It is the departmental practice to assess intact PTH (iPTH) level for patients with total thyroidectomy on first post operative day (24 hour of surgery) and serum calcium level on second post operative day. Serum calcium concentration is adjusted for albumin in all patients to determine serum adjusted calcium (SAC) level. SAC is calculated according to formula "serum adjusted calcium = serum total calcium level (mg/dl) + 0.8 (4-serum albumin in gm/dl)". A normal serum calcium concentration is defined as a calcium concentration in the range of 8.6 to 10.2 mg/dl which is an assay-specific reference range of our hospital. Symptom based management of postoperative early hypocalcemia is done. Oral supplementation of calcium $\pm$ activated vitamin D is done either in patients with symptoms or in patients with severe biochemical hypocalcemia (SAC < 7.5 mg/dl) as this severity is associated with serious complications. Intravenous calcium gluconate is administered to patients with severe hypocalcemia as required. These patients requiring supplementation are discharged with oral calcium 1 gm twice a day to four times a day along with calcitriol. The patients with mild to moderate hypocalcemia but asymptomatic are managed with active observation and discharged to follow up with serum calcium report. Most of the patients of total thyroidectomy are discharged by 4th POD after removal of negative vacuum drain.

The descriptive analysis of demographic variables and the risk factors were done.

The primary outcome measures defined for study were occurrence of early and late postoperative hypocalcemia. The finding of SAC of < 8.6 mg/dl on second post operative day was termed as early hypocalcemia and the persistence of hypocalcemia requiring supplementation with oral calcium with or without calcitriol even after six months of total thyroidectomy was termed late hypocalcemia. This was according to BAETS guideline which defines late hypocalcemia as need for calcium $\pm$ vitamin D supplementation even after 6 months follow up.⁴ The post operative early hypocalcemia was classified biochemically as mild to moderate (SAC $\geq$ 7.5 to < 8.6 mg/dl) and severe (SAC < 7.5 mg/dl).

The analysis of occurrence of early and late hypocalcemia according to preoperative status of thyroid function and level of vitamin D, extent of neck dissection along with total thyroidectomy, intraoperative status of parathyroid (PT) gland (preservation/implantation) along with number of PT gland identified and preserved intraoperatively and

iPTH as secondary outcome analysis was carried out. Age has been identified as less reliable predictor for PTHC, hence its relationship was not studied.^{9,10}

The effectiveness of the selective supplementation was studied with the rate of readmission of the patients after discharge for hypocalcemic symptoms.

Categorization of the patients with postoperative early hypocalcemia into asymptomatic mild to moderate hypocalcemia, symptomatic mild to moderate hypocalcemia and severe hypocalcemia (as identified with serum calcium measurement in second post-operative day) was done to assess the relationship with iPTH level on first post-operative day.

Statistical analysis was done using Python in Google Colab notebook. Fisher's exact test was performed for categorical variables as the expected cell count was less than 5 for all categories. Independent t-test was used to compare the means. For inference of statistical significance, P value of less than 0.05 ($p < 0.05$) was taken.

RESULTS

The total of 51 medical charts that full filled the inclusion criteria could be retrieved for analysis. The mean age of patients at the time of surgery was 43.86 years (20 to 80 years, standard deviation 14.93). Out of 51 patients, 46 were female and five were male.

The frequency distribution of status of thyroid function, vitamin D level, category of thyroidectomy, intraoperative PT gland status, number of PT gland preserved intraoperatively are shown in table 1.

The missing data were present for the category of preoperative vitamin D level. Twelve medical charts did not have data for this variable. Majority of the patients had diagnosis of papillary carcinoma of thyroid (60.78%), followed by multinodular goiter (31.37%), medullary carcinoma of thyroid (5.88), and Graves' disease with follicular carcinoma of thyroid (1.96%).

Primary outcome measure

The occurrence of hypocalcemia is detailed in table 2. One patient with Graves' disease with follicular carcinoma did not develop either early or late hypocalcemia or hypoparathyroidism.

Out of total patients, 58.8% (30/51) patients were given oral calcium $\pm$ vitamin D, and 80% of them (24/30) recovered. Only 20% (6/30) developed late hypocalcemia, out of which one patient had early biochemical normocalcemia.

