

## FREQUENCY OF POST-OPERATIVE HYPOCALCAEMIA WITH OR WITHOUT PRE-OPERATIVE CALCIUM SUPPLEMENTATION AFTER TOTAL THYROIDECTOMY IN HYPERTHYROIDISM

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### ABSTRACT

**Background:** Hypocalcemia after thyroid surgery is significant and serious complication with estimates ranging from 0.5% to 75%. While symptomatic hypocalcemia is self-limiting in most cases, it is of special concern owing to a delay in its presentation and the concomitant need for extended hospital stays or re-admission.

**Objective:** To determine the frequency of post-operative hypocalcaemia with and without pre-operative calcium supplementation after total thyroidectomy in hyperthyroidism

**Methods:** A RCT was conducted in West Surgical Ward, Mayo Hospital, Lahore from June 7, 2017 to December 7, 2017. Total 176 patients were included in study. They were randomly allocated into two groups using lottery method. Group-A (treatment group) received Tab calcium carbonate 1gm per orally 8 hourly for two weeks prior to surgery. Group-B (control group) did not receive Tab calcium carbonate before surgery. All the patients underwent total thyroidectomy preserving parathyroid glands performed by same team of surgeons. Symptoms and signs of Hypocalcemia were noted. Using SPSS v24.0 data were entered and analysed. Chi-square test was used to compare proportions between both groups. Age and gender were matched to address the effect modifiers. A p-value  $\leq 0.05$  was labelled as significant.

**Results:** Total 176 patients were enrolled in the research. Patients were broken down into two study groups i.e. Group-A (Treatment) and Group-B (Controls). Group-A included 18(20.5%) males and 70(79.5%) females, while Group-B had 12(13.6%) males and 88(86.4%) females. In group-A, mean age was  $45.0 \pm 15.4$  years and  $44.9 \pm 15.9$  years in group-B. In group-A, 26(29.5%) had hypocalcemia, while 44(50.0%) suffered in group-B, which is statistically significant (p-value=0.006).

**Conclusion:** Incidence and severity of hypocalcemia following total thyroidectomy in hyperthyroidism can be reduced effectively by preoperative oral calcium supplementation given routinely.

**Keywords:** *Calcium, hyperthyroidism, total thyroidectomy, hypocalcemia*

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### INTRODUCTION

Total thyroidectomy is well-known for its complication regarding compromise of parathyroid glands leading to symptomatic transient hypocalcaemia or even possibly permanent hypoparathyroidism.<sup>1</sup>

This potential hazard has always troubled thyroid surgeons and has contributed to improvements in the operating procedure over the course of history, including subtotal thyroidectomy to save parathyroid glands from

disruption and the abandoning the ligation of main trunk of inferior thyroid artery.<sup>2</sup>

With the passage of time understanding of parathyroid glands' blood supply improved greatly, resulting in safe total thyroidectomy (TT) now performed routinely by dividing branches of inferior thyroid artery entering directly into gland's capsule.<sup>3</sup>

In addition to modifications to the surgical procedure, there has been various improvements in clinical practice to avoid symptomatic hypocalcaemia. It includes routine oral calcium supplementation for all patients after total thyroidectomy or targeted calcium and vitamin D supplementation based on levels of parathyroid hormone done postoperatively.<sup>4</sup>

Patients undergoing total thyroidectomy for graves disease have much higher rates of symptomatic

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hypocalcaemia as compared to those undergoing TT for other thyroid disorders.<sup>5</sup>

Various factors contribute to this enhanced risk of hypocalcemia following thyroid surgery in hyperthyroidism including substantial amount of calcitonin being released during surgical manipulation of gland, thyrotoxic osteodystrophy secondarily leading to hungry bones as well as technically more demanding operation due increased friability and inflammation of gland in graves patients and thus contributing to the increased risk of parathyroid gland injury.<sup>6</sup>

