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Original Research Article

Serum calcium slope is a predictor of post-thyroidectomy hypocalcemia

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ABSTRACT

Background: Hypocalcemia is a common complication following thyroidectomy. The effects of hypocalcemia can range from simple numbness to life-threatening seizures. Barring stridor, haemorrhage and hypocalcemia, other complications of thyroidectomy are not seriously morbid and hence patients can be sent home. This study sought to determine whether early postoperative calcium levels can predict hypocalcemia following thyroidectomy, to help decide on early discharge.
Methods: This was a prospective cohort study, conducted between July 2016 and June 2017 among 80 consecutive patients who underwent total thyroidectomy in our department. Serum calcium values were obtained pre-operatively and at 6 and 24 hours post-operatively. Serum calcium slopes were calculated and the receiver operating characteristic curve constructed to evaluate the accuracy of risk prediction.
Results: The mean total calcium levels of patients with hypocalcemia were significantly lower than the levels of the normocalcemic group. The slope of change between total calcium measurements at 6 and 24 hours in patients with hypocalcemia was found to be significantly steeper than the slope in the case of normocalcemic patients.
Conclusions: It is possible to predict post-thyroidectomy hypocalcemia based on the characteristics of the early post-operative serum calcium slope. On the basis of the slope's features, all patients except those at risk can be safely discharged home early. This can cut down on the patients' total cost of treatment as well as save unnecessary wastage of health resources.

Keywords: Hypocalcemia, Parathyroid, Serum calcium, Thyroidectomy

INTRODUCTION

The beginning of modern thyroid surgery was supposed as early as the 1860s with the inauguration of the school by Billroth in Vienna.[1] However, the mortality associated with thyroidectomy was high at that time. Recurrent laryngeal nerve injuries were common, and tetany was thought to be caused by nothing but "hysteria." It was not until 1880 that human parathyroid glands were discovered by sandstrom.[2] Nevertheless, the fact that hypocalcemia was the definitive cause of tetany was not entirely accepted until several decades later. It was the meticulous surgical technique of kocher that greatly reduced the mortality and operative morbidity of thyroidectomy for goiters.[3] By the early part of 20th century, advances in thyroid surgery had reached such a point that Halsted, in 1920 referred to this operation as a "feat which today can be accomplished by any competent operator without danger of mishap".[1]

In today's environment where cost efficiency is given equal importance as patient safety, increasing interest in post-thyroidectomy care has focused on the major complications of this procedure, namely, haemorrhage/hematoma, hypocalcemia, and recurrent laryngeal nerve injury. Haemorrhage and recurrent laryngeal nerve injury are often evident in the first 8 hours after surgery and hence unlikely to be missed.[4] Hypocalcemia, on the other hand, usually manifests in the period between 24 to 48 hours or even later.[5]

Hypocalcaemia is the supposedly most common complication following thyroid surgery.[6] The reported incidence ranges broadly from 5.4% to 83% in various studies depending on the definition of hypocalcemia.[7,8] As per literature, permanent hypocalcaemia (need of treatment to maintain normocalcemia at six months) was found in 12.1% of patients.[9] Injury to the parathyroid glands (PTG) is generally accepted as the most common cause of post-thyroidectomy hypocalcaemia. This may be due to inadvertent excision of the glands, or more commonly their devascularisation and obstruction to venous drainage. Other mechanisms proposed for post-thyroidectomy hypocalcaemia include hungry bone syndrome and intra-operative haemo-dilution. Of late, evidence is coming up to the effect that calcitonin release during gland manipulation can cause hypocalcemia even in the absence of hypoparathyroidism.[10]

In the past, hospital stays of 3 to 5 days after thyroidectomy was necessary for all patients to ensure a stable calcium status in the postoperative period.[11] The modern scenario of resource constraints and insurance-led healthcare has led to efforts to perform thyroid surgery on a day-care or 23 h stay basis.[12,13] However, some patients may not develop hypocalcaemia until two to four days post-operatively.[5] Therefore, some means to identify patients at risk of hypocalcaemia is necessary to facilitate early discharge. Routine intra-operative parathyroid hormone measurements may identify at-risk patients but these tests are expensive and hence may not be affordable for most patients. An alternative approach is to determine the rate of change in serum calcium measurements in the first few hours following surgery.[14,15]

With this background, patients undergoing thyroid surgery were studied to determine whether serum calcium slope could be used as an independent predictor of hypocalcaemia, thus identifying those with potential risk. Being a major tertiary level institution, thyroidectomies are carried out routinely in our centre for a wide variety of indications ranging from cosmesis to malignancy and even retro-sternal extension. The objective of the current study was to determine whether the serum calcium slope can be used to predict the occurrence of hypocalcemia in patients after a total thyroidectomy.

