

## Original research article

## To determine the association pre-operative vitamin D3 levels with post-operative hypocalcemia in patients undergoing total thyroidectomy

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### Abstract

**Aim:** to determine the association pre-operative vitamin D3 levels with post-operative hypocalcemia in patients undergoing total thyroidectomy.

**Material and methods:** A Prospective study was conducted in the Department of General Surgery, Patna Medical College and Hospital, Patna, Bihar, India for 17 months. Total 80 patients who underwent total thyroidectomy for benign thyroid disorders were included for this 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. 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.

**Results:** 80 patients were subjected to total thyroidectomy for benign disease. The mean age was 45.77 years with interquartile range of 53.68-34.89 years. Mean serum albumin and serum PTH (post-operative day 1) levels of study group were estimated as 4.31 (g/dl) and 26.39 (pg/ml) respectively. Patients were divided into two groups, one with lower pre-operative vit D levels (group A, 25 hydroxy <30 ng/dl, n=20) and other group with normal preoperative vit D levels (group B, 25 hydroxy ≥30 ng/dl, n=60). The mean preoperative vitamin D concentration was 15.27±3.2 ng/ml, in group A and it was 33.65±10.88 ng/ml in group B patients. Mean preoperative serum calcium levels of the study group were estimated as 7.89 (mg/dl). Mean 24 hour post-operative calcium was 8.06 mg/dl in group A and 8.74 mg/dl in group B. During postoperative course, 24 of 80 (30%) of the study group became symptomatically hypocalcemic, which was statistically significant (p=0.034), 18 of 24 (75%) patients who developed symptomatic hypocalcemia had preoperative vitamin D3 levels between 20-30 ng/dl; another 25% (6 of 24) had preoperative Vitamin D3 levels <20 ng/dl. Post operatively, 24/80 patients developed hypocalcemic symptoms. This included 18 in group A and 6 in group B (p<0.05) which was statistically significant. The mean 24 hour postoperative calcium in group A was 8.06 mg/dl whereas 8.74 mg/dl in group B, that was significantly lower or normal in group A. No difference was found in the postoperative PTH concentrations (34±32 vs. 31±44 pg/ml, respectively, p=0.72). The total length of hospital stay was significantly longer in the group A as compared with the group B (6.7±2.5 vs 3.4±1.7 days, p=0.02).

**Conclusion:** the 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.

**Keywords:** Postoperative hypocalcemia, Serum vitamin D3, Total thyroidectomy

### Introduction

Temporary hypocalcemia is a common event following total thyroidectomy and has been reported in up to 35% of patients.<sup>1</sup> Until the recent publication of national audits from Sweden and the United Kingdom<sup>2</sup>, the incidence of temporary hypocalcemia and permanent hypoparathyroidism reported by specialist centers has underestimated the true incidence following total thyroidectomy. In fact, post thyroidectomy hypocalcemia affects 27% of patients following total thyroidectomy in the United Kingdom. Permanent hypoparathyroidism in the United Kingdom is also far higher than the 2% benchmark frequently quoted for specialist centers.<sup>3-5</sup> Hypocalcemia after thyroidectomy is not without cost as it may lead to a longer postoperative inpatient stay, extra medication, the need for more blood tests, and extra outpatient visits. Many factors are associated with an increased risk of hypocalcemia, including old age and Graves' disease.<sup>6-8</sup> More important are surgical technique, large surgical volume, and the surgeon's experience, which have all been shown to decrease the risk.<sup>6-8</sup> 25-Hydroxycholecalciferol (vitamin D) deficiency has recently been shown to be an independent risk factor for hypocalcemia following total thyroidectomy for benign goiters<sup>7</sup> and is suggested as a risk factor for Graves' disease.<sup>9</sup> Intuitively, prescribing active vitamin D and calcium prophylactically after thyroidectomy reduces the incidence of hypocalcemia, a practice that has been confirmed on more than one occasion.<sup>10-12</sup> It has also been suggested that the combination of calcitriol and hydrochlorothiazide after thyroidectomy reduces the risk of hypocalcemia<sup>13</sup>, as might be expected. The health implications of vitamin D deficiency have become a key area of interest owing to the ubiquitous nature of vitamin D receptors in the body. Vitamin D deficiency has been associated with bone disease, cancer, lipid metabolism defects, diabetes, and heart disease. Reference ranges for normal vitamin D levels and the levels at which pathological correlation can be made differ among the various diseases studied, and those for post thyroidectomy hypocalcemia are unknown.<sup>14</sup> Evidence of the adverse effect of hypovitaminosis D on the outcome after total thyroidectomy is until now unproven. Demonstration of a link between vitamin D deficiency and the risk of postoperative hypocalcemia for all thyroid pathology would provide an inexpensive and easily correctable risk factor that could be addressed before surgery. The aim of this study was to determine the correlation between preoperative vit D3 with postoperative hypocalcemia.

