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INCIDENCE OF HYPOCALCEMIA IN THIRTY PATIENTS WITH TOTAL THYROIDECTOMY

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ABSTRACT

BACKGROUND: Hypocalcemia frequentlly encountered after thyroid surgery causes considerable morbidity, escalates cost and time of stay in hospital. The aim of this prospective observational study was to determine the incidence, onset and duration of hypocalcemia after total thyroidectomy and assess the possible causative factors. **STUDY DESIGN/MATERIALS & METHODS**:In this prospective study we analyzed data of 30 patients who underwent total thyroidectomy for various thyroid disorders. In addition to routine hematological, biochemical and clinical examinations, calcium, phosphorous, magnesium, total proteins, albumin and globulins were estimated preoperatively and post operatively after 24 and 48 hours. All patients were clinically examined for symptoms of hypocalcemia and whether positive for Trousseau's sign and Chvostek's sign. Statistical analysis was performed to determine the incidence of hypocalcemia associated with total thyroidectomy. **RESULTS**: Transient symptomatic hypocalcemia developed in 6.66% patients within 24 hours (1st day), post operatively and these patients also had low normal serum magnesium levels. Administration of magnesium sulphate and calcium gluconate to these patients resolved the serum calcium to normal levels within 48 hours (2nd day). Patients who developed transient symptomatic hypocalcemia were females below 40 years of age operated for papillary carcinoma with a mean operative time of more than 3hours. **CONCLUSIONS:**The low incidence of transient symptomatic hypocalcemia and the absence of persistent hypocalcemia indicated that refined surgical techniques and expertise lead to the preservation of the parathyroid glands which in turn lowered the incidence of total thyroidectomy associated hypocalcemia. Monitoring serum calcium levels at 24 hours post surgery and co administration of magnesium with calcium enabled early resolution of symptomatic hypocalcemia, and reduce cost and duration of hospitalization.

Keywords: Hypocalcemia Thyroidectomy

1.INTRODUCTION

The burden of global surgical disease is currently receiving much attention, especially in counters experiencing epidemiological transition. The mortality after thyroid surgeries is nearly zero and these surgeries have no severe morbidity associated with the procedure. But the common complications are superior and inferior nerve injury and hypocalcaemia (1,2).

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Due to this many biochemical and hormonal tests have to be performed for the patients and their length of hospital stay increases in order to extend treatment to these patients. For alleviating the symptoms of hypocalcaemia and decreasing the clinical complications intravenous calcium administration is essential. Although hypocalcaemia regresses in most of the patients it may become permanent when irreversible injury occurs to the parathyroid gland. With the increasing preference for shorter hospital stay there has been renewed interest in post thyroidectomy hypocalcaemia (3-6). Various strategies have to be adopted to minimize the incidence of hypocalcaemia such as prediction of hypocalcaemia at an early and appropriate time

point after surgery. This is important so that cost and duration of hospital stay can be reduced and readmission of patients due to hypocalcaemia can be avoided. The aim and objectives of this prospective study were to determine the incidence, onset, and duration of hypocalcaemia in post thyroidectomy patients and to assess the possible factors associated with hypocalcaemia in post thyroidectomy patients.

2.MATERIALS AND METHODS

This prospective observational study was conducted on patients who were operated for various thyroid disorders in the department of Raja Muthiah Medical College and Hospital, RMMCH, Annamalai Nagar, Tamilnadu. The detailed protocol was approved by the Institutional Ethics Committee. Written informed consent was obtained from the patients who underwent thyroid surgery and participated in the study.

The conditions present in patients for which they were excluded from this investigation were patients with history of previous thyroid or parathyroid surgery,with confusing factors like hypoalbuminemia, chronic renal failure, those having hyperparathyroidism and thyrotoxic patients. Patients taking any form calcium supplement pre-operatively and those on drugs causing hypocalcemia like anti-convulsants, chlorphomazine, diazepin, oral contraceptives, steroids and mithracin were also excluded from the study.Patients who were already hypocalcemic due to thiazides, vitamin A, Vitamin D, lithium and absorbable antacids, and patients who received blood transfusion within the first 24 hrs after surgery were also excluded from the study.

