Original Paper

Role of Prophylactic Postoperative Calcium Supplementation Following Total Thyroidectomy in Preventing Hypocalcemia

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Abstract

Background: Hypocalcemia remains a major post-operative complication of total thyroidectomy causing potentially serious side effects and tension in influenced patients and expanding hospitalization time. Accurate prediction and appropriate management may help reduce morbidity and hospital stay.

Aim of study: To evaluate the effect of Ca supplementation following thyroidectomy in preventing hypocalcemia.

Patients and Methods: A randomized prospective study including 74 patients who underwent total thyroidectomyin the surgical unit, Department of Surgery, Al-Khidhir Hospital in Al-Muthanna provinceduring a period of two years and six months from Oct, 2015 – April, 2018. Group A - patients who didn't receive any supplement (37 patients), group B - patients who received Ca therapy immediately after operation (37 patients). Laboratory tests for S.Ca were done preoperatively and postoperatively at day 0, day one, day two, day three, and then after 10 days and for patient who developed hypocalcaemia, another reading was done after 10 – 20 days and followed monthly.

Results: No significant differences ($P \geq 0.05$) between study groups regarding age, BMI and duration of goiter. At day zero and day one postoperatively, no significant association between prevalence of hypocalcemia and receiving Ca postoperatively ($P \geq 0.05$) while at day two and three, this association was significant and hypocalcemia occurred more prevalent in patient of group A. Patients of group B were discharged earlier than patients of group A (58.9% versus 41.1%).

Conclusion: Routine Ca supplementation following total thyroidectomy is better than no supplement. Although they do not completely eliminate the occurrence of postoperative hypocalcemia.

Keywords: Thyroidectomy, calcium, Muthanna, Iraq, hypocalcemia

Introduction

The second most common endocrine disease following diabetes mellitus was disorders of the thyroid gland and the prevalence of nodular goiter and thyroid autonomy is expanded in regions with chronic Iodine Deficiency (ID) [1]

Total thyroidectomy (TT) is a commonly performed surgery worldwide. It is the definitive management option and gold standard for benign and malignantthyroid diseasesdue to suspicion of cancer, patient's desire for rapid and definitive treatment, or symptoms of local compression[2,3]. Also, it is accepted as a safe operation, and has lower morbidity and accepted postoperative outcomes resulting in a shorter hospital stay. It is even performed as day surgery[4, 5].

Bleeding, recurrent laryngeal nerve injury, and hypocalcemia were themain postoperative complications depending on the extent of surgery and experience of the

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surgeon [2]. Muscle cramps, perioral and peripheral paresthesia, carpopedal spasm or tetany, and/or confusion may be presented due to hypocalcemia, secondary to hypoparathyroidism and this will result in extended hospitalizationsleading to increased healthcare costs. Depending on the extent of parathyroid gland damage, hypocalcemia may be transient, resolving within a few months, or permanent, requiring lifelong oral calcium and vitamin D supplementation[6]. The incidence of transient hypocalcemia, defined as hypocalcemia occurring within six months of surgery, has been variedly reported to be 13%–38% [7]. Permanent hypocalcemia persists after that period (six months), with an incidence from 0% to 13% [1].

Hypocalcemia symptoms are uncommon unless serum calcium level is below 8.0 mg/dL (2.0 mmol/L) [8]. Symptoms depend on a degree and rapidity of hypocalcemia onset, ranging from mild paresthesia and tingling to more severe cramps, tetany, seizures, laryngospasm, congestive heart failure, and arrhythmias due to prolonged QT intervals [9]. Inpatient admission and close monitoring of postoperative serum calcium level has been proposed to decrease or prevent postoperative symptoms related to hypocalcemia [10]. However, this approach has been criticized mainly due to the fact that the lowest concentration of serum calcium is usually not reached until 48–72 hours after thyroidectomy; therefore, it has major challenge for safe early discharge planning [11].