Among all patients, there were two readmissions. One of the supplemented patients required single readmission for symptoms of early hypocalcemia within a week and another supplemented patient required multiple readmissions for late hypocalcemia. None of the patients not supplemented

Table 1. Frequency distribution of preoperative and intraoperative factors in patients of total thyroidectomy

Preoperative and intraoperative factors	Number of patients	Percentage
Thyroid function		
Euthyroid	44	86.27
Hypothyroid	2	3.92
Hyperthyroid	5	9.80
Vitamin D level		
Sufficient	13	33.33
Insufficient/deficient	26	66.66
Category of thyroidectomy		
Total thyroidectomy	23	45.09
Total thyroidectomy with central compartment neck dissection (CND)	9	17.64
Total thyroidectomy with central compartment neck dissection and lateral neck dissection	19	37.25
Intraoperative Parathyroid gland status		
Identification and preservation ($\geq$ one PT gland)	47	92.15
Identification and preservation ($\geq$ one PT gland) + implantation	3	5.88
Implantation only	1	1.96
No. of Parathyroid gland identified and preserved		
Less than two	6	11.76
Two or more	45	88.23

Table 2. Incidence of early and late hypocalcemia after total thyroidectomy

Total number of patients (N)	Early hypocalcemia (n)	Percentage (%)	Late hypocalcemia (n)	Percentage (%)
51	35	68.62	6	11.76

with calcium and/or vitamin D had to be readmitted and treated for hypocalcemic symptoms.

Among the patients treated with supplementation, 24 patients had biochemical hypocalcemia and 6 patients had biochemical normocalcemia.

Eleven out of 35 patients with early mild to moderate biochemical hypocalcemia were asymptomatic and thus not given supplements. None of them developed late hypocalcemia.

Secondary outcome measure

Statistical analysis was restricted to observations with non-missing values. None of the preoperative and intraoperative factors studied were found to be significantly associated with occurrence of early hypocalcemia with p value more than 0.05. Likewise, no significant association of these parameters was seen with occurrence of late hypocalcemia.

The analysis of association of serum PTH level (iPTH) with serum calcium level in patients with postoperative early

hypocalcemia was carried out. The Pearson correlation coefficient between iPTH obtained on first post operative day and SAC level obtained on second post operative day was 0.47 (p value = 0.004) indicating moderate positive linear relationship between two variables as visualized with a scatter plot shown in figure 1.

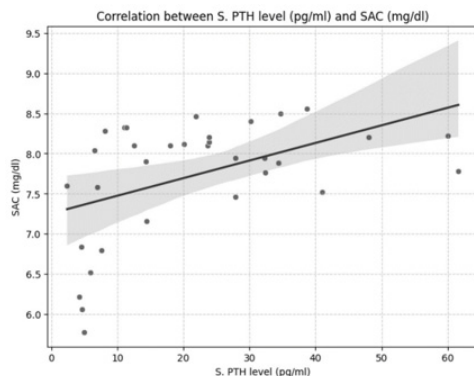


Figure 1. Scatter plot showing a moderate positive correlation between intact PTH on first postoperative day and SAC on second postoperative day in patients with early hypocalcemia.

Patients with the symptoms of hypocalcemia ranged from perioral numbness, tingling sensation to carpopedal spasms and tetany, and were managed accordingly either with oral calcium $\pm$ vitamin D or with intravenous calcium.

The mean iPTH level (first POD) in asymptomatic and symptomatic categories of early hypocalcemia is shown in table 3. Independent t-test for mean iPTH levels in between asymptomatic early hypocalcemia group and symptomatic early hypocalcemia group showed statistically significant difference. None of the asymptomatic patients had severe biochemical hypocalcemia.

Table 3. Intact PTH level in asymptomatic and symptomatic category of patients with early biochemical hypocalcemia in patients of total thyroidectomy

Category of early hypocalcemia	Mean iPTH (Range) (pg/ml)	Standard deviation	P value
Asymptomatic (mild to moderate) hypocalcemia	33.76 (21.9 to 61.6)	12.27	0.002
Symptomatic (mild to moderate and severe) hypocalcemia	16.89 (2.4 to 60)	14.19	

The cross tabulation of asymptomatic hypocalcemia (mild to moderate) and symptomatic (mild to moderate and severe combined) with iPTH level (first POD) is shown in table 4 and is depicted in figure 2. Analysis of iPTH level as a predictor of symptomatic early hypocalcemia and hence the need for oral calcium $\pm$ supplementation was carried out.