All 30 patients included in this study were evaluated thoroughly. The past history of recurrence of the disease of these 30 patients was looked up in detail. Detailed clinical examination was done with reference to symptoms like heat tolerance, palpitations, dysponea, insomnia, restlessness, fatigue, muscle cramps, frequent bowel movements, weight loss in hyperthyroid patients cold in tolerance, lethargic feelings, sleepiness, constipation and weight gain in hypothyroid patients was noted. All the clinical investigations were recorded in the Performa.

All patients included in this study were subjected biochemical and laboratory tests like routine hematological investigations,blood sugar, blood urea, serum electrolytes, creatinine and serum alkaline phosphatase estimations. Total and ionized serum calcium, phosphorous, magnesium, albumin globulin and total protein and were determined. Preoperatively and post operatively.Thyroid function tests included serum TSH, serum free T3 and T4. Radiological examination performed were chest X-ray including soft tissue of neck and ultrasound of neck, CT Scan neck chest in a few areas and indirect laryngoscopy.All patients were subjected to FNAC preoperatively. Collected samples were sent to histopathology for arriving at preliminary pre operative diagnosis. Post Operative histopathological examination of surgery samples was also carried out.

All blood samples were collected from patients in an aseptic manner. All collected blood samples were immediately transferred to the concerned laboratory for analysis and reporting. Total and Ionised calcium levels were monitored pre operatively and post operatively. Calcium levels were monitored again 24 hours post surgery and again after 48 hours post operatively.Post operatively patients were completely monitored for clinical signs and symptoms of hypocalcemia. Patients with biochemical and/or clinical evidence of hypocalcemia were followed up with subsequent estimations and investigations.

Symptomatic hypocalcemia was detected by clinical examination of patients in order to study whether they were positive for Chvostek's sign and Trousseau's sign.If classical symptoms of hypocalcemia were absent and patients did not possess overt signs, the underlying neuromuscular excitability was detected by simple physical examination of patients.

Hypocalcemia was defined as serum calcium level below 8.5 mgs/dl. Permanent hypocalcemia is defined as persistent hypocalcemia after 6 months of thyroidectomy.Operation was performed by a team of surgeons under general anaesthesia. The results were subjected to statistical analysis by one way analysis of variance (ANOVA)with the Bonferroni Test using SPSS version 5in graph pad prism. A value with $P< 0.05$ was considered significant.

3.RESULTS

Post operative transient hypocalcemia is a common complication after total thyroidectomy. The reason for hypocalcemia whether transient or permanent is incidental removal of parathyroid glands. Under such circumstances decreased serum calcium secondary to hypoparthyroidism may present along with muscle cramps, carpopedal spasm or tetany. The extended hospitalization of such patients amounts to increased health care costs.

Therefore post operativehypocalcemia is an important consideration for the early discharge of patients and cost cutting after total thyroidectomy. Therefore the study was designed and conducted to determine the incidence of hypocalcemia and the time of onset and duration of hypocalcemia following total thyroidectomy. The causative features for post total thyroidectomy hypocalcemia were also analysed.

In this pre operative observational study a total of 30 patients were included and their clinical data was analyzed before and after total thyroidectomy. Patients with various thyroid disorders were included in this study. As explained earlier based on the exclusion criteria patients were selected for this analysis. Briefly patients who had one or more risk factors for hypocalcemia were excluded from this study. Out of 30 patients 25 subjects were females (83.33 %) and 5 subjects were male (16.66 %). The female:male ratio was 5:1. The sex ratio was in favour of females. The mean age of the patients analyzed in this study was 38.4 years. The distribution of patients according to age and gender, incidence of hypocalcaemia and time and duration of hypocalcaemia are presented in Tables1, 2 and 3.