It is imperative to minimize the risk of post-operative hypocalcemia as total thyroidectomy is now the procedure of choice for the surgical treatment of graves disease and toxic nodular goiter.<sup>7</sup> Supplementing calcium pre-operatively in the patients of hyperthyroidism has been proposed by some authors, however how this proposed clinical practice influences the outcome has not been reported yet.<sup>8</sup>

In a study, it was concluded that, the incidence of symptomatic and laboratory hypocalcaemia decreased in the treatment cohort receiving the supplemental calcium as compared to the control group not receiving the supplemental calcium: 24% versus 44%.<sup>9</sup>

Thus the aim of our study was to find the frequency of post-operative hypocalcaemia either with or without calcium supplementation in patients of hyperthyroidism to incorporate evidence into the knowledge base. In Pakistan, there is dearth of published literature related to this query and no prior study is available on this topic till now.

## METHODS

With IRB approval, a randomized controlled trial was conducted in West Surgical Ward of Mayo Hospital, Lahore from June 7, 2017 to December 7, 2017 using non-probability consecutive sampling technique. The estimated sample size was of 176(88 in each group) using 95% confidence interval and 80% power of study with an expected incidence of post-operative hypocalcaemia with calcium supplementation 24% and without calcium supplementation 44%.<sup>9</sup>

The study population included patients of both gender aged between 20-70 suffering from hyperthyroidism with diffuse and/or nodular goiter controlled on medications (anti-thyroid drugs and beta blockers) and patients with recurrent toxic goiter. While the patients with concomitant parathyroid disease, history of extensive lymph node dissection because of thyroid malignancy, patients with corrected serum calcium <8 mg/dl prior to study, history of using calcium supplementation for any chronic disease before the

operation and known cases of abnormal renal function and hypoalbuminemia were excluded from the study.

A total of 176 patients meeting the inclusion criteria were admitted from Department of General Surgery at Mayo Hospital. Before inclusion in the study, informed consent was taken from all patients. It was approved by the institutional review board(IRB) of KEMU. Lottery method was used to randomly allocate patients in both groups. Group-A (treatment group) received Tab calcium carbonate 1gm per orally 8 hourly for two weeks prior to surgery. Group-B (control group) did not receive Tab calcium carbonate before surgery. All the patients underwent total thyroidectomy preserving parathyroid glands performed by same team of surgeons. All patients were given lugol's iodine 10 drops three times a day for 10 days immediately before the surgery.

Symptoms and signs of Hypocalcemia were noted in all cases. Serum calcium was measured at day of surgery, post-operative day-1 and 1-2 weeks after surgery. All patients were given routine oral calcium supplementation post operatively and those developing symptomatic hypocalcaemia were treated with IV calcium therapy until serum calcium was normalized. All the data were collected through a pre-designed proforma.