Strong association of occurrence of symptomatic hypocalcemia was seen with iPTH value of less than 15 pg/ml. This association was statistically significant as shown

Table 4. Crosstabulation of asymptomatic and symptomatic patients of early biochemical hypocalcemia with intact PTH level in patients of total thyroidectomy

S. PTH level / iPTH (pg/ml)	Asymptomatic hypocalcemia	Symptomatic hypocalcemia	P value
< 15	0	15	0.0005
15-65	11	9	

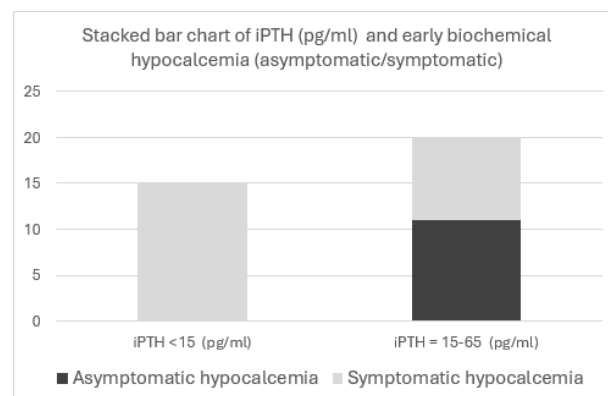


Figure 2. Stacked bar chart showing relation of iPTH < 15 pg/ml with symptomatic status in patients with early post-thyroidectomy hypocalcemia.

by p value of 0.0005. None of the patients with early asymptomatic biochemical mild to moderate hypocalcemia with serum PTH > 15 pg/ml developed late hypocalcemia.

The odds of developing late hypocalcemia in a subset of patients with serum PTH < 15 pg/ml was nine times higher than in a group with serum PTH > 15 pg/ml, however, the association was not found to be statistically significant as shown in table 5. Only one out of 9 early symptomatic hypocalcemic patients with serum PTH > 15 pg/ml developed late hypocalcemia.

Table 5. Crosstabulation of occurrence of late hypocalcemia with intact PTH level in patients of total thyroidectomy

S. PTH status	Late hypocalcemia		p value
	Yes	No	
< 15 pg/ml	5	16	0.69
15 – 65 pg/ml	1	29	

DISCUSSIONS

The occurrence of postoperative hypocalcemia is dependent on multiple factors.¹¹ The study showed 68.62% incidence of early hypocalcemia. The incidence of transient and permanent hypocalcemia following thyroidectomy described in literature ranges from 19 to 38% and 0% to 3% respectively.¹⁰

A female sex is described as an independent factor for transient hypocalcemia.^{10,12} The cohort of this study also had very large percentage (90.19%) of female patient. Likewise, the rate of temporary and permanent hypothyroidism is

higher for total thyroidectomy with central neck dissection (CND) than for total thyroidectomy alone.^{13,14} The risk of permanent hypoparathyroidism is increased to 15% when CND is done along with total thyroidectomy.² Presence of malignant pathology and neck dissection are identified as most important factor for postoperative symptomatic transient hypocalcemia.¹² More than half of the patients in our study underwent total thyroidectomy with either CND alone or with lateral neck dissection for papillary carcinoma of thyroid.

Intraoperative injury to parathyroid itself or to its vascular supply is the most common cause for post thyroidectomy hypocalcemia.¹⁰ The incidence of accidental removal of PT gland ranges from 4% to 22% and un-intentional removal due to its intrathyroidal location occurs in 0.7-4%.^{13,15-18} The auto transplantation of one or more PT gland and identification and preservation of greater number of PT gland is shown to be associated with transient hypocalcemia, however, the association with permanent hypocalcemia is not clear.¹⁰ A large scale study showed that at least two parathyroid glands should be identified and preserved in total thyroidectomy to avoid postoperative hypoparathyroidism.^{2,11} In contrast, one retrospective study showed that incidence of hypocalcemia was less with identification of one or two parathyroid glands than in cases of identification of 3 to 4 parathyroid glands.¹⁹ Some literatures suggest for PT gland auto transplantation after intraoperative histological confirmation in case of doubtful viability (either ischemic or hemorrhagic) despite of anatomical preservation to prevent permanent hypocalcemia.^{13,20} On the contrary, some suggest that discolored PT gland lead to transient hypocalcemia and can be left as such to recover.²¹ The viability of the PT gland cannot be decided only on the basis of the color of the gland, rather confirmation of intact vascular pedicle should be done.² The role of auto transplantation of PT gland is to prevent permanent hypocalcemia as it takes around six months to become functional.^{2,22}