Table 1. DISTRIBUTION OF PATIENTS ACCORDING TO AGE AND GENDER

Age group	Male		Female		Total	
	No.	%	No.	%	No.	%
10 – 20	0	0	2	6.6	2	6.6
21 – 30	2	6.6	7	23.3	9	30
31 – 40	2	6.6	6	20	8	26.6
41 – 50	0	0	6	20.0	6	20
51 – 60	1	3.3	3	10.0	4	13.3
61 – 70	1	3.3	0	0.0	1	3.3
Total	6	20	24	80	30	100

Table 2. INCIDENCE OF HYPOCALCEMIA

Type	No.of cases	% Cases
Transient hypocalcemia	2	6.66
Persistanthypocalcemia	0	0
Normocalcemia	28	93.33
Total	30	100

Table 3. ONSET & DURATION OF HYPOCALCEMIA

Hypocalcemia	Time in hrs
Onset	24
Resolution	48
Duration	24

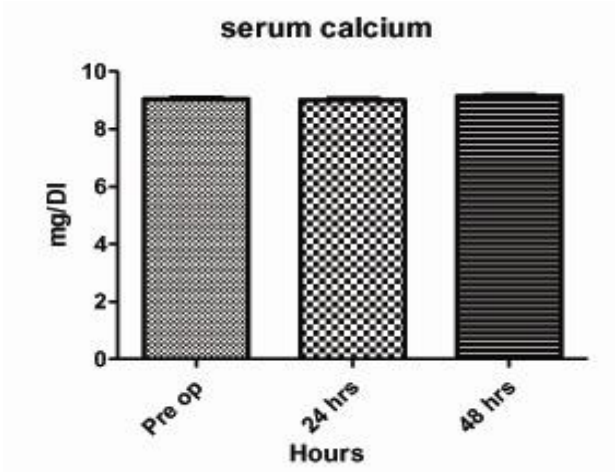

Figure.1 Pre operative and post operative mean serum calcium levels in patients who underwent total thyroidectomy

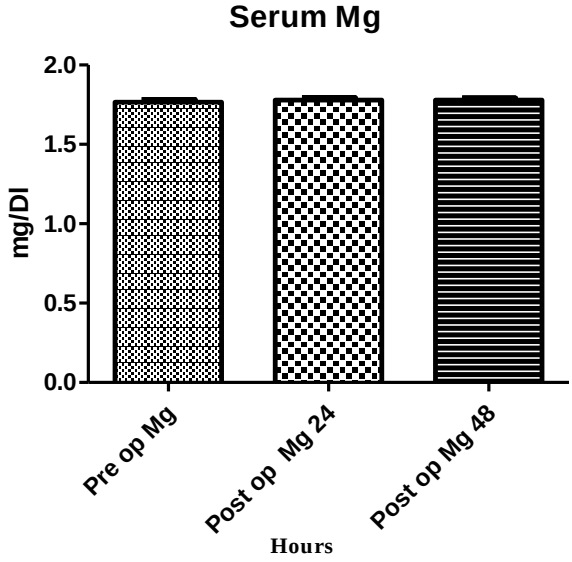

Figure 2. pre and postoperative mean serum magnesium levels in patients who underwent total Thyroidectomy.

In this study the calcium levels of all 30 patients in the pre operative period ranged from 8.7 to 9.4 mg/dl. The mean pre operative calcium level was 9.1 mgs/dl. The post operative calcium level ranged from 8.1 mg/dl to 9.4 mg/dl) in the first day and 8.7 mgs/dl in the second day to 9.4 mgs/dl). The post operative mean serum calcium was 9.15 mg/dl on the first day and the post operative mean serum calcium levels was mg/dl as shown in Figure 1. The preoperative mean serum magnesium levels ranged from 1.6mg/dl to 1.9mg/dl. The post operative mean serum magnesium levels ranged from 1.6mg/dl to 1.8mg/dl after 24hrsand the same after 48hrs was 1.6 mg/dl to 1.9 mg/d as shown in Figure 2. The mean operation time of patients included in this study was between 90 and 245minutes. The mean operation time of the 6,66 % patients who developed post operative hypocalcemia was 242.5 minutes.

Among the patients included in this study there were cases with, MNG, nodular colloidal goiter, papillary carcinoma, follicular neoplasm, and adenamatous goiter. All patients were euthyroid prior to surgery. For none of the patient'sparathyroid gland was found in the specimen after thyroidectomy. None of the patients were found to be hypocalcemic on pre operative biochemical testing.