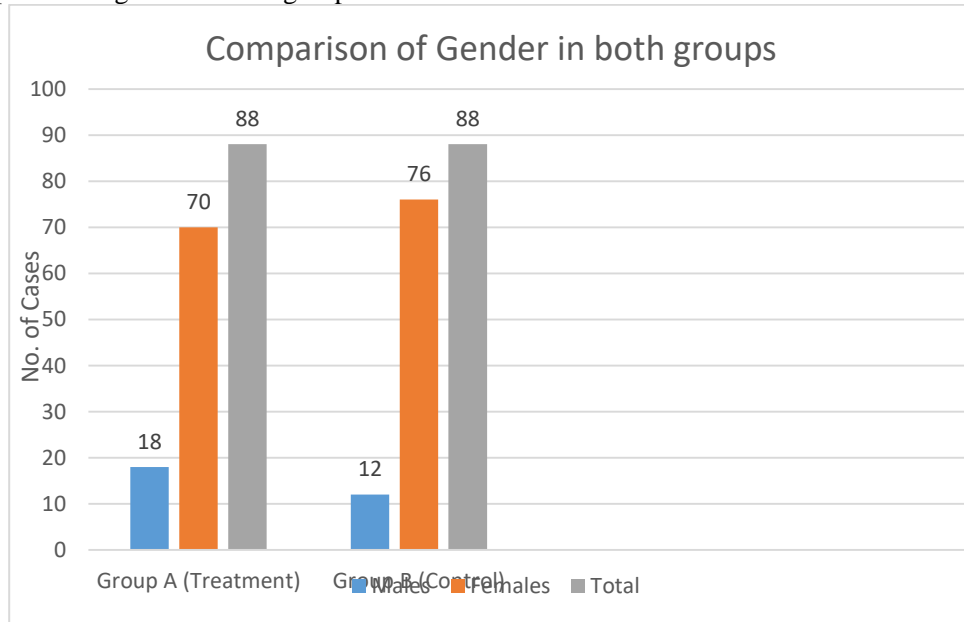
Using SPSS v24.0, data were entered and analyzed. Frequencies and percentages were used for qualitative data like Gender, sign & symptoms and Hypocalcaemia. Quantitative data like Age and serum calcium were presented by using Mean±S.D. Chi-square test was used to compare proportions between both groups. Age and gender were matched to address the effect modifiers. A p-value of ≤0.05 was labelled as significant.

## RESULTS

A total of 176 patients were enrolled for this study. Patients were divided into two groups i.e. Group-A (Treatment) and Group-B (Controls). In group-A, there were 18(20.5%) males and 70(79.5%) females, while in group-B, there were 12(13.6%) males and 76(86.4%) females (**Figure.1**). In group-A, 36(40.9%) patients were in 20-35 years age group, while 22(25.0%) and 30(34.1%) were in 36-50 and >50 years age groups respectively. In group-B, 38(43.2%) patients were in 20-35 years age group, while 19(21.6%) and 31(35.2%) were in 36-50 and >50 years age groups respectively (**Table.1**). In group-A, mean age was 45.0±15.4 years and 44.9±15.9 years in group-B. Mean serum calcium in group-A was 8.5±1.1 and 8.1±0.7 in group-B. In group-A, 26(29.5%) had numbness and 37(42.0%) in group-B. In group-A, 22(25.0%) had tingling and 36(40.9%) in group-B. In group-A, 10(11.4%) had tetany and 37(42.0%) in group-B. In group-A, 18(20.5%) had trousseau's sign and 35(39.8%) in group-B. In group-A,

16(18.2%) had chvostek's sign and 37(42.0%) in group-B(Table.2). In group-A, 26(29.5%) had hypocalcemia, while 44(50.0%) in group-B, which is statistically significant with a p-value of 0.006(Table.3).

**Figure1:** Comparison of gender in both groups



**Table 1:** Comparison of age in both groups

Age groups	Groups		Total
	Treatment	Controls	
20-35 years	36	38	61
	40.9%	43.2%	34.7%
36-50 years	22	19	41
	25.0%	21.6%	23.3%
>50 years	30	31	74
	34.1%	35.2%	42.0%
<b>Total</b>	88	88	176
	100.0%	100.0%	100.0%

**Table 2:** Comparison of Clinical Signs & Symptoms of Hypocalcemia in both groups

Clinical Signs & Symptoms of Hypocalcemia		Groups		Total
		Treatment	Controls	
Numbness	Yes	26	37	63
		29.5%	42.0%	35.8%
	No	62	51	113
		70.5%	58.0%	64.2%
<b>Total</b>		88	88	176
		100.0%	100.0%	100.0%
Tingling	Yes	22	36	58
		25.0%	40.9%	33.0%
	No	66	52	118
		75.0%	59.1%	67.0%
<b>Total</b>		88	88	176
		100.0%	100.0%	100.0%