However, the functional outcome cannot be solely attributed to auto transplantation only as residual function of other preserved glands may also be responsible.² Hence, identification of PT glands with minimal surgical trauma and preservation with intact vascular pedicle is the mainstay for prevention of postoperative hypoparathyroidism.² In our study, most of the patients (88.23%) had two or more than two PT glands identified and preserved and only two patients (3.92%) had auto transplantation. The preservation of PT vascularity was not commented in the surgical notes.

The higher rate of hypocalcemia seen in this study can be attributed to significantly large population of female patients, and higher number of total thyroidectomy with either CND alone or with lateral neck dissection. One patient of Graves' disease, despite of preoperative insufficient vitamin D did not develop either early or late

hypocalcemia or hypoparathyroidism probably due to adequate preoperative vitamin D supplementation.

None of the factors among preoperative thyroid function and vitamin D status, type of surgery, status of PT gland and number of PT gland identified and preserved, were shown to have significant association with occurrence of early or late hypocalcemia. This finding could be due to a small cohort of patients and multifactorial causes for postoperative hypocalcemia.

The assessment of serum calcium unlike serum PTH was done on day two as it is well accepted that its decline lags behind that of serum PTH, the lowest level occurring 24 to 72 hours after total thyroidectomy.¹ The assessment of iPTH on first postoperative day i.e. within 24 hours is identified as an early predictor of postoperative hypocalcemia.²³ The moderate positive linear correlation was seen between iPTH level and serum calcium level in patients with hypocalcemia. This infers that if serum PTH is low, the serum calcium can also expected to be low. However, it is not universally observed in all cases due to multifactorial effects on serum calcium level like preop vitamin D level and renal absorption.^{2,10}

Patients with early asymptomatic mild to moderate hypocalcemia have significantly higher levels of intact PTH (iPTH) as compared to the patients with symptomatic (mild to moderate and severe) hypocalcemia. In our analysis, statistically significant association between serum PTH level of less than 15 pg/ml with symptomatic early hypocalcemia is observed which is in concurrence with ATA statement that PTH level < 15 pg/ml helps in predicting impending hypocalcemia. Its sensitivity and specificity to predict hypoparathyroidism are reported to be of 97.7% and 82.6% in one literature.²⁴ This serum PTH parameter can, therefore, guide surgeon in deciding on postoperative calcium supplementation when selective supplementation is practiced. The iPTH level on day one combined with serum calcium level on day two along with clinical parameter of symptoms and signs can be used to start the calcium supplementation to those who really need either due to transient or permanent parathyroid dysfunction. This will also help surgeons to identify patients requiring supplementation to recover from transient parathyroid dysfunction as recovery is described to hasten with aggressive calcium and calcitriol supplementation.²⁵ This type of supplementation is also called parathyroid splinting which is described to enable gradual parathyroid recovery at rest and then after the supplements are tapered over time.² It is also advised to start oral calcium supplementation along with calcitriol when serum PTH is less than 15 pg/ml so as to prevent symptoms and expedite the discharge.² This also prevents emergency department (ED) visits for hypocalcemic symptoms. Some clinicians practicing symptoms based treatment advocate counseling asymptomatic patients before discharge for the probability

of experiencing symptoms at home and advise them to self-start oral supplementation.⁸ A prospective study on cohort of more than 400 patients has concluded that supplementation with calcium and vitamin D based on PTH level reduced both the number of symptomatic patients and critically low calcium levels.^{26,27} ATA guideline has also recommended for either use of prophylactic calcium or for selective use in patients according to their serum PTH and calcium report and evidence based protocols.¹ There are some proponents for all-inclusive prophylactic supplementation in all patients of total thyroidectomy citing its cost effective advantage to prevent hypocalcemia.^{2,28}