For management of hypocalcemia postoperatively, most practitioners obtain serial serum calcium measurements and respond appropriately to low levels [12]. Oral supplementation is started with elemental calcium with/without Vitamin D3 for immediate management of post-surgical hypoparathyroidism [13]. For patients whose symptoms persist despite oral replacement therapy, intravenous calcium replacement and closer monitoring are indicated to be obtain [11]. Moreover, some centers routinely supplement all patients after surgery to facilitate early discharge from hospital [14]. Despite the different methods to evaluate and predict postoperative hypocalcemia, there is no consensus on the role of routine calcium following thyroid surgery.

The aim of this study is to evaluate the effect of calcium supplementation in an attempt to assist surgeons in which is best for patient regarding no supplement, or calcium supplement.

Patients and Methods

Study Design and Setting: This is a randomized prospective study that was conducted in the surgical unit, department of surgery, Al-Khidhir Hospital in Al-Muthanna province during a period of two years and six months fromOct, 2015 – April, 2018 (The first two years for collection of sample and the last six months for follow up of patients).

Study Population and sample size: The study population included 86 patients who underwent total thyroidectomy, 12 of them missed follow up post operatively, or need more time for follow up for hypocalcaemia, so the total number of patients who completed this study were 74.Only patients who were subjected to total thyroidectomy were included in this study. Patients who had signs and/or symptoms indicating metabolic disease of bone, patients were on medications that affect calcium whether increase or decrease, such as oral calcium/ vitamin D supplementation, anti-restorative agents, hormone replacement therapy for postmenopausal women, anabolic agents, diuretics thiazide type, or antiepileptic agents, known to affect serum calcium metabolism, patients with renal insufficiency, or any patient who didn't perform serum calcium pre-operative or post-operatively or patients who were subjected to less radical surgery or had recurrent goiter were excluded from this study. The patients were randomly assigned to two groups: group A - patients who

didn't receive any supplement (37 patients), group B - patients who received calcium therapy immediately after operation started with i.v calcium. 1500 mg given in three divided doses (37 patients). In randomization we allocate patient number one to group A and patient number two into group B and we repeat that for next patients. Signs and symptoms of hypocalcaemia were recorded and laboratory tests for serum calcium were done preoperatively and postoperatively at day 0, day one, day two, day three, and then after 10 days andfor patient who developed hypocalcaemia, another reading was done after 10 – 20 days and followed monthly. Routine total thyroidectomy was performed for all patients with ligation of branches of inferior thyroid artery and bipolar cautery of smaller branches. Special care was taken for identifying parathyroid glands and at least two of them should be identified. Patients were monitored for clinical and biochemical hypocalcemia. Symptoms monitored for mild hypocalcaemia are per-oral numbness, tingling, paresthesia of the distal extremities, and occasional muscle cramping, moderate hypocalcemia, more severe muscle cramps and for severe hypocalcemia, tetanic muscle cramps, carp pedal spasm, seizures, life-threatening laryngospasm, and coma were considered[9]. Standard Chvostek's and Trousseau's sign were monitored in the postoperative period every six hours. S. Ca (corrected) <8.0 mg/dL is considered biochemical hypocalcemia. The cutoff values for mild, moderate, and severe hypocalcemia are 7.50–7.99, 7.00–7.49, and <7.0 mg/dL respectively. Intravenous (IV) calcium was administered for patients who had moderate and severe symptomatic hypocalcemia irrespective of biochemical calcium values. Patients who had mild symptomatic hypocalcemia were managed with oral calcium and Vitamin D. Follow up was continued for those who showed hypocalcemia for six months to diagnose persistent hypocalcemia.

Statistical Analysis

The data analysed using Statistical Package for Social Sciences (SPSS) version 25. The data presented as mean, standard deviation and ranges. Categorical data presented by frequencies and percentages. T-test was used to compare the continuous variables among study groups accordingly. Pearson's Chi–square test was used to assess statistical association between certain variables and study groups. ROC curve used to find cutoff point of s. calcium between patients who developed hypocalcemia and patients who didn't. A level of p – value less than 0.05 was considered significant.

