

Post-Operative Hypocalcemia after given Supplementation pre Operatively in Patients Underwent for Total Thyroidectomy

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ABSTRACT

Objective: To determine the effect of preoperative calcium supplementation on postoperative hypocalcemia among patients having total thyroidectomy.

Study Design: Quasi-experimental study.

Place and Duration of Study: Combined Military Hospital Malir, Pakistan from Oct 2022 to Mar 2023.

Methodology: Patients aged 18 years and above of either gender undergo total thyroidectomy and completion thyroidectomy following hemithyroidectomy were enrolled. Half of the patients received oral calcium supplementation of 500 mg, once a day one week prior to surgery and while the remaining did not receive pre-supplementation. Postoperative hypocalcemia was defined as serum calcium levels lower than 2.2 mmol/L measured 24 hours after surgery.

Results: A significant association of postoperative hypocalcemia was observed in patients with and without preoperative calcium supplementation, i.e., 5(22.7%) and 17(77.3%) respectively (p -value 0.003). Regression analysis showed that after controlling for other covariates, postoperative hypocalcemia was 7.25 times higher among patients without preoperative calcium supplementation (aOR 7.25, 95% CI 2.06 to 25.55), age (aOR 4.27, 95% CI 1.08 to 16.83), and hypertension (aOR 3.75, 95% CI 1.15 to 12.26). A significant difference was observed in the pre-and post-calcium level, i.e., 2.11 ± 0.25 mmol/L vs. 2.32 ± 0.29 mmol/L respectively (p -value <0.001, 95% CI -0.22 to -0.17).

Conclusion: Preoperative calcium supplementation reduces postoperative hypocalcemia in patients having total thyroidectomy.

Keywords: Calcium supplementation, Hypocalcemia, Postoperative Complications, Thyroidectomy.

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INTRODUCTION

Postoperative hypocalcemia is a common complication of total thyroidectomy, as this surgery involves removal of the parathyroid glands which are responsible for regulating calcium level in the body.^{1,2} The incidence of postoperative hypocalcemia varies depending on the extent of thyroid surgery, with rates ranging from 50-68%.³

After a total thyroidectomy, complications may develop that are either anatomical or hormonal.^{4,5} Parathyroid removal, devascularization, and injury, which result in a hypoparathyroidism state may cause post-thyroidectomy hypocalcemia. The parathyroid glands are located at the posterior side of the thyroid gland and can be removed during total thyroidectomy. The parathyroid glands monitor blood calcium levels via the chief or principal cells that release the parathyroid hormone. They are responsible for increasing blood calcium levels via increased

absorption in the gut and kidney and release of calcium stores from the bones.^{6,7} The lack of this hormone and henceforth calcium homeostasis can be deadly leading to tetany and cardiac rhythm anomalies.⁸ Therefore, it is of utmost importance to keep track of calcium to prevent catastrophic events after the thyroidectomy procedure.

Symptoms of postoperative hypocalcemia can include numbness and tingling around the mouth and fingertips, muscle cramps and spasms, and in severe cases, seizures.⁹ Treatment typically involves calcium and vitamin D supplementation, and in some cases, oral or intravenous calcium infusions.¹⁰

The rationale of this study is to investigate the effect of intake of calcium supplementation one week prior to the total thyroidectomy on the magnitude of postoperative hypocalcemia 24 hours after the surgery. Moreover, in this study, the status of postoperative hypocalcemia will assist biochemically in two groups, i.e., that is one who will receive calcium supplementation and other who will not receive calcium supplementation. The finding will help in the

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understanding of the effect of early calcium intervention on postoperative hypocalcemia. In case the effect of this intervention founds to be satisfactory then the same will be suggested for future management of patients with total thyroidectomy.

METHODOLOGY

The quasi-experimental study was conducted at department of Surgery, Tertiary Care Hospital Karachi from Oct 2022 to March 2023. The hospital institutional review committee granted ethical approval, and the patient provided signed informed consent before participating in the study [IERB #100/2023/ERC]. All patients were enrolled via non-probability consecutive sampling technique. Open Epi sample size calculator is used for the estimation of sample size. Two-sided confidence interval was taken as 95%, power as 97%, ratio (unexposed: exposed): 1, reported percentage of hypocalcemia in pre-supplementation group: 1.9%, reported percentage of hypocalcemia in no pre-supplementation group 33.9%.¹¹ The final sample size came out to be 86, i.e., 43 in each group.