<b>Tetany</b>	Yes	10	37	47
		11.4%	42.0%	26.7%
	No	78	51	129
		88.6%	58.0%	73.3%
<b>Total</b>	88	88	176	
	100.0%	100.0%	100.0%	
<b>Trousseau sign</b>	Yes	18	35	53
		20.5%	39.8%	30.1%
	No	70	53	123
		79.5%	60.2%	69.9%
<b>Total</b>	88	88	176	
	100.0%	100.0%	100.0%	
<b>Chvostek sign</b>	Yes	16	37	53
		18.2%	42.0%	30.1%
	No	72	51	123
		81.8%	58.0%	69.9%
<b>Total</b>	88	88	176	
	100.0%	100.0%	100.0%	

**Table 3:** Comparison of Hypocalcemia in both groups

<b>Hypocalcemia</b>	<b>Groups</b>		<b>Total</b>	<b>p-value</b>
	Treatment	Controls		
Yes	26	44	70	0.006
	29.5%	50.0%	39.8%	
No	62	44	106	
	70.5%	50.0%	60.2%	
<b>Total</b>	88	88	176	
	100.0%	100.0%	100.0%	

**Table 4:** Stratification of Hypocalcemia in both groups with respect to gender

<b>Gender</b>	<b>Hypocalcemia</b>	<b>Groups</b>		<b>Total</b>	<b>p-value</b>
		Treatment	Controls		
Male	Yes	2	6	8	0.018
		11.1%	50.0%	26.7%	
	No	16	6	22	
		88.9%	50.0%	73.3%	
<b>Total</b>	18	12	30		
	100.0%	100.0%	100.0%		
Female	Yes	24	38	62	0.055
		34.3%	50.0%	42.5%	
	No	46	38	84	
		65.7%	50.0%	57.5%	
<b>Total</b>	70	76	146		
	100.0%	100.0%	100.0%		

**Table 5:** Stratification of Hypocalcemia in both groups with respect to age

Age groups	Hypocalcemia	Groups		Total	p-value
		Treatment	Controls		
20-35 years	Yes	7	18	25	0.011
		19.4%	47.4%	33.8%	
	No	29	20	49	
		80.6%	52.6%	66.2%	
Total	36	38	74		
	100.0%	100.0%	100.0%		
36-50 years	Yes	9	10	19	0.453
		40.9%	52.6%	46.3%	
	No	13	9	22	
		59.1%	47.4%	53.7%	
Total	22	19	41		
	100.0%	100.0%	100.0%		
>50 years	Yes	10	16	26	0.149
		33.3%	51.6%	42.6%	
	No	20	15	35	
		66.7%	48.4%	57.4%	
Total	30	31	61		
	100.0%	100.0%	100.0%		

**DISCUSSION**

Advancement in operative surgery technique has resulted in significant reduction in severe post-operative complications following surgical treatment of thyroid, such as recurrent laryngeal nerve injury and post-operative hypocalcemia, and surgeons are evaluating whether single day stay in hospital after total thyroidectomy would be feasible.<sup>10</sup>

Short hospital stay is limited by presentation of severe hypocalcemia after thyroid surgery, as a significant number of patients may develop tetany after going home following early discharge. Identifying perioperative risk factors associated with an increased risk of tetany following thyroid surgery is imperative for selecting patient for safe early discharge.<sup>11</sup>

Hypocalcemia can cause serious complications and require close monitoring of the patient and intravenous calcium infusion along with oral supplementation to alleviate the clinical symptoms. Hypocalcemic symptoms usually occur in the first 24 to 48 hours after total thyroidectomy.<sup>12</sup>

This report presents the first evidence of preoperative calcium supplementation for patients undergoing total thyroidectomy (TT) for hyperthyroidism, and shows its effectiveness in reducing postoperative hypocalcemia. Although this approach has been suggested by other authors, no one has recorded specific patient outcomes.<sup>13</sup>

In a study, it was concluded that, the incidence of symptomatic and laboratory hypocalcaemia decreased in

the treatment cohort receiving the supplemental calcium as compared to the control group not receiving the supplemental calcium: 24% versus 44%.<sup>9</sup> Similarly our study demonstrated significantly reduced rates of hypocalcemia in group receiving preoperative oral calcium for two weeks prior to surgery as compared to group not receiving any calcium supplementation i.e. 29.5% versus 50.0% which is statistically significant with a p-value of 0.006. Also our study reported reduced rates of tetany and other hypocalcemic signs & symptoms in treatment group.

Hypocalcemia following total thyroidectomy in hyperthyroid patients has multifactorial etiology irrespective of parathyroid function. Serum thyroxine has a directly activates osteoclasts, which results in increased bone turn over. This, in turn, leads to increased serum osteocalcin, serum alkaline phosphatase, urinary deoxyypyridinoline, and urinary calcium.<sup>13,14</sup>

Increased bone metabolism due high thyroid hormones levels and subsequent loss of calcium in urine leads to thyrotoxic osteodystrophy resulting in depleted calcium stores of whole body. Thus, preoperative calcium supplementaion helps in restoration of whole body calcium stores. While addressing this contributing factor with preoperative calcium supplementation, patients undergoing TT for hyperthyroidism demonstrates similar rates of hypocalcemia as compared to patients undergoing TT for other thyroid disorders.<sup>13,15</sup>

Although concomitant vitamin D deficiency place patients at enhanced risk for developing hypocalcemic symptoms or tetany following total thyroidectomy in

hyperthyroidism as has been demonstrated by previous authors, though there is no evidence that this deficiency is caused fundamentally by the hyperthyroidism.<sup>16</sup>

Finally, it was also postulated that calcitonin is released abnormally during the manipulation of the gland during surgery.<sup>17</sup> While serum calcitonin, osteocalcin, alkaline phosphatase or urinary deoxythymidine and calcium were not evaluated in this study, the similar post-operative PTH levels favor these alternative explanations.

Damage to parathyroid gland during total thyroidectomy due to its location near gland capsule and its shared blood supply from inferior thyroid artery still contributes to hypocalcemia following this operation for any diagnosis. For all diagnoses, the literature reports hypocalcemia rates ranging from 6 to 72 per cent after total thyroidectomy.<sup>14,18,19</sup>

The wide range in reported transient hypocalcemia rates is due, in part, to study-to-study variability in definition. Recurrent goiter, thyroid resection extent, Graves' disease, female gender and hospital volume are the additional factors identified as placing patients at enhanced risk of transient/permanent hypocalcemia following thyroid surgery.<sup>18</sup>

Ligation of the main trunk of inferior thyroid artery compromises the blood supply of parathyroid gland resulting in much increased rates of hypoparathyroidism, as reported by Thomusch et al in another study.<sup>20</sup>

Total thyroidectomy, radioactive iodine ablation (RAI), and anti-thyroid drugs are listed as the "three effective and relative safe initial treatment options" for patients diagnosed with Graves' disease according to ATA guidelines for the management of hyperthyroidism.<sup>21</sup>

Given this recommendation, a recent report of three leading global endocrinology organizations membership showed that surgery as first-line treatment is used worldwide only 0.7 percent of the time, and in the United States only 0.9 percent of cases.<sup>22</sup>

## CONCLUSION

To conclude, routinely administering supplemental oral calcium in the immediate preoperative period for two weeks is effective in reducing the incidence and severity of signs & symptoms of hypocalcemia following total thyroidectomy in hyperthyroidism.

## ETHICAL APPROVAL

Ethics committee approval for the study was received from the King Edward Medical University (No. 437/RC/KEMC, 04/07/2020)

## AUTHORS' CONTRIBUTION:

**MAS:** Concept & Design, Data Collection & Analysis, Editing, Proof reading

**AS, SM, HMA, SHB, GA :** Substantial contribution to conception and design, Acquisition of data, drafting of article, Approval of the version

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