### Material and methods

A Prospective study was conducted in the Department of General Surgery, Patna Medical College and Hospital, Patna, Bihar, India for 17 months. after taking the approval of the protocol review committee and institutional ethics committee. total 80 patients who underwent total thyroidectomy for benign thyroid disorders were included for this study. 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 pre-existing 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 i.v. 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  $\leq 8.5$  mg/dl was considered as biochemical hypocalcemia.

### Results

Data wise 80 patients were subjected to total thyroidectomy for benign disease during the study period. The mean age was 45.77 years with interquartile range of 53.68-34.89 years. Mean serum albumin and serum PTH (post-operative day 1) levels of study group were estimated as 4.31 (g/dl) and 26.39 (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=20) and other group with normal preoperative vit D levels (group B, 25 hydroxy  $\geq 30$  ng/dl, n=60). The mean preoperative vitamin D concentration was  $15.27 \pm 3.2$  ng/ml, in group A and it was  $33.65 \pm 10.88$  ng/ml in group B patients. Mean pre operative serum calcium levels of the study group were estimated at 7.89 (mg/dl). Mean 24 hour post-operative calcium was 8.06 mg/dl in group A and 8.74 mg/dl in group B.

**Table 1: Demographic and clinical profile of patients**

<b>Total number cases</b>	<b>80</b>
Age (mean $\pm$ SD) in years	45.77 $\pm$ 10.22
Male/female	23 (28.75%)/57 (71.25%)
Mean Hb% ( $\pm$ SD) gm%	12.74 $\pm$ 2.21
Mean serum albumin ( $\pm$ SD) gm/dl	4.31 $\pm$ 0.29
Mean serum PTH ( $\pm$ SD) pg/ml	26.39 $\pm$ 11.84

**Table 2: Mean serum calcium levels**

	<b>Group A</b>	<b>Group B</b>	<b>P value</b>
Number of patients	20	60	$<0.00001$
Mean preoperative Vit D3	15.27 $\pm$ 3.2 ng/ml	33.65 $\pm$ 10.88 ng/ml	$<0.003$
Mean preoperative serum calcium	7.89	9.31	$<0.0007$
Mean postoperative 24 hour serum calcium	8.06	8.74	$<0.005$

During postoperative course, 24 of 80 (30%) of the study group became symptomatically hypocalcemic, which was statistically significant ( $p=0.034$ ), 18 of 24 (75%) patients who developed symptomatic hypocalcemia had preoperative vitamin D3 levels between 20-30 ng/dl; another 25% (6 of 24) 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;  $p=0.011$ ).

Post operatively, 24/80 patients developed hypocalcemic symptoms. This included 18 in group A and 6 in group B ( $p<0.05$ ) which was statistically significant. The mean 24 hour postoperative calcium in group A was 8.06 mg/dl whereas 8.74 mg/dl in group B, that was

significantly lower or normal in group A. No difference was found in the postoperative PTH concentrations ( $34\pm 32$  vs.  $31\pm 44$  pg/ml, respectively,  $p=0.72$ ).

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 4 out of 6 patients who had complications in the group A (66.67%), and in the group B, only 2 patient had hypocalcemia resulting in prolonged length of stay (33.33%).

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 50 % of the patients required calcium and / or calcitriol supplements at the time of discharge in one group, 20 % 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 ( $6.7\pm 2.5$  vs  $3.4\pm 1.7$  days,  $p=0.02$ ).

### Discussion

Transient hypocalcemia is a common complication following total thyroidectomy, occurring in 13-38 % of patients<sup>15</sup> 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.<sup>16</sup> 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 embraces the correlation between preoperative Vit D3 and postoperative occurrence of hypocalcemia. Tripathi et al.<sup>17</sup> conducted a prospective study where patients were divided 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.

In our study during postoperative course, 24 of 80 (30%) of the study group became symptomatically hypocalcemic, which was statistically significant ( $p=0.034$ ), 18 of 24 (75%) patients who developed symptomatic hypocalcemia had preoperative vitamin D3 levels between 20-30 ng/dl; another 25% (6 of 24) 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;  $p=0.011$ )

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 ( $\geq 75$  nmol/l). They found that 54% of patients in the severe deficiency group developed hypocalcemia compared to 3.1% of those with sufficient levels.<sup>16</sup>

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.<sup>18</sup>

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.<sup>19</sup>

In this study we found post operatively, 24/80 patients developed hypocalcemic symptoms. This included 18 in group A and 6 in group B ( $p<0.05$ ) which was statistically significant. The mean 24 hour postoperative calcium in group A was 8.06 mg/dl whereas 8.74 mg/dl in group B, that was significantly lower or normal in group A. No difference was found in the postoperative PTH concentrations ( $34\pm 32$  vs.  $31\pm 44$  pg/ml, respectively,  $p=0.72$ ).

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, and these also would account for overall economic costs of hypocalcemia afterthyroidectomy.<sup>20</sup>

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

We concluded that the 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.

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