Inclusion Criteria: Patients aged 18 years and above of either gender undergoing for total thyroidectomy and completion thyroidectomy following hemithyroidectomy were enrolled.

Exclusion Criteria: Patients who had concurrent lymph node dissection, pre-existing hypocalcaemia, who underwent parathyroid auto-transplantation, and refuse to give consent to participate in the study were excluded.

The flow diagram showing recruitment of patients is shown in Figure. A pre-designed proforma was used to collect the socio-demographic characteristics, clinical characteristics, pre-operative and post-operative laboratory characteristics of the patients. Socio-demographics variables included age and gender of the patients. Clinical characteristics such as preoperative diagnosis, comorbidities, pre-operative serum calcium (in mmol/L) and post-operative serum calcium level in (mmol/L) were observed.

All patients received oral calcium supplementation of 500 mg, once a day one week prior to surgery. Surgical procedure was performed by experienced general surgeons having more than 5 years of experience of thyroidectomy. Serum calcium level was measured before commencing operation and

24 hours after operation. Postoperative hypocalcemia was defined as serum calcium levels lower than 2.2 mmol/L measured 24 h after surgery.

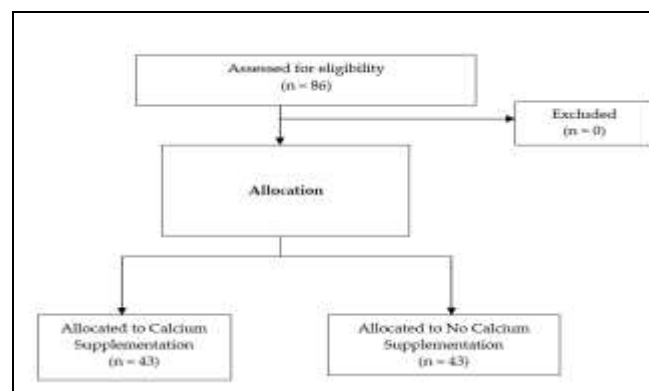


Figure: Patient Flow Diagram

Statistical Package for Social Sciences (SPSS) version 24 was used for statistical analysis. Mean $\pm$ SD was computed for quantitative variables such as age, weight, height, body mass index, pre-operative serum calcium and post-operative serum calcium level. Frequency and percentages were calculated for qualitative variables such as gender, comorbidities, and post-operative hypocalcemia at 24 hours. Mean change in the serum calcium level pre and post operatively was computed using paired-t-test. While mean difference in pre and post calcium level was explored using unpaired t-test. Furthermore, Chi-square/Fisher-Exact test was applied to see the association of post-operative hypocalcemia at 24 hours with pre-calcium supplementation and other predictor variables. The *p*-value of ≤ 0.05 was considered as significant. Binary logistic regression was applied to see the association of hypocalcemia at 24 hours with independent variables. Both univariable and multivariable analysis were applied. All those variables found significant at univariable analysis were included in the multivariable regression analysis.

RESULTS

Of 86 patients, the mean age was 37.30 ± 8.75 years. There were 41(47.7%) males and 45(52.3%) females. The mean height, weight, and BMI of the patients were 159.82 ± 8.98 cm, 75.39 ± 16.09 kg, and 29.41 ± 5.33 kg/m² respectively. There were 51 (59.3%) patients with ≤ 30 kg/m² BMI. Diabetes mellitus was observed in 15(17.4%) and hypertension in 27(31.4%) patients. Pre-operative diagnosis showed that multinodular goiter was observed in 18(20.9%), total

Patients Underwent for Total Thyroidectomy

multinodular goiter in 37(43%), Grave's disease in 23(26.7%), and differentiated thyroid cancer in 8(9.3%) patients. Except preoperative diagnosis (p -value 0.031), a non-significant association of general characteristics were observed in patients with and without preoperative calcium supplementation (Table-I).