METHODS

The study was designed as a prospective cohort study at the General surgery department of Government Medical College, Trivandrum. The duration of the study period was from July 2016 to June 2017. The study population included all patients undergoing total thyroidectomy admitted to the General Surgery wards of our institution. Institutional Ethics Committee clearance was obtained before commencing the study. Patients fulfilling inclusion criteria are enrolled and informed consent obtained for including in the study.

Patients with low pre-operative serum albumin and those with low pre-operative serum calcium were excluded. Sample size was calculated using the formula

$$N = \frac{(Z\ 1\text{-}\alpha/2 + Z1\text{-}\beta)2}{(r2/1\text{-}r2)}$$

Where, r=correlation coefficient=0.34, as found from the reference study by Walsh et al.[16] Z=significance level=5%, power of study=90%.

The sample size for the study was calculated as 80. So, 80 patients who underwent total thyroidectomy were taken as study subjects. All blood samples were taken from a peripheral vein contra-lateral to the one used for venous access, without tying tourniquet. Three samples were taken from each patient: pre-operative, 6 hours after completion of the surgery and 24 hours after completion of the surgery.

Hypocalcaemia was defined as a serum calcium level lower than 2.15 mmol/dL or 8.6 mg/dL.[20] Serum Calcium was calculated with corrected calcium levels using Payne's formula: Corrected calcium (mmol/L)=serum calcium (mmol/L)+0.8{4.0 - serum albumin (g/L)} where 4.0 represents the average albumin level.

Serum calcium slope was calculated using the formula:

$$\frac{(\text{Calcium at time \#1- calcium at time \#0})}{(\text{Time \#1-time \#0})}$$

where, time#0: pre-operative serum calcium, time#1: serum calcium at 6 hour and 24 hour post-operatively.

Slope values were calculated for time #0 to 6 hours and for time #0 to 24 hours post-operatively. Patients were divided into those who developed hypocalcaemia and those who did not.

Data was entered in excel sheet & analyzed using EpiInfo software (CDC). Calcium slopes and known risk factors for hypocalcaemia were compared between the groups using pearson chi-square or fisher's exact tests wherever appropriate. Continuous variables (age, serum calcium levels, slope) were examined by independent sample t-tests. Data were examined to check if there was any correlation between the occurrence of hypocalcemia and patient factors including age, gender, socio-economic status and education status. Also, data was analyzed to check for any correlation between the occurrence of hypocalcemia and co-morbidities including systemic hypertension, diabetes mellitus, dyslipidemia and bronchial asthma. Results were considered statistically significant wherever the two-sided p value was less than 0.05. The 5% confidence level was considered significant. Multivariate analysis was done using binary logistic regression. A receiver operating characteristic (ROC) curve was constructed to evaluate the accuracy of risk prediction.

RESULTS

Middle aged patients formed the bulk of the patients. 31.25% of patients were between the age group of 41 and 50 years. Majority of the patients were found to be females (91.25%). Hypocalcemia was evident within post-operative period of 24 hours in 18 (22%) patients. There was no statistically significant association between patient factors including age, gender, socio-economic status, education status and post-operative serum calcium levels. There was no statistically significant association between co-morbidities including systemic hypertension, diabetes mellitus, dyslipidemia, bronchial asthma and post-operative serum calcium values. Also, there was no statistically significant association between pre-operative thyroid function status and post-operative serum calcium levels.

Table 1: Comparison between 6 hour and 24-hour serum calcium slope among normocalcemic and hypocalcemic patients.

Serum calcium slope	Hypocalcemia Mean (SD)	Normocalcemia Mean (SD)	P value
0-6 hour	-0.158 (0.069)	-0.026 (0.024)	<0.001
0-24 hour	-0.070 (0.031)	-0.012 (0.009)	<0.001

Table 2: Binary logistic regression of serum calcium slope.

Serum calcium slope	B	S.E	P value
0-6 hour	1.237	0.268	<0.001
0-24 hour	6.232	1.517	<0.001

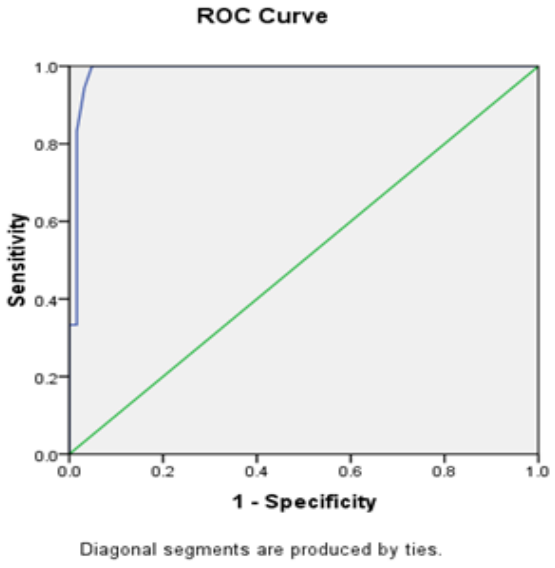

Figure 1: Binary logistic regression of serum calcium slope.

The mean total calcium levels of hypocalcemic patients at both predetermined times (6 hours and 24 hours) were significantly lower than the levels of those of the normocalcemic group (Table 1). The slope of change between total calcium measurements at the 6 and 24 hours in hypocalcemic patients was found to be significantly steeper than the slope in the case of normocalcemic patients (Table 2).

When the receiver operating characteristic (ROC) analysis was carried out, the area under the curve was found to be 0.987 for the calcium level at 6 hours after surgery. The optimal cut off was found to be -0.075 mg/dl/hour, with a sensitivity of 94.4% and a specificity of 96.8% (Figure 1). In the case of calcium level at 24 hours after surgery, the area under the curve was 0.987. The optimal cut off is was -0.023 mg/dl/hour, with a sensitivity of 94.4% and a specificity of 91.9% (Figure 2).

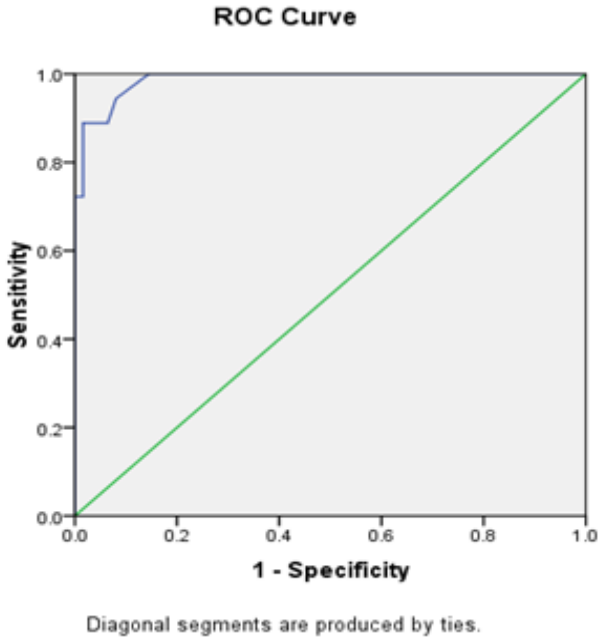

Figure 2: ROC curve for serum calcium level at 24 hours.

DISCUSSION

The results of our study show that middle aged females commonly undergo thyroidectomy. Thus, is in line with the general demographics of patients in our part of the country. In our study, no significant association was found between gender and occurrence of hypocalcemia post-thyroidectomy (p=0.586). There are conflicting reports in the literature with regard to associations with gender. In some studies, gender has not been shown to affect calcium homeostasis postoperatively.[17,18] In contrast, a large body of literature reports that females have significantly higher incidence of hypocalcemia than males.[19,20] In a study by Noureldine et al, 76% and 79%

of patients who developed postoperative mild and significant hypocalcemia were females.[21]

There was no significant association between thyroid status and development of post-operative hypocalcemia (p=0.159). Very few studies have found relation between abnormal thyroid function tests and post-thyroidectomy hypocalcemia. Elevated free thyroxine level (p=0.0064) was found to be independent risk factor for post-thyroidectomy hypocalcemia in a study by Abboud et al.[22]

In our study, the mean total calcium levels of hypocalcemic patients at both predetermined times periods were significantly lower than the levels of the normocalcemic group. At 6 hours, mean post-operative serum calcium of hypocalcemic patients was 8.1 mg/dl which reduced to 7.4 mg/dl at 24 hours post-operatively. This difference was found to be highly significant (p<0.001). Nemade et al retrospectively analyzed the charts of 150 adults who had undergone total or partial thyroidectomy, and found that the patients who turned out to have prolonged hypocalcemia had significantly lower early levels of serum calcium than did the patients who later developed only transient hypocalcemia (p=0.000002).[23]

It was found from this study that patients who develop hypocalcaemia have a steeper slope of serum calcium in the first 6 hours post-operatively: -0.0158 mg/dl versus -0.026 mg/dl; and in the 24th hour post-operatively: -0.070 mg/dl versus -0.012 mg/dl in patients with hypocalcemia and normocalcemia respectively. A post-operative 6-hour serum calcium slope of -0.075 mg/dl/hour has a sensitivity of 94.4% and a specificity of 96.8% for predicting patients at risk for developing post total thyroidectomy symptomatic hypocalcaemia. A post-operative 24-hour serum calcium slope of -0.023 mg/dl/hour has a sensitivity of 94.4% and a specificity of 91.9% for predicting those patients at risk for developing post total thyroidectomy symptomatic hypocalcaemia.

A study conducted by Leahu et al showed that 96.2% patients with positive calcium trend shows normocalcemic pattern.[24] The same study showed that the patients with negative calcium trend post-thyroid surgeries may go on to develop hypocalcaemia in 51.6% of patients. From this pattern of results, they concluded that patients with positive calcium trend can be discharged earlier without the fear of hypocalcaemia and patients with negative calcium trends should be monitored some more days for hypocalcaemia or at least oral supplementation of calcium started. In a study by Marohn et al serum calcium levels were obtained at 8, 14, and 20 hours.[5] Their results suggest a positive slope was uniformly able to predict normocalcemia in the postoperative period.

Adams et al similarly looked at postoperative calcium levels and slope to predict hypocalcemia.[15] Their retrospective study looked at 2 calcium levels in the first 24 hours after thyroid or parathyroid surgery. They found that a positive slope in non-parathyroid surgeries predicted normocalcemia in all patients. They further examined the level at which hypocalcemia would develop. 36% of patients with an initial negative slope developed hypocalcaemia.

These patients had a much steeper negative slope, almost twice that of normocalcemic patients. In the study by Husein et al standardization of the timing of calcium measurement was attempted to determine whether early postoperative calcium levels could predict normocalcemia or hypocalcemia.[25] The application of the patient care algorithm decreased the hospital stay for these patients to 1.5 days.

Limitations

The relatively small sample size. Study population belongs to the group of patients presented to one institution only; hence the findings can be generalized only after conducting the study on a larger population. The serum total calcium levels were measured instead of ionized calcium which is the active form. Estimation of ionized calcium could change the values and the associations. Patients were followed up only for a few days till they were discharged and not for longer periods and hence the long-term effects are not assessed.

CONCLUSION

In this study, the mean total calcium levels of hypocalcemic patients at both predetermined study times were significantly lower than the levels noted in the normocalcemic group. The study proves that it is possible to predict hypocalcemia on the basis of the early post-operative serum calcium slope. Calculation of the slope is possible from simple biochemical investigations. This slope will certainly enable us to identify at-risk patients early and retain them, while discharging the large majority of patients who are unlikely to develop hypocalcemia. Adoption of this technique can cut down significantly on the cost to the patients as well as eliminate undue utilization of precious healthcare resources.

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