The frequency distribution of asymptomatic (biochemical mild to moderate) hypocalcemia, symptomatic (biochemical mild to moderate and severe) hypocalcemia in relation to iPTH value as either more or less than 15 pg/ml was statistically significant. All patients of early hypocalcemia (SAC < 8.6 mg/dl) with less than 15 pg/ml of PTH were having symptomatic (biochemical mild to moderate and severe) hypocalcemia. It has been stated that low iPTH level predicts patients at risk of early hypocalcemia, and a normal level excludes permanent hypoparathyroidism.²⁹ All the asymptomatic but mild to moderate biochemical hypocalcemia had serum PTH of > 15 pg/ml and none of them in our study developed late hypocalcemia. This might be due to the intact phenomenon of rise in serum PTH due to mild to moderate decrease in serum calcium possible when parathyroid glands are adequately preserved both anatomically and functionally preventing development of late hypocalcemia. This is also explained as parathyroid stress testing which is the phenomenon of stimulation of residual parathyroid tissue by mild hypocalcemia or mechanism of parathyroid cell growth leading to increased PTH hormone secretion.² The absence of late hypocalcemia in asymptomatic but biochemically hypocalcemic (mild to moderate) patients justifies our protocol of avoiding supplementation in such group of patients which can be predicted by the presence of serum PTH level of more than 15 pg/ml. This approach prevented the possibility of hypercalcemic symptoms due to overtreatment with supplementation. Moreover, the effectiveness of this approach can be inferred from the absence of readmissions in patients not supplemented either with calcium or in combination with vitamin D for hypocalcemic symptoms.

The postoperative hypocalcemia in presence of normal PTH is usually self-limiting and is possibly due to vitamin D deficiency, hemodilution and secondary hyperparathyroidism.¹⁰ This study also showed similar finding as only one out of nine symptomatic hypocalcemic patients with serum PTH > 15 pg/ml developed late hypocalcemia.

Only 23% (5/21) of patient with less than < 15 pg/ml of serum PTH value developed late hypocalcemia which is explained by the occurrence of the transient parathyroid

dysfunction in majority due to impaired vascularity to the parathyroid gland that improves with transient supplementation (parathyroid splinting). The odds of developing late hypocalcemia in a subset of patients with serum PTH < 15 pg/ml was nine times higher than in a group with serum PTH > 15 pg/ml. The relationship between the occurrence of late hypocalcemia and the PTH level is not found to be statistically significant in our study. Their relation can be studied further with a large cohort of prospective patients.

Some patients postoperatively remain normocalcemic despite of low PTH.^{2,10} This may be the first phase of postoperative hypoparathyroidism wherein serum calcium levels are still maintained.³⁰ It is well accepted that hypocalcemia can occur without hypoparathyroidism, however hypoparathyroidism ultimately leads to hypocalcemia through reduced intestinal calcium absorption, reduced 1, 25-dihydroxy-vitamin D synthesis and inhibition of bone resorption.² Use of PTH assay in first postoperative day helps in detecting acute hypoparathyroid condition despite normocalcemia (symptomatic and asymptomatic both). In our study, 6 out of 16 normocalcemic patients had postoperative hypoparathyroidism. Only two patients were asymptomatic, hence did not receive oral calcium supplementation. And none of these two patients developed late hypocalcemia. The only normocalcemic patient who developed late hypocalcemia was symptomatic and received oral supplementation. In symptom based treatment study, almost 50% of patients who visited the ED for calcium related symptoms had biochemical normocalcemia.⁸ The treatment protocol based only on biochemical level of calcium may not benefit this category of normocalcemic patient. In this scenario, the iPTH at or within 24 hours can guide clinicians for the treatment of the biochemically normocalcemic patients by identifying the subset of patients at risk of developing symptoms and subsequent late hypocalcemia without having to do serial calcium monitoring. There are multiple evidences lately for the use of postoperative iPTH level as a predictor for hypocalcemia in total thyroidectomy patients.³¹⁻³⁴

Significant number of in-patient charts were excluded because of incomplete data and failure of retrieval leading to smaller cohort of patients. Long term management of the patients with late hypocalcemia were out of scope of this study.

CONCLUSION

The findings of this study gives evidence to the effectiveness of symptom based treatment of post thyroidectomy hypocalcemia. It generates evidence for the supporting role of iPTH at 24 hours as a predictor for early symptomatic hypocalcemia. The absence of hypoparathyroidism in early postoperative period is significant evidence to omit

the supplementation of asymptomatic but biochemically hypocalcemic patients thereby avoiding unnecessary treatment. None of the other factors studied were found to be significantly associated with occurrence of either early or late hypocalcemia which could be due to small cohort of the patients studied. Prospective cohort analysis with larger cohort would be beneficial for more robust evidence.

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