Risk factors of hypocalcemia after thyroid surgery

Amir Fawzy Abdelhamid, Hossam Ramadan Moussa

Department of General Surgery, Faculty of Medicine, Tanta University, Tanta, Egypt

Correspondence to Amir Fawzy Abdelhamid, MD, Gastrointestinal and Laparoscopic Surgery Unit, General Surgery Department, Faculty of Medicine, Tanta University, Tanta, 31527, Egypt. Tel :+20403337544; fax +20403337544; e-mail: amirfawzyshaban@gmail.com

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Background
Hypocalcemia is a common complication that may be encountered after thyroid surgery. This study was conducted to evaluate the risk factors for postoperative hypocalcemia after thyroid operations.
Patients and methods
We retrospectively reviewed the data of 200 consecutive cases that underwent thyroidectomy at our department between January 2017 and December 2019. The following data were collected; age, sex, systemic comorbidities, disease nature, preoperative calcium levels, operation type, need for neck lymph node dissection, operative time, surgeon experience, and postoperative calcium and parathyroid hormone levels.
Results
Temporary hypocalcemia was encountered in 36 (18%) cases. The hypocalcemic group showed higher female prevalence (P=0.045), more toxic cases, more malignant cases (P=0.005), more total thyroidectomy operations (P=0.039), lower preoperative calcium levels (0.015), more low experienced surgeons (P=0.021), and lower postoperative parathyroid hormone levels ($P<0.001$).
Conclusion
Toxic goiter, malignancy, total thyroidectomy, level D surgical experience, and preