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Original Research Article

Correlation of pre-operative vitamin D3 levels with post-operative hypocalcemia in patients undergoing total thyroidectomy

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ABSTRACT

Background: Total thyroidectomy (TT) is a commonly performed procedure for various thyroid disorders, with parathyroid insufficiency manifesting as hypocalcaemia being a well-known complication. Albeit, vitamin D is well implicated in calcium homeostasis, the association between hypovitaminosis D and postoperative hypocalcaemia is yet to be concluded. The aim of our study is to evaluate the correlation of preoperative serum vitamin D3 levels with occurrence of post-operative hypocalcemia in patients undergoing TT.
Methods: A prospective study was conducted on 50 patients undergoing TT for benign thyroid diseases from November 2016 to May 2018. Pre-operative vitamin D3 levels were estimated. Serum calcium levels was measured pre- and post- operatively at 24hours, 1st week and 4th week. Serum calcium level ≤8.5 mg/dl was considered as biochemical hypocalcemia. A data of demographic, clinical, biochemical and intraoperative findings were documented and analysed.
Results: Statically 14 (28%) patients developed symptomatic hypocalcemia. Out of these, 11 (78.5%) patients had preoperative vitamin D levels of <30 ng/dl (p=0.034). 24 hours postoperative serum calcium level was significantly lesser in patients with lower preoperative vitamin D levels (p=0.015), suggesting that postoperative hypocalcemia (24 hr) is statistically related to pre-operative vitamin D3 levels.
Conclusions: It could be concluded from our study that preoperative serum vitamin D3 levels can predict post-operative occurrence of symptomatic and/or biochemical hypocalcemia. Thus, it could be hypothesized that supplementing vitamin D preoperatively could curb the incidence of hypocalcaemia following TT. However, further relevant trials are needed to attest to this.

Keywords: Postoperative hypocalcemia, Serum vitamin D3, Total thyroidectomy

INTRODUCTION

Total thyroidectomy (TT) is considered to be the definitive management option for thyroid malignancies as well as for benign diseases that warrants surgery. It is a safe procedure besides entailing the expertise of the operating surgeon. Major postoperative complications observed include haemorhage, recurrent laryngeal nerve injury, and parathyroid insufficiency.[1]Parathyroid insufficiency can present either as transient or permanent hypocalcemia.

Hypocalcemia manifests usually with circumoral or digital numbness and paraesthesia, carpopedal spasm, Chvostek sign, Trousseau's sign, laryngeal spasm, cardiac arrythmias. Transient hypocalcemia has been reported in up to 50% of cases, but permanent hypoparathyroidism occurs <2% of the time and most

cases present dramatically 2-5 days after operation but, very rarely, the onset is delayed for 2-3 weeks or if a patient with marked hypocalcemia is asymptomatic.[1,2] Despite being self-limiting in most patients, symptomatic hypocalcemia is of particular concern because of a delay in its manifestation, repeated biochemical testing and the consequent need for prolonged patient hospitalization or readmission.[3-7] Parathyroid insufficiency occurs due to inadvertent removal of the parathyroid glands or infarction through damage to the parathyroid end artery; often, both factors occur together. Vascular injury is probably far more important than inadvertent removal.[1] However, this explanation has been challenged in recent times as hypocalcemia was observed in many instances with no obvious parathyroid injuries and it seemed unlikely that the parathyroid glands could be injured or damaged in almost all thyroidectomies . Many factors are postulated to increase the risk of hypocalcemia, including old age, extent of surgery, thyroid cancers, surgical techniques, concomitant neck dissection, ethnicity, large surgical volumes. Thyroidectomy is widely advocated by many surgeons as an outpatient procedure with several studies establishing safe implementation of ambulatory thyroid surgery.[8-13] After watchful monitoring for bleeding or hematoma in the first 24h, The main discharge-limiting factor thereafter is the development of hypocalcemia. The interest in outpatient and short-stay thyroid surgery makes it especially helpful for surgeons to be able to identify patients at risk of developing hypocalcemia. Vitamin D plays a critical role in calcium homeostasis.[14] Insufficiency in calcium absorption due to low vitamin D concentration leads to an increase in parathyroid hormone (PTH) secretion. Increased PTH stimulates the synthesis of calcitriol and thereby improves calcium absorption efficiency. A wealth of literature emphasize the significance of preoperative Vit D levels to the occurrence of postoperative hypocalcaemia Identifying risk factors can lead, in turn, to a reduction in morbidity and expenditure associated with repeated blood samplings in monitoring the development of hypocalcemia as well as costs associated with prolonged hospitalization.[15,16]

The aim of this study was to determine the correlation between preoperative vit D3 with postoperative hypocalcemia.

METHODS

A prospective study was conducted on 50 patients who underwent total thyroidectomy for benign thyroid disorders in Victoria Hospital affiliated to Bangalore Medical College and Research Institute, Bengaluru from November 2016 to May 2018. Prior Ethical Committee approval was taken and each patient gave an informed written consent before being enrolled in the study.

Patients with benign thyroid disorders was included, posted for TT and patients willing to give informed written consent. Patients with thyroid malignancy, Patients who are undergoing recurrent thyroid surgery, pregnancy, low serum iPTH levels (<10 pg/ml) on post operative day 1, patients with preexisting musculoskeletal disease, other malignancy, lipid metabolism defects, hyperparathyroidism and medications known to affect calcium metabolism, patients with deranged renal function test and patients who did not give informed written consent were excluded from the study.

Preoperatively, serum calcium and vitamin D3 levels of all patients were measured. Postoperatively, serum calcium was measured at 24 hours, 1st and 4th week.

A data of patient demographics, indication for surgery, operative findings, pre- and postoperative biochemical laboratory results and clinical outcomes were collected and analysed. We focused on postoperative calcium concentrations, total length of hospital stay and also on the use of intravenous calcium for the treatment of hypocalcemia and the need for calcium and/or calcitriol supplementation at the time of discharge.

Hypocalcemia was clinically assessed by perioral or digital tingling sensation, facial paresthesia, Chvostek or Trousseau sign, carpopedal spasm or tetany. Meticulous dissection was carried out to ensure not to injure the Parathyroid gland or to compromise its vascular supply. Those who developed symptomatic hypocalcemia were treated accordingly using oral or iv calcium therapy. Patients were followed up with serum calcium levels at the end of 1st week and 4th weeks of postoperative period. The reference range for normal serum calcium was considered as 8.5-10.5 mg/dl. Serum calcium level ≤8.5 mg/dl was considered as biochemical hypocalcemia.

Statistical analysis

The frequency of hypocalcemia was documented as the number and percentage of patients who experienced hypocalcemia. Demographic and Clinical characteristics were expressed as means for continuous variables or proportions for categorical variables. Statistical analysis was performed with SPSS, version 20.0. The p value of less than 0.05 was considered statistically significant.

RESULTS

Data wise 50 patients were subjected to total thyroidectomy for benign disease during the study period. The mean age was 44.96 years with interquartile range of 54.86-35.06 years. Mean serum albumin and serum PTH (post-operative day 1) levels of study group were estimated as 4.264 (g/dl) and 25.97 (pg/ml) respectively (Table 1). Patients were divided into two groups, one with lower pre-operative vit D levels (group A, 25 hydroxy <30 ng/dl, n=8) and other group with normal preoperative vit D levels (group B, 25 hydroxy ≥30 ng/dl, n=42). The mean preoperative vitamin D concentration was 14.8±2.4 ng/ml, in group A and it was 32.0±9.8 ng/ml in group B patients. Mean preoperative serum

calcium levels of the study group were estimated as 9.68 (mg/dl). Mean 24 hour post-operative calcium was 8.68 mg/dl in group A and 9.11 mg/dl in group B.

Table 1: Demographic and clinical data.

Total number cases	50
Age (mean±SD) in years	44.96±9.957
Male/female	14 (28%)/36 (72%)
Mean Hb% (±SD) gm%	12.346±2.0028
Mean serum albumin (±SD) gm/dl	4.264±0.3355
Mean serum PTH (±SD) pg/ml	25.976±10.0409

Table 2: Mean serum calcium levels.

	Group A	Group B	P value
Number of patients	8	42	<0.00001
Mean preoperative Vit D3	14.8±2.4 ng/ml	32.0±9.8 ng/ml	<0.004
Mean preoperative serum calcium	8.68	9.11	<0.0009
Mean postoperative 24 hour serum calcium	7.88	8.22	<0.005

During postoperative course, 14 of 50 (28%) of the study group became symptomatically hypocalceamic, which was statistically significant (p=0.034), 10 of 14 (68.5%) patients who developed symptomatic hypocalcemia had preoperative vitamin D3 levels between 20-30 ng/dl; another 28.5% (4 of 14) had preoperative Vitamin D3 levels <20 ng/dl. In our study, we found that biochemical hypocalcemia at 24 hour postoperative period was significantly associated with lower preoperative vitamin D levels (<30 ng/dl; p=0.015).

Post operatively, 14/50 patients developed hypocalceamic symptoms. This included 11 in group A and 3 in group B (p<0.05) which was statistically significant. The mean 24 hour postoperative calcium in group A was 7.88 mg/dl whereas 8.22 mg/dl in group B, that was significantly lower or normal in group A. No difference was found in the postoperative PTH concentrations (35±29 vs. 30±30 pg/ml, respectively, p=0.69).

No other complication of thyroid surgery was observed apart from hypocalcemia in all the operated patients. Hypocalcemia was the main reason for prolonged length of stay in three out of four patients who had complications in the group A (75%), and in the group B, only one patient had hypocalcemia resulting in prolonged length of stay (33%).