All patients who showed symptomatic hypocalcemia did so within 24 hrs after surgery. However symptomatic hypocalcemia in the patients was only transient and did not persist beyond 48 hrs. Serum calcium levels returned to normal levels within 48 hours after administration of magnesium sulphate and calcium gluconate intravenously.
Hypocalcemia was diagnosed when serum calcium level dropped below 8.5 mgs/dl. Permanent hypocalcemia was diagnosed as hypocalcemia that persisted even after 6 months of thyroidectomy. In this study none of the patients had permanent hypocalcemia. Among 30 patients in the study, 2 patients (6.66%) demonstrated transient symptomatic hypocalcemia. The occurrence of hypocalcemia was 24 hrs post thyroidectomy. However the hypocalcemia was only transient and was present for a duration of 24hrs. The hypocalcemiaresolved and within 48 hours post thyroidectomy following calcium and magnesium administration and patients became normocalcemic by 48hrs.i.e 2nd post operative day. Both these patients who became hypocalcemic were positive for Chvostek's sign and Trouesseau's sign. In this study the 6.66% patients who developed symptomatic hypocalcemia had near normal serum magnesium values. This demonstrated that low normal levels of magnesium was positively correlated with hypocalcemia.

4.DISCUSSION

Post operativehypocalcemia after total thyroidectomy is a major reason for morbidity (7-10). If patients develop hypoalcemia after thyroid surgery it increases the duration of hospital stay and escalates expenses for the patient warranting readmission and more number of hospital visits for follow up. If hypocalcemia is persistant then more complications and treatment add to the patient's burden in terms of treatment time, cost factor and discomfort (11). In persistent hypocalcemia treatment in the form of calcium

and vitamin D supplement cannot be discontinued even after a follow up for 6 months. When irreversible damage to parathyroid gland occurs it leads to permanent hypocalcemia (12-16).

Whether transient or permanent if hypocalcemiaoccurs, various clinical, biological and surgical factors contribute to reduction in serum calcium levels(17). Increase in serum calcitonin which is the secondary effect of manipulation of the thyroid gland is suspected to participate in serum calcium reduction. But this fact has not yet been confirmed. Moreover phosphorus also decreases slightly at 24 hours. Hemodilution during post operative period may be attributed to this decrease in serum phosphorus(18).

Incidence of hypocalcemia

Although hypocalcemia is well documented in the thyroid literature the incident rates of hypocalcemia reported range widely. Many studies reported that anywhere from 0.3% to 66.2% of patients develop hypocalcemia after thyroid surgery (19,20). Most series report an incidence around 20% to 30% and symptoms ranged from mild paresthesia and tingling to more severe cramps, carpopedal spasm or tetany, and convulsions (10). The reason for this variation in incidence is due to the fact that reports differ in the thyroid surgery procedure assessed. These studies not only include patients who underwent total thyroidectomy but also less extensive procedures like thyroid lobectomy (21). Such reports can underestimate the incidence of hypocalcemia and may lead to misinterpretation.In our prospective studythe results demonstrated that 6.66% of patients who underwent total thyroidectomy developed hypocalcemia which is in the lower side of the wide range reported in literature.

Time of onset and duration of hypocalcemia

In our study hypocalcemia was detected by 24 hrs and resolved by 48 hrs in the 6.66% patients. The nadir for hypocalcemia typically occurs at around 24-48hrs post operatively but may be as delayed as day 4 resulting in longer patients stay in hospital than required. Therefore it is of great significance in post thyroidectomy hypocalcemia (22,23). One group reported that the onset of hypocalcemia was delayed upto 3rd post operative day in their study (24). In their study hypocalcemia manifested late in the immediate post operative period (72 hrs) and this may be due to latent hypocalcemia present undetected upto 3rdpost operative day. Our results showed that hypocalcemia manifested in the early part of immediate post operative phase (24 hrs/i.e., 1st day) whose detection and immediate treatment helped to resolve it by 48 hrs i.e2nd post operative day. This facilitated discharge of patients from hospital in normocalcemia state without complications and avoid readmission.

Moderate asymptomatic hypocalcemia is observed at 12 hours following bilateral or unilateral thyroidectomy which spontaneously resolves in 24hrs (9). Our study brought to limelight the fact that hypocalcemia might occur even at 24 hrs, although patients may be normocalcemic upto 12 hrs. Our study finding highlighted the importance of serum calcium estimation at 24 hrs (2nd day) post surgery which facilitated treatment and resolution of symptoms by 48 hrs i.e. 2nd day. If one misses the 24 hrs serum calcium level estimation and fails to detect hypocalcemia by the 1st day then the situation might become complicated.