Results

This study involved 74 patientswho underwent total thyroidectomy and completed follow up postoperatively. The mean age of the patients was 48.9±11.8 years; 66.2% were females; 85.1% were from urban areas and 44.6% were overweighed. Goiter was non-toxic in 68.9% of study patients and presented for less than three years in 89.2% of them. No retrosternal extension or tracheal compression observed in most of the patients (93.2% and 94.6% respectively). By FNA, benign type was diagnosed in the highest proportion of study patients (54.1%). (Table 1 and Figure 1) Comparison between study groups by age, BMI, and duration of goiter is shown in table (2). In this study, there was no statistical significant differences ($P \geq 0.05$) between studies groups regarding all variables listed in the table

Preoperatively, all study patients didn't show any laboratory or clinical signs of hypocalcemia with a serum calcium ranging from 8.7 to 10.4 mg/dl.

At day zero postoperatively, serum calcium of patients was ranging from 6.3 to 10.2 mg/dl with a mean of 8.3 ± 0.83 mg/dl. The highest proportion of study patients didn't show clinical or laboratory evidence of hypocalcaemia (90.5%).

Table 1. Distribution of study patients by certain characteristics

Variable	No. (n=74)	Percentage (%)
Age (Years)		
< 40	23	31.1
40 – 59	34	45.9
≥ 60	17	23.0
Gender		
Male	25	33.8
Female	49	66.2
Residence		
Urban	63	85.1
Rural	11	14.9
BMI level		
Normal	21	28.4
Overweight	33	44.6
Obese	20	27.0
Goiter Toxicity		
Toxic	23	31.1
Non-toxic	51	68.9
Goiter duration (Years)		
< 3	66	89.2
≥ 3	8	10.8
Tracheal Compression		
YES	4	5.4
NO	70	94.6
Retrosternal Extension		
YES	5	6.8
NO	69	93.2

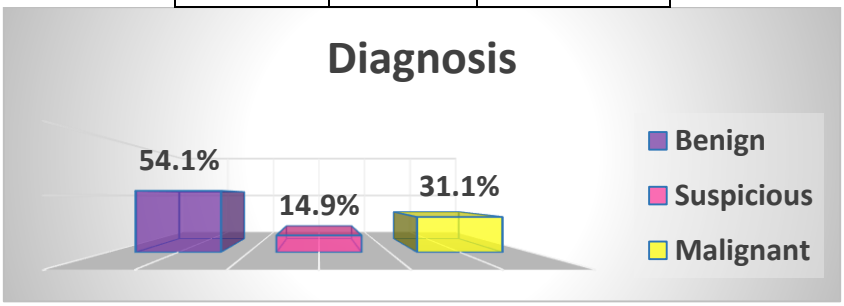

Figure 1. Distribution of study patients by diagnosis

Table 2. Comparison between study groups by age, BMI, and duration of goiter

Variable	Study Group		P- value
	Group A Mean ± SD	Group B Mean ± SD	
Age (Years)	46.83 ± 9.2	50.97 ± 14.4	0.146
BMI (kg/m^2)	29.2 ± 3.14	28.69 ± 2.04	0.409
Goiter duration (Years)	2.93 ± 1.72	2.27 ± 1.23	0.062

The highest prevalence of patients showed hypocalcaemia at day (0) postoperatively was found in patients of Group A (didn't receive calcium postoperatively) (57.1%) but the association between prevalence of hypocalcemia and receiving calcium postoperatively was statistically not significant (P=0.691). (Table 3).

At day one postoperatively, serum calcium of patients was ranging from 5.8 to 9.9 mg/dl with a mean of 8.1 ± 1.23 mg/dl. The highest proportion of study patients didn't show clinical or laboratory evidence of hypocalcaemia (83.8%). The highest prevalence of patients showed hypocalcaemia at day (one) postoperatively

was found in patients of Group A (didn't receive calcium postoperatively) (75%) but the association between prevalence of hypocalcemia and receiving calcium postoperatively was statistically not significant (P=0.058). (Table 4)

