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ASSOCIATION OF PREOPERATIVE CALCIUM AND CALCITRIOL THERAPY WITH POSTOPERATIVE HYPOCALCEMIA IN PATIENTS UNDERGOING NEAR TOTAL THYROIDECTOMY, A RANDOMIZED CONTROLLED TRIAL

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Abstract

Background: *Postoperative hypocalcemia is a common and potentially serious complication following near-total thyroidectomy, primarily due to parathyroid gland trauma or devascularization. Although the prophylactic use of calcium and calcitriol has shown promise in total thyroidectomy, limited evidence exists regarding its utility in near-total procedures.*

Methods: *This randomized controlled trial was conducted at Holy Family Hospital, Rawalpindi, Pakistan, over six months. A total of 110 adult patients scheduled for near-total thyroidectomy were randomized into two groups: Group A (n=55) received oral calcium carbonate (1000 mg every 8 hours) and calcitriol (0.5 µg every 12 hours) for five days preoperatively, while Group B (n=55) received no supplementation. Postoperative serum calcium levels, intravenous calcium requirement, length of hospital stay, and clinical signs of hypocalcemia were recorded. Statistical analysis was conducted using SPSS v26, with $p < 0.05$ considered significant.*

Results: *Transient hypocalcemia occurred significantly less frequently in the intervention group (12.7%) than in the control group (36.4%) ($p = 0.004$). The need for intravenous calcium was also reduced in Group A (5.5%) compared to Group B (25.5%) ($p = 0.006$). Fewer patients in Group A required hospitalization longer than two days (7.3% vs. 29.1%, $p = 0.003$). Age ≥45 years, presence of cardio-metabolic comorbidities, and failure to preserve at least two parathyroid glands were found to be significant predictors of postoperative hypocalcemia, with parathyroid preservation emerging as the strongest risk factor (OR ≈ 19, $p < 0.000001$).*

Conclusion: *Preoperative supplementation with calcium and calcitriol significantly reduces the risk of transient hypocalcemia following near-total thyroidectomy. Surgical preservation of at least two parathyroid glands is critical in minimizing hypocalcemia risk. These findings support the adoption of routine prophylactic supplementation protocols in high-risk thyroidectomy patients.*

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INTRODUCTION

Near-total thyroidectomy, the commonly recommended procedure for thyroid disorders, involves removing nearly the entire thyroid gland while preserving a small remnant (~1 g) to maintain parathyroid function and reduce the risk of nerve injury (1). Post-thyroidectomy hypocalcemia, a common complication caused by parathyroid gland trauma or devascularization, results in reduced parathyroid hormone secretion, impaired conversion of vitamin D to calcitriol, decreased intestinal calcium absorption, and subsequent neuromuscular symptoms such as numbness, cramps, and seizures]. Bone resorption can also decrease if PTH is low, further reducing calcium levels (2). Additional contributing factors include vitamin D deficiency, decreased preoperative calcium reserves, and extensive neck dissection or removal of central compartment lymph nodes (3). Hypocalcemia can be defined either by biochemical analysis (serum calcium level<8mg/dl) or by the clinical scenario (4). Hypocalcemia commonly presents with neuromuscular symptoms such as perioral numbness, tingling in the extremities, muscle cramps, carpopedal spasms, tetany, and, in severe cases, laryngospasm. Hypocalcemia may also present with Chvostek's sign (facial muscle twitching with facial nerve tap) and Trousseau's sign (carpal spasm with BP cuff inflation), along with cardiovascular effects like prolonged QT interval, hypotension, arrhythmias, and rarely heart failure. CNS symptoms can include irritability, confusion, and seizures, while chronic hypocalcemia may cause bone resorption, rickets, osteomalacia, and dermatologic changes such as dry skin, brittle nails, and eczema-like rashes (5). Hypocalcemia is classified as transient or permanent based on duration; transient hypocalcemia occurs 24–48 hours post-surgery and resolves within six months, often due to temporary parathyroid dysfunction, while permanent hypocalcemia persists beyond six months due to irreversible hypoparathyroidism (6). It is estimated that 49% of patients undergoing near total thyroidectomy develop postoperative hypocalcemia (7). Studies have shown the effectiveness of routine use of calcium and vitamin D supplements in reducing the incidence of postoperative hypocalcemia after total thyroidectomy7–9 as well as in decreasing the length of postoperative hospitalization (8). .A study conducted by Sittitrai & colleagues compared the efficacy of perioperative versus postoperative calcium and vitamin D supplementation to prevent symptomatic hypocalcemia after total thyroidectomy and demonstrated that preoperative supplementation significantly reduces the risk of hypocalcemia (9). A similar study conducted in Pakistan concluded that preoperative administration of Vitamin D and Calcium reduces postoperative transient hypocalcemia after total thyroidectomy, with 6.5 % of those receiving the supplementation developing hypocalcemia against 26.1% of those who did not receive it (10).