Actually the true and accurate prevalence of hypocalcemia due to removal of parathyroids during total thyroidectomy as treatment for various thyroid disorders has been under estimated. In our study we came across transient hypocalcemia (Ca 8.5 mg/dL at 24 hrs) which was also symptomatic and was rectified to normal serum levels by 48 hrs in 6.66% of patients after total thyroidectomy. Parathyroid insufficiency syndrome is a common complication after total thyroidectomy, especially permanent hypoparathyroidism which will result in permanent hypocalcemia and necessitates for life long medication, regular follow up care and high costs. This is a medical burden on the patient. Hence excellence in infrastructure, surgical expertise and new and novel surgical strategies are essential for total thyroidectomy in order to avoid high expenditure and readmission of patients to treat hypocalcemia.

In our prospective study since by testing and detecting hypocalcemia in the early post operative period and taking measures to correct it, hypocalcemia resolved before patients were discharged from hospital. Since patients had only transient hypocalcemia which was corrected before they were discharged from hospital there was no need for these patients follow up as far as serum calcium level was concerned.

Causative factors associated with hypocalcemia

1.Malignancy of thyroid gland

In patients in whom thyroidectomy is performed for thyroid carcinoma there are studies demonstrating hypocalcemia following the operationfor thyroid carcinoma (25,26). Our results were similar to this in that the 6.66% who developed transient hypocalcemia were those patients who underwent total thyroidectomy for papillary carcinoma of thyroid gland. The fact that patients who are operated for carcinoma of thyroid developed transient hypocalcemia may be because preservation of parathyroid gland may be jeopardized in thyroid cancer surgery due to technical difficulties. Mc Henry et al found that in their series of unilateral thyroid lobectomy and bilateral thyroid resection, 40% and 49% of patients developed transient hypocalcemia respectively, and 15% of patients were symptomatic. In this study the three independent risk factors for hypocalcemia were thyrotoxicosis, at initial presentation, substernal thyroid disease and thyroid carcinoma (27). In Henry et al study, surgery for carcinoma of the thyroid increased the risk of transient hypoparathyroidism. In our study patients with thyrotoxicosis were not included. The 6.66% of patients who developed symptomatic transient hypocalcemia were only those who were operated for papillary carcinoma of the thyroid gland. This could be due to the fact that surgery for carcinoma is very extensive and hence there are greater chances of removal of parathyroid glands or impairment of parathyroid blood flow during dissection.

2.Gender

Different results have been reported in studies demonstrating the relationship between gender and hypocalcemia. Although some studies show that gender has no significant effect on hypocalcemia (9,28,) there are many studies whichfound that the rates of both transient and permanent hypocalcemia were significantly higher in women (12,26,29-31).The results of our study was similar in that female gender appeared to be one of the patient related factors for hypocalcemia in that the 6.66% patients who had transient hypocalcemia were females.

3. Age

Patients aged 45years to 84 years were less likely to have post operative hypocalcemia compared with their younger and older counterparts according to the report of one group who also found that older age had a protective effect (20). A previous study showed that older patients in the study had higher rates of total complications consistent with a recent series (32,33). Our results also showed that 6.66% patients who developed transient hypocalemia were females in the age group below 40 years of age and were operated for papillary carcinoma of thyroid gland. Our results corroborated with those of another group which demonstrated that younger patients may be more likely to undergo bilateral surgery for malignancy which would expectedly result in an association between young age and hypocalcemia (34).

4.Hypomagnesemia

Our study also suggested that another biochemical factor such as low post operativeserum magnesium levels was also found to be associated with post total thyroidectomy hypocalcemia. Aftertotal thyroidectomy magnesium levels decreased and were low normal in the 6.66% patients who had symptomatic hypocalcemia. Administration of magnesium along with calcium gluconate to these patients reverted not only magnesium but also serum calcium levels to normal levels and resolved the hypocalcemia. There are reports that most patients who have symptomatic hypocalcemia after thyroid surgery responded to calcium and vitamin D supplementation therapy. Our study findings demonstrated the fact that patients benefited from magnesium replacement as well. In our study, those patients who had symptomatic hypocalcemia also had low normal serum magnesium levels.We administrated magnesium along with calcium to resolve symptoms. Administration of only calcium to correct severe hypocalcemia when magnesium is low may only prolong symptoms and not lead to resolution of symptoms.