At day two postoperatively, total number of patients was 58. Serum calcium of patients was ranging from 5.1 to 9.5 mg/dl with a mean of 7.7 ± 0.91 mg/dl. The highest proportion of study patients didn't show clinical or laboratory evidence of hypocalcaemia (69%). The highest prevalence of patients showed hypocalcaemia at day (two) postoperatively was found in patients of Group A (didn't receive calcium postoperatively) (77.8%) and the association between prevalence of hypocalcemia and receiving calcium postoperatively was statistically significant (P=0.02). (Table 5)

At day three postoperatively, total number of patients who investigated for s. calcium was 18. Serum calcium of patients was ranging from 4.4 to 8.9 mg/dl with a mean of 6.9 ± 1.11 mg/dl. The highest proportion of study patients showed clinical or laboratory evidence of hypocalcaemia (77.8%). The highest prevalence of patients showed hypocalcaemia at day (three) postoperatively was found in patients of Group A (didn't receive calcium postoperatively) (92.9%) and the association between prevalence of hypocalcemia and receiving calcium postoperatively was statistically significant (P=0.003). (Table 6)

Table 3. Association between receiving calcium postoperatively and prevalence of hypocalcemia at day zero postoperatively

Hypocalcemia at Day zero postoperatively	Study Group		Total n = 74	P-value
	A n = 37	B n = 37		
Yes	4 (57.1)	3 (42.9)	7 (9.5)	0.691
No	33 (49.3)	34 (50.7)	67 (90.5)	

Table 4. Association between receiving calcium postoperatively and prevalence of hypocalcemia at day one postoperatively

Hypocalcemia at Day one postoperatively	Study Group		Total n = 74	P-value
	A n = 37	B n = 37		
Yes	9 (75.0)	3 (25.0)	12 (16.2)	0.058
No	28 (45.2)	34 (54.8)	62 (83.8)	

Table 5. Association between receiving calcium postoperatively and prevalence of hypocalcemia at day two postoperatively

Hypocalcemia at Day two postoperatively	Study Group		Total n = 58	P- value
	A n = 32	B n = 26		
Yes	14 (77.8)	4 (22.2)	18 (31.0)	0.02
No	18 (45.0)	22 (55.0)	40 (69.0)	

Table 6. Association between receiving calcium postoperatively and prevalence of hypocalcemia at day three postoperatively

Hypocalcemia at Day three postoperatively	Study Group		Total n = 18	P- Value
	A n = 14	B n = 4		
Yes	13 (92.9)	1 (7.1)	14 (77.8)	0.003
No	1 (25.0)	3 (75.0)	4 (22.2)	

After 10 to 14 days of thyroidectomy, s. calcium of patients was ranging from 6.2 to 10.32 mg/dl with a mean of 8.2 ± 0.64 mg/dl. The highest proportion of study patients didn't show clinical or laboratory evidence of hypocalcaemia (86.5%). The highest prevalence of patients showed hypocalcaemia after 10 to 14 days postoperatively was found in patients of Group A (didn't receive calcium postoperatively) (86.5%) but the association between prevalence of hypocalcemia and receiving calcium postoperatively was statistically not significant (P=0.173). (Table 7)

Table (8) shows the early discharged patients (before day three postoperatively) according to study groups. More than three quarters of patients (75.7%) discharged well from hospital, it was obvious that the highest proportion of those who discharged early was seen in patients of group B (58.9%), with a significant association (P=0.006) between early discharge from the hospital and calcium supplement postoperatively.

Duration of patients' recovery (Patients who diagnosed with hypocalcemia after 10 to 14 days postoperatively and then recovered after follow up) is shown in figure (3). In this study, number of recovered patients was nine while one patient (In Group A) was assigned permanent hypocalcaemia which represented 10% of all hypocalcemic patients. The highest proportion of study patients were recovered in duration less than six months (77.8%)

ROC curve represents sensitivity, specificity and cut point of S. Ca between study patients who developed hypocalcemia post thyroidectomy and patients who didn't. The cut point of S. Ca was 8.98 mg/dl with AUC= 76.7%, sensitivity= 82.7%, specificity= 74.1%, accuracy= 75.6%, PPV= 32%, NPV= 94.3%, LR+= 2.25, and LR-= 0.27,so this mean that all patients after thyroidectomy with S. Ca ≥ 8.98 at day zero postoperatively can discharged safely without any future risk of hypocalcemia as shown in figure (4).

Table 7. Association between receiving calcium postoperatively and prevalence of hypocalcemia after10 to 14 days postoperatively

Hypocalcemia after 10 to 14 days postoperatively	Study Group		Total n = 74	P- Value
	A (n = 37)	B (n = 37)		
Yes	7 (70.0)	3 (30.0)	10 (13.5)	0.173
No	30 (46.9)	34 (53.1)	64 (86.5)	

Table 8. Early discharged patients (before day three postoperatively) according to study groups

Early discharge (Before day three postoperatively)	Study Group		Total n = 74	P- Value
	A n = 37	B n = 37		
Yes	23 (41.1)	33 (58.9)	56 (75.7)	0.006
No	14 (77.8)	4 (22.2)	18 (24.3)	

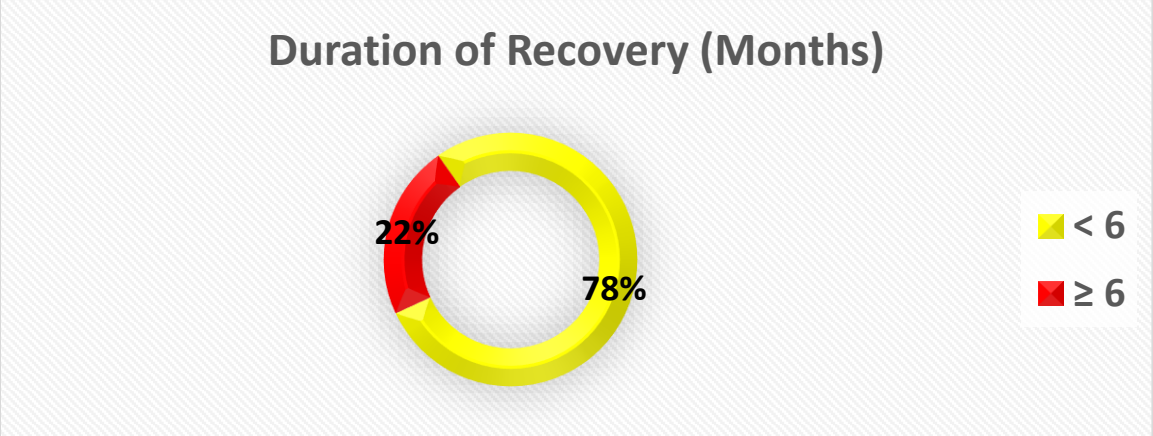

Figure 3. Duration of patients' recovery

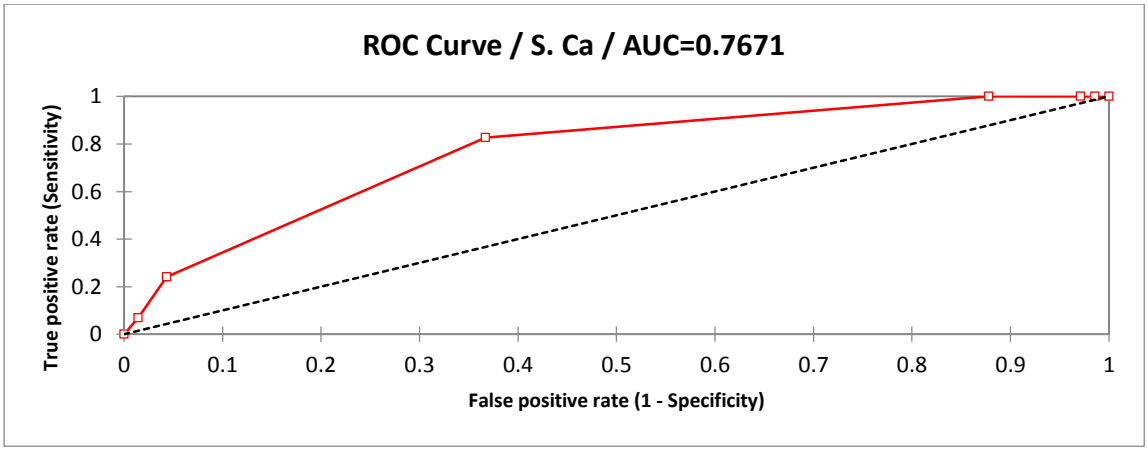

Figure 4. ROC curve represents sensitivity, specificity and cut point of S. Ca between study patients who developed hypocalcemia post thyroidectomy and patients who didn't

Discussion

Hypocalcemia remains a major post-operative complication of total thyroidectomy causing potentially severe symptoms and anxiety in affected patients and increasing hospitalization time. In order to decrease hypocalcemia symptoms, some surgeons prefer to use calcium prophylactically, whereas some prefer treating patients with postoperative hypocalcemia. In this study, age, BMI, and duration of goiter did not affect occurrence of hypocalcemia in contrary to two Turkish studies in 2007 [(15)] and 2009 [(16)] whentheyreported that advancing age is a risk factor for hypocalcemia.

In the current study, preoperatively, no laboratory or clinical signs of hypocalcemia observed, while at day zero, day one and after 10 to 14 days postoperatively, no significant association observed between hypocalcaemia and receiving calcium postoperatively (P≥0.05). Statistically significant association (P<0.05) were observed in day two and three postoperatively where prevalence in group A were (77.8% and 92.9% respectively). Similar results observed in Canada, as they reported hypocalcemia developed more in patients without calcium Supplementation andfound that the use of prophylactic calcium (5g/day) alone reduced the risk of hypocalcemia crisis [(17)], in USA [(18)], a study showed the rate of symptomatic hypocalcemia in groups treated with Vitamin D and calcium was significantly decrease in comparison to no prophylaxis used, which was Similar to Italian results were shown that early and combined oral administration of both calcium and Vitamin D has great efficacy in preventing postoperative hypocalcemia [(19)]. Different result in Japanese study (2006) used i.v Ca.