Table-I: Characteristics of the Patients with and without Preoperative Calcium Supplementation (n=86)

Variables	Study Groups		p-value
	With Calcium Supplementation (n=43)	Without Calcium Supplementation (n=43)	
	n (%)	n (%)	
Age, years			
≤38	14(41.2)	20(58.8)	0.186
>38	29(55.8)	23(44.2)	
Gender			
Male	24(58.5)	17(41.5)	0.131
Female	19(42.2)	26(57.8)	
BMI, kg/m2			
≤30	28(54.9)	23(45.1)	0.272
>30	15(42.9)	20(57.1)	
Diabetes Mellitus			
Yes	9(60.0)	6(40.0)	0.394
No	34(47.9)	37(52.1)	
Hypertension			
Yes	12(44.4)	15(55.6)	0.486
No	31(52.5)	28(47.5)	
Pre-Operative Diagnosis			
Multinodular Goiter	14(77.8)	4(22.2)	0.031
Total Multinodular Goiter	16(43.2)	21(56.8)	
Grave's Disease	8(34.8)	15(65.2)	
Differentiated Thyroid Cancer	5(62.5)	3(37.5)	

There were 22(25.6%) patients with postoperative hypocalcemia. A significant association of postoperative hypocalcemia was observed in patients with and without preoperative calcium supplementation, i.e., 5(22.7%) and 17(77.3%) respectively (p -value 0.003). Moreover, a significant association of postoperative hypocalcemia was observed with age (p -value 0.018) and hypertension (p -value 0.003) as well. (Table-II) Regression analysis showed that after controlling for other covariates, postoperative hypocalcemia was 7.25 times higher among patients without preoperative calcium supplementation (aOR 7.25, 95% CI 2.06 to 25.55), age (aOR 4.27, 95% CI 1.08 to 16.83), and hypertension (aOR 3.75, 95% CI 1.15 to 12.26) (Table-III).

A significant difference was observed in the pre and post calcium level, i.e., 2.11 ± 0.25 mmol/L vs. 2.32 ± 0.29 mmol/L respectively (p -value <0.001, 95% CI -0.22 to -0.17). Groupwise comparison showed a non-significant difference of pre-operative calcium level in patients with and without preoperative calcium

supplementation, i.e., 2.14 ± 0.15 mmol/L vs 2.09 ± 0.32 mmol/L (p -value 0.366, 95% CI -0.05 to 0.16). However, a significant difference of pre-operative calcium level was observed in patients with and without preoperative calcium supplementation, i.e., 2.41 ± 0.21 mmol/L vs. 2.22 ± 0.34 mmol/L respectively (p -value 0.003, 95% CI 0.06 to 0.31) (Table-IV).

Table-II: Comparison of Hypocalcemia at 24 hours with General Characteristics of the Patients (n=86)

Characteristics of the Patients (n=86)			
Variables	Hypocalcemia at 24 hours		p-value
	Yes (n=22)	No(n=64)	
	n(%)	n(%)	
Age, years			
≤38	4(11.8)	30 (88.2)	0.018
>38	18 (34.6)	34 (65.4)	
Gender			
Male	7 (17.1)	34 (82.9)	0.084
Female	15 (33.3)	30 (66.7)	
Body Mass Index , kg/m2			
≤30	11 (21.6)	40 (78.4)	0.303
>30	11 (31.4)	24 (68.6)	
Diabetes Mellitus			
Yes	6 (40.0)	9 (60.0)	0.159
No	16 (22.5)	55 (77.5)	
Hypertension			
Yes	13 (48.1)	14 (51.9)	0.003
No	9 (15.3)	50 (84.7)	
Pre-Operative Diagnosis			
0.279	0.279	0.279	0.279
0.279	0.279	0.279	
0.279	0.279	0.279	

Table-III: Regression Analysis of factors Associated with Hypocalcemia at 24 Hours (n=86)

	OR (95% CI)	p -value	aOR (95% CI)	p -value
Study Groups				
Without Calcium Supplementation	4.96 (1.63-15.15)	0.005	7.25 (2.06-25.55)	0.002
With Calcium Supplementation	Ref		Ref	-
Age, years				
>38	3.97 (1.21-13.05)	0.023	4.27 (1.08-16.83)	0.038
≤38	Ref		Ref	
Gender				
Male	0.41 (0.15-1.15)	0.089	-	-
Female	Ref		-	-
Body Mass Index , kg/m²				
≤30	0.60 (0.23-1.59)	0.305	-	-
>30	Ref		-	-
Diabetes Mellitus				
Yes	2.29 (0.71-7.40)	0.166	-	-
No	Ref		-	-
Hypertension				
Yes	5.16 (1.83-14.54)	0.002	3.75 (1.15-12.26)	0.029
No	Ref		Ref	
Pre-Operative Diagnosis				
Multinodular Goiter	2.69 (0.26-27.82)	0.406	-	-
Grave's Disease	4.50 (0.47-42.97)	0.191	-	-
Differentiated Thyroid Cancer	Ref		-	-

DISCUSSION

As per the results of the current study, 25.6% of the patients experienced postoperative hypocalcemia. The study findings also revealed a noteworthy association between postoperative hypocalcemia and

both preoperative calcium supplementation and the lack of it in patients.