Intravenous calcium therapy for hypocalcemia was required for three patients in group A, but no patient in the group B (p=0.05) received it. If 48 % of the patients required calcium and / or calcitriol supplements at the time of discharge in one group, 30 % of the patients required it in the other group. The total length of hospital stay was significantly longer in the group A as compared with the group B (6.3±2.4 vs 3.2±1.5 days, p=0.03).

DISCUSSION

Transient hypocalcemia is a common complication following total thyroidectomy, occurring in 13-38 % of patients 17 and serum calcium reach lowest level approximately 24 hours postoperatively. Calcitriol increases calcium absorption by promoting expression of calcium binding protein in intestinal cells, thus increasing intestinal calcium transport across the mucosa into the blood.18 Therefore, preoperative calcitriol estimation in patients undergoing thyroidectomy would be expected to predict post-operative hypocalcemia (symptomatic and biochemical).

The aim of this study was to estimate the predictive capacity of pre-operative vitamin D3 with incidence of post thyroidectomy hypocalcemia. In this study, patients in the study group had their serum vitamin D3 levels estimated immediately prior to surgery. The short time-frame allows preoperative prediction of post-operative hypocalcemia to be accomplished without unduly delaying definitive surgical treatment of the underlying thyroid disorder. The low cost and simplicity of pre-operative evaluation in the study encouraged adherence to the pre-operative evaluation.

Significant number of publications strongly embrace the correlation between preoperative Vit D3 and postoperative occurrence of hypocalcemia. Tripathi et al.19 conducted a prospective study where patients were dived into 2 groups based on pre-operative vitamin D3 levels in patients undergoing total thyroidectomy and was found that Pre-operative serum vitamin D levels have got positive correlation with serum calcium levels in early post-operative period. Patients with serum vitamin D levels <20 ng/ml are likely to develop early post-operative hypocalcemia and the difference between pre-operative and post-operative serum calcium levels in vitamin D deficient patients was significant (p<0.001). Therefore, they recommended the early use of Vitamin D in addition to calcium supplement in patients undergoing TT postoperatively.

A retrospective study by Al-khatib et al, evaluated the role of vitamin D deficiency in post-thyroidectomy hypocalcemia in 213 consecutive patients who underwent total and completion thyroidectomies. Patients were grouped into the following categories based on vitamin D

status: severely deficient (<25 nmol/l); deficient (<50 nmol/l); insufficient (<75 nmol/l) and sufficient (≥75 nmol/l). They found that 54% of patients in the severe deficiency group developed hypocalcemia compared to 3.1% of those with sufficient levels.[18]

In an another study by Kirkybot on 166 consecutive total thyroidectomies, significant difference was found in postoperative hypocalcemia rates between those with vitamin D levels >50 nmol/l (>20 ng/ml) and those with a level of <25 nmol/l (<10 ng/ml) and it was also that vitamin D deficiency led to a delay in discharge owing to a higher likelihood of hypocalcemia.[16]

In a meta-analysis of predictors for postoperative hypocalcemia, where in 115 observational studies were included, one of the Independent predictors of transient hypocalcemia was levels of preoperative calcium and preoperative 25-hydroxyvitamin D.[20]

Postoperative hypocalcemia is of considerable complication of thyroid surgery as it serves as only detrimental factor in discharging patients early and is fraught with increase expenditure in view of repeated blood samplings and prolonged hospital stay.

The cost factor was analysed in a study by Niaki, et al and they found that hypocalcemic patients were hospitalized for a longer period of time after neck drain removal (2.5 versus 0.8 days), and hospitalization costs per patient after neck drain removal were higher in this group as well (8,367.35$ versus 2,534.33$). They posit that these additional costs were attributed to the monitoring and treatment of hypocalcemia, as other causes of prolonged hospitalization were excluded. They also point that, the added costs of missed workdays, additional hospital visits, outpatient medication, and outpatient laboratory testing due to hypocalcemia were not accounted for in their estimation but however, these also would account for overall economic costs of hypocalcemia after thyroidectomy.[21]

In this study, it was found that low pre-operative vitamin D3 levels was associated with hypocalcemia (symptomatic and biochemical) that was statistically significant. Those subjects who had preoperative vit.D3 levels <30 ng/dl, were more likely to develop both symptomatic and biochemical hypocalcemia postoperatively. Preoperative vit D3 serves as an important predictor of postoperative hypocalcemia and thus not just reduces the morbidity indeed, reduces hospital stay, missed workdays, apprehension in patients, financial loss due to multiple blood samplings and prolonged stay in the hospital.

CONCLUSION

Preoperative serum vitamin D3 estimation seems to predict significantly postoperative occurrence of symptomatic and/or biochemical hypocalcemia following TT. Thus necessary means to supplement vitamin D, preoperatively can curb the incidence of hypocalcemia following TT, thereby reducing associated morbidity. However, further relevant trials are needed to attest to this.

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