noticed that Ca. levels at the 1st Postoperative day was significantly higher in those used Ca. (P<0.0001), and Prophylactic infusion of calcium reduced the prevalence of hypocalcemic symptoms from 8.6% to 2.1% [20].

More than half of group B in this study discharged early (58.9%), with a significant association (P=0.006) with calcium supplement postoperatively, which is similar to Iranian and American study, in which observed duration of hospitalization was significantly lower in the patients who received Ca and vitamin D and oral calcium administration may lead to sooner discharge on the 2nd postoperative day without hypocalcaemia [21, 22]. In this study, number of recovered patients was nine while one patient (In Group A) was assigned permanent hypocalcaemia (10% of all hypocalcemic patients). All this means the administration of calcium is better than non-supplement, although they do not completely terminate the development of hypocalcemia that might cause by transient decrease in calcium in patients with total thyroidectomy and ascertained on the basis of the preserved parathyroid tissue taking a few days to recover from the trauma of surgical dissection which produces temporary parathyroid insufficiency before resuming normal function. Furthermore, Thyrotoxicosis will alter calcium metabolism due to thyrotoxic osteodystrophy. The duration of hyperthyroidism and more importantly the duration of euthyroid state preceding definitive management of hyperthyroidism have a major impact on the postoperative timing and duration of hypocalcemia [23].

The current study observed that cut point of S. Ca (at day zero postoperatively) at which patients can discharged safely without any risk of hypocalcemia was 8.98 mg/dl and this was in agreement with two Italian studies, in 2015 [24] and in 2014 [25] in which the Ca cut points were higher than 9 mg/dl in both at 1st postoperative day and can be considered a feasible cut-off to exclude the appearance of hypocalcemia in both studies.

Finally, comparing to the above studies, we found a reliable and feasible calcium cut-off point that we can depend on it as an indicator for the possible occurrence of hypocalcemia in patients undergone an operative thyroidectomy.

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