The reasons for low normal magnesium levels in patients who had symptomatic hypocalcemia could be multifactorial like changes in serum calcium after total thyroidectomy. Decreased tubular reabsorption of magnesium by the kidneys, extracellular volume expansion due to increased magnesium secretion and temporary hypoparathyroidism due to injury may be some of the reasons for magnesium was reaching low normal levels. Moreover there is evidence that hypomagnesemia contributes to increased catabolism of parathormone and also diminishes the end organ responsiveness to PTH in humans and experimental animals. Inspite of work published on the significance of hypomagnesemia especially when it co-exists with hypocalcemia, still it can be said that sufficient publications are not available on the link between hypomagnesemia and total thyroidectomy (35).

Some researchers suggested that magnesium might compete with calcium for binding to the parathyroid cell. It is postulated that 'calcium' receptor acts by a trans membrane signal transduction systemand inhibits PTH secretion. When the extracellular calcium levels are elevated. When there is hypomagnesemia, relative number of calcium ions available for binding to PTH is higher and as a result PTH secretion might be inhibited. Thus hypomagnesemia may inhibit PTH secretion. Rude et al showed that administration of magnesium to patients with hypocalcemia secondary to hypomagnesemia resulted in increase in serum PTH levels within 1 minute of injection (36). Hence In our future work, studies will be conducted to get information on PTH levels also before and after so that the role of parathyroid gland injury during (surgery) total thyroidectomy can be elucidated. Also the parathyroid hormone level as a reliable tool in pre and postoperative follow up can be understood.

However there are some studies like that of Mc Henry et al where they did not find any correlation between post thyroidectomy hypocalcemia and serum magnesium and phosphorous changes (27). As all patients in these investigations did not undergo total thyroidectomy it is difficult to compare the results of these two studies with our study results.However in our prospective study in cases whenever there was hypocalcemia, levels of magnesium was also low.

5.Incidental parathyroid gland excision or injury

It has been also reported that parathyroid gland injury and accidental parathyroid excision were significant risk factors for hypocalcemia (24,29).But some consider parathyroid gland identification as not a risk factor for hypocalcemia (37).There are reports that total thyroidectomy coupled to central compartment dissection was associated with high incidence of hypocalcemia. Inferior parathyroid glands are at risk of inadvertent removal or vascular damage during total thyroidectomy.

In our study we identified all four parthyroid glands peroperatively and preserved the same during surgery. The parathyroids were not demonstrated in in any of the biopsy specimens. This was the attributing factor towards the low incidence of transient hypocalcaemia. Hence from our study it is clear that parathyroid glands can be protected by a meticulous surgery.

5.Operation time

The operation time for total thyroidectomy in thisstudy varied from about 90 minutes to about 245 minutes depending on the thyroid disorder. The mean operation time of the 6.66% patients who were operated for papillary carcinoma and developed post operative hypocalcemia was about 243 minutes. The cases whowere operated for malignant thyroid disorders required extensive surgery

involving bilateral neck dissection which is a time consuming procedure. Hence longer period of surgery of about 3 to 4 hours may be required for its completion. Therefore it can be said that longer operation time was associated with post total Thyroidectomy hypocalcaemia
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5.CONCLUSION

The low incidence of 6.66% transient hypocalcemia occurred in females below 40 years of age operated for papillary carcinoma with longer duration of surgery and larger gland volume. The low incidence of 6.66% transient hypocalcemia could be attributed to the important role of refined surgical techniques and expertise in avoiding injury to parathyroid glands and subsequent hypocalcaemia. Also this study highlighted the importance of monitoring serum calcium levels within first 24 hours after thyroidectomy for the timely detection of hypocalcaemia. Detection of hypocalcaemia using serum calcium levels as marker in the early post operative phase will be very useful to extend immediate medical treatment before patient discharge from hospital.This will in turn help in cost cutting due to extended hospital stay.

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