While the prophylactic use of preoperative calcium and calcitriol has been studied in total thyroidectomy patients, limited research explores its impact in near-total thyroidectomy. This study therefore, seeks to investigate whether preoperative calcium and calcitriol supplementation can reduce the risk of postoperative hypocalcemia in patients undergoing near-total thyroidectomy, potentially improving.

Methodology;

Study Design

This was a randomized controlled trial designed to evaluate the effect of preoperative calcium and calcitriol supplementation on the incidence of postoperative hypocalcemia in patients undergoing near-total thyroidectomy.

Study Setting

The study was conducted in the Department of General Surgery Unit 1at Holy Family Hospital, a tertiary care hospital in Rawalpindi, Pakistan.

Study Population

The study included adult patients undergoing near-total thyroidectomy for benign thyroid conditions, with normal baseline serum calcium levels.

Study Duration

Data were collected over a six-month period.

Sample Size

A total sample size of 110 patients (55 in each group) was calculated using G*Power version 3.1, based on an alpha error of 5% ($\alpha = 0.05$), study power of 80%

Frontier in Medical & Health Research

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(1–β = 0.80), and an anticipated effect size of 0.53 (11).

Ethical Approval

Ethical approval was obtained from the Ethical Review Board of Rawalpindi Medical University. Reference letter no. 66/SU-I/HFH.

Sampling Technique

Participants were selected using a random sampling technique.

Randomization

Each participant was assigned a unique number, and a lottery method was used to randomly allocate them into either the intervention group (Group A) or the control group (Group B).

Blinding

Although full blinding was not feasible due to the nature of the intervention, efforts were made to reduce bias by standardizing surgical and postoperative procedures across both groups. Surgeons and outcome assessors were not informed of group allocation at the time of surgery and early outcome documentation.

Inclusion Criteria

- Adults aged 18–60 years.
- Scheduled for near-total thyroidectomy.
- Normal preoperative serum calcium levels.
- Provided informed consent.

Exclusion Criteria

- Pre-existing hypocalcemia.
- Vitamin D deficiency or parathyroid disorders.
- Chronic kidney disease.
- History of prior neck surgery.
- Use of calcium or vitamin D supplementation within the past 3 months.

Data Collection Tool

A structured Performa was used to collect data on patient demographics, comorbidities, surgical details, and calcium-related biochemical markers. Clinical evaluations included signs and symptoms of hypocalcemia, while laboratory measurements included serum calcium levels at predefined intervals.

Intervention

Participants were divided into two groups:

Group A (Intervention Group): Patients received oral calcium carbonate 1000 mg every 8 hours and calcitriol 0.5 µg every 12 hours, starting five days before surgery.

Group B (Control Group): Patients received no preoperative supplementation.

All participants underwent a standardized pre-anesthetic assessment and near-total thyroidectomy performed by experienced consultant surgeons. Postoperative serum calcium levels were assessed 24 hours after surgery. Intravenous calcium was administered if serum calcium levels fell below 8.0 mg/dL. Patients were monitored for clinical signs of hypocalcemia, length of hospital stay, and recovery progress. Follow-up was conducted over a period of three months. At each follow-up visit, serum calcium levels and symptoms of hypocalcemia were assessed to determine whether the hypocalcemia was transient or had become permanent.

Data Analysis Procedure

Data were entered in Microsoft Excel and analyzed using SPSS version 26. Categorical variables were summarized as frequencies and percentages, while continuous variables such as age were reported as mean ± standard deviation (SD). The normality of age distribution was assessed using the Shapiro–Wilk test, and since the data were approximately normally distributed, an independent-samples t-test was used to compare mean age between Group A and Group B. Categorical variables including sex, transient hypocalcaemia, length of hospital stay greater than two days, age group (<45 vs ≥45 years), presence of cardio-metabolic co-morbidities (diabetes mellitus, hypertension, and ischemic heart disease), and parathyroid preservation status (≥2 glands vs <2 glands preserved) were analyzed using the Pearson Chi-square test. In cases where the expected cell count was less than 5—specifically for variables such as severe hypocalcaemia (serum calcium < 7.5 mg/dL) and intravenous calcium requirement—the Fisher's exact test was applied for more accurate results. All patients were biochemically sufficient in

Frontier in Medical & Health Research

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terms of pre-operative calcium, phosphate, vitamin D, and parathyroid hormone levels; therefore, no between-group statistical comparisons were conducted for these variables.

Results;

Incidence of Post-operative Hypocalcaemia;

Out of 110 patients, 55 were assigned to the intervention group (Group A) and 55 to the control group (Group B). Transient hypocalcemia occurred in 12.7% of patients in Group A compared to 36.4% in Group B, which was statistically significant (p = 0.004). Similarly, the need for intravenous calcium was significantly lower in the intervention group (5.5%) compared to the control group (25.5%; p = 0.006). The length of hospital stay beyond two days was more frequent in the control group (29.1%) than in the intervention group (7.3%; p = 0.003) as shown in table 1.

Table 1;

Comparison of Post-Thyroidectomy Hypocalcaemia Outcomes Between Group A (intervention) and Group B (control), With Statistical Tests Applied (Independent-Samples t-Test, Pearson χ^2 Test, or Fisher Exact Test as Appropriate)

Variable	Group A (n = 55)	Group B (n = 55)	p-value
Mean Age (years)	42.5 ± 10.1	43.2 ± 9.5	0.67
Female (%)	45 (81.8%)	47 (85.5%)	0.60
Transient hypocalcemia	7 (12.7%)	20 (36.4%)	0.004
Severe hypocalcemia (<7.5)	1 (1.8%)	6 (10.9%)	0.05
IV calcium required	3 (5.5%)	14 (25.5%)	0.006
Length of stay >2 days	4 (7.3%)	16 (29.1%)	0.003

Factors Associated with the Development of Post-Operative Hypocalcaemia

Biochemical markers;

Pre-operative levels of serum calcium, serum phosphate, vitamin D and PTH were measured to evaluate how these biochemical markers affects calcium metabolism postoperatively. All 110 patients (group A+ group B) had sufficient levels of all these biochemical markers. Despite that, 34 (30.9%)patients, 8 from group A and 26 from group B develop postoperative hypocalcemia and 76 patients' were fine. As all patients had normal pre-operative serum concentrations of these biomarkers, therefore no between-level comparison was possible.

Demographic Characteristics;

Patients' age and gender also affected the development of hypocalcemia post-operative as shown in table 2. Patients were divided into two age groups <45 and >45 and similarly two genders male and female. Patients aged ≥ 45 years were significantly more likely to develop post-operative hypocalcaemia compared to those aged < 45 years, with an estimated odds ratio (OR) of approximately 6.2. This indicates that older patients had over six times the odds of experiencing hypocalcaemia following thyroid surgery, a statistically significant association (p < 0.001), highlighting age as a strong risk factor. In contrast, no statistically significant difference was observed based on patient gender. Although more females were represented overall, the incidence of hypocalcaemia did not differ significantly between males and females (p = 1.000), suggesting that gender alone did not independently influence the risk of developing post-operative hypocalcaemia in this cohort.

Table 2; Distribution of Age, Sex, Cardio-metabolic Comorbidities, and Parathyroid-Gland Preservation According to Post-operative Hypocalcaemia Status in Group A and Group B

Frontier in Medical & Health Research

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Variables	Group A				Group B			
	Post-op hypocalcemia (n=8)		No post-op hypocalcemia (n= 47)		Post-op hypocalcemia (n=26)		No post-op hypocalcemia (n=29)	
Age	<45	>45	<45	>45	<45	>45	<45	>45
	2	6	28	19	6	20	22	7
Gender	Female	Male	Female	Male	Female	Male	Female	Male
	6	2	39	8	22	4	25	4
Comorbids	Yes	No	Yes	No	Yes	No	Yes	No
	3	5	7	40	10	16	2	27
Parathyroid preservation	Yes	No	Yes	No	Yes	No	Yes	No
	3	5	39	8	4	22	24	5

Co-Morbidities;

The presence of at least one of the specified co-morbidities—namely diabetes mellitus, hypertension, or ischemic heart disease—was significantly associated with an increased risk of developing post-operative hypocalcaemia as shown in table 1. Among patients who developed hypocalcaemia, a higher proportion had one or more of these co-morbid conditions compared to those who maintained normal calcium levels post-surgery. Statistical analysis using the Chi-square test yielded a p-value of 0.003, indicating a significant association. The estimated odds ratio (OR) was approximately 3.6, suggesting that patients with any of these co-morbidities were more than three times as likely to experience hypocalcaemia after thyroidectomy compared to those without. These findings underscore the importance of identifying and monitoring high-risk patients with underlying cardio-metabolic disorders in the perioperative period.