Table-IV: Mean Difference of Serum Calcium Level Pre and Post Intervention (n=86)

	Mean $\pm$ SD	p-value	95% CI
Pre-post Comparison			
Pre-operative calcium level, mmol/L	2.11 $\pm$ 0.25	<0.001b	-0.22 to -0.17
Post-operative calcium level, mmol/L	2.32 $\pm$ 0.29		
Group-wise Comparison			
Preoperative Calcium level, mmol/L			
With calcium supplementation	2.14 $\pm$ 0.15		-0.05 to 0.16
Without calcium supplementation	2.09 $\pm$ 0.32		
Postoperative Calcium level, mmol/L			
With calcium supplementation	2.41 $\pm$ 0.21	0.003 a	0.06 to 0.31
Without calcium supplementation	2.22 $\pm$ 0.34		

alIndependent t-test applied, bpaired t-test applied, p-value <0.05 considered as significant

aIndependent t-test applied, bpaired t-test applied, p-value <0.05 considered as significant

A recent study has reported 49% incidence of hypocalcemia in the first 24 hours after thyroidectomy, and 63.6% following 48 hours of the surgery.¹² Another study reported overall incidence of hypocalcaemia as 23.6% whereas permanent hypocalcaemia as 1.61%.¹³ The continuous monitoring of hypocalcemia will help with earlier hospital discharge and lesser postoperative complications. Findings from published studies suggested that gender, surgical procedure and perioperative changes in serum calcium are some of the important factors that influence early hypocalcemia development.¹²⁻¹⁴

According to the current study findings, increased age is also one of the contributing factors for postoperative hypocalcemia. There is inconsistency in the findings regarding the relationship between age and the occurrence of postoperative hypocalcemia. In a study conducted by Sousa *et al.*¹⁵ it was found that patients who were over 50 years of age who underwent total thyroidectomy were more likely to experience postoperative hypocalcemia. According to a meta-analysis conducted by Edafe *et al.*, age at the time of surgery did not show a significant correlation with the occurrence of postoperative hypocalcemia.¹⁶ Recently, Alqahtani *et al.* also reported that age has no significant relationship with the occurrence of hypocalcemia.¹⁷ The exact reason behind association of age is not fully understood, but it may.

Be related to age-related changes in calcium metabolism or decreased parathyroid function. Irrespective of the controversial findings, all patients who undergo total thyroidectomy should be closely monitored for postoperative hypocalcemia and managed appropriately to prevent potential complications.

Preoperative calcium supplementation has been studied as a potential prophylactic measure for preventing postoperative hypocalcemia in total thyroidectomy patients. However, it should be noted that the optimal dose and duration of preoperative calcium supplementation are still unclear, and excessive calcium intake may increase the risk of other complications such as hypercalcemia and renal stones. According to Rowe and colleagues, administering high-dose cholecalciferol prior to thyroidectomy did not result in a significant reduction in the overall incidence of hypocalcemia following the procedure.¹⁸ In the current study, oral calcium supplementation of 500 mg, once a day one week prior to surgery. Reducing the incidence of postoperative hypocalcemia is important because it can cause significant morbidity and prolong the hospital stay of patients who have undergone total thyroidectomy. Severe cases of postoperative hypocalcemia can result in muscle spasms, seizures, and even cardiac arrhythmias. In addition, prolonged hypocalcemia can lead to osteoporosis and other long-term complications.^{19,20}

The results of this study should be interpreted in the light of limitation that it was a single- centre study with lack of some important predictor variables such as vitamin D level, magnesium level and parathyroid hormone level. Additionally, due to the constraints of the study time duration, a large number of patients were not included, which may have affected the overall findings. Despite of these limitations, this study is of significance importance as it has prospectively reported findings from Pakistan which was scarce previously. Further large- scale multicentre studies are recommended to preclude the findings of this study.

CONCLUSION

The results of the study showed that preoperative calcium supplementation had a significant effect in reducing the incidence of postoperative hypocalcemia. In addition, the study identified increased age and hypertension as significant risk factors for developing postoperative hypocalcemia.

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Authors Contribution

Following authors have made substantial contributions to the manuscript as under:

MT & IA: Conception, study design, drafting the manuscript, approval of the final version to be published.

NA & SMMZ: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

SWAZ & CK: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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