Intra operative factors;

One relevant factor was considered that was preservation of parathyroid gland. Failure to preserve at least two parathyroid glands during thyroidectomy emerged as the strongest independent predictor of post-operative hypocalcaemia as shown in table 2. Among patients who developed hypocalcaemia, the majority had fewer than two parathyroid glands preserved in situ, whereas those who retained two or more glands were significantly less likely to experience calcium imbalance. Statistical analysis revealed a highly significant association ($p < 0.000001$), with an estimated odds ratio of approximately 19. This indicates that patients with inadequate parathyroid preservation were nearly 19 times more likely to develop post-operative hypocalcaemia compared to those with sufficient gland preservation. This finding reinforces the critical role of meticulous surgical technique in identifying, preserving, and maintaining the vascular integrity of parathyroid tissue during thyroid surgery. It also highlights the necessity of intraoperative strategies aimed at minimizing parathyroid trauma or inadvertent excision, which directly impacts patient outcomes.

Discussion;

This randomized controlled trial demonstrates that pre-operative supplementation with oral calcium carbonate and calcitriol significantly reduces the incidence of post-operative hypocalcaemia in patients undergoing near-total thyroidectomy. The intervention group showed a 23.7% absolute reduction in transient hypocalcaemia, along with a significant decrease in the need for intravenous calcium and prolonged hospitalization. Independent predictors of hypocalcaemia included age ≥ 45 years, presence of cardio-metabolic co-morbidities, and failure to preserve at least two parathyroid glands in situ—each demonstrating a statistically significant association with the outcome. Notably, parathyroid

Frontier in Medical & Health Research

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preservation had the most profound impact, with a nearly 19-fold increased risk when fewer than two glands were preserved. In contrast, gender and sufficient preoperative biochemical markers did not significantly influence hypocalcaemia risk.

Our findings align with several international studies demonstrating the effectiveness of calcium and vitamin D supplementation in reducing hypocalcaemia after thyroidectomy (11, 12).While most prior research has focused on total thyroidectomy, this study highlights similar benefits in near-total procedures, which have received comparatively less attention. The observed transient hypocalcaemia rate in the control group (36.4%) falls within the 20–50% range reported globally (13, 14). Advanced age as a risk factor has been supported in studies linking reduced renal conversion of vitamin D and decreased bone buffering capacity to calcium fluctuations postoperatively (15). Our findings showing a more than six fold increased risk in patients ≥ 45 years are consistent with this biological explanation and previous cohort data (16). Similarly, co-morbidities such as diabetes and cardiovascular disease have been associated with impaired calcium and bone metabolism, which may predispose patients to hypocalcaemia following thyroid surgery (17). The most impactful risk factor in our study was insufficient preservation of parathyroid tissue. This finding is consistent with work by Bergenfelz et, who reported that visual identification and preservation of at least two parathyroid glands significantly lowers hypocalcaemia risk (18). Parathyroid gland autotransplantation has been suggested in some studies as a backup strategy, though outcomes vary (19). Notably, sex did not emerge as an independent predictor of post-operative hypocalcaemia in our study. While some earlier studies reported a slightly higher incidence in females, this is likely attributable to the higher prevalence of thyroid disorders among women rather than to any inherent physiological susceptibility (20).

These findings support the routine use of short-term preoperative calcium and calcitriol supplementation in near-total thyroidectomy, particularly for high-risk populations such as older adults and those with comorbidities. In addition, preserving parathyroid glands should remain a priority during surgery to prevent transient or permanent hypocalcaemia (21). Implementation of a simple pre-operative protocol could improve patient outcomes and reduce hospital resource utilization, especially in settings with limited access to postoperative monitoring.

Limitations of this study include the single-centre design, limited sample size, and lack of long-term follow-up to assess permanent hypocalcaemia. Additionally, serum PTH levels were not tracked post-operatively, which may have provided deeper insights into gland function and recovery. Future research should focus on larger, multicentric trials and consider cost-effectiveness analyses and patient-reported outcomes.

Conclusions;

Preoperative calcium and calcitriol supplementation effectively reduces the incidence of transient hypocalcaemia following near-total thyroidectomy. Age ≥ 45 years, cardio-metabolic co-morbidities, and inadequate parathyroid gland preservation significantly increase hypocalcaemia risk. A combination of prophylactic supplementation and surgical diligence in preserving parathyroid glands may provide optimal patient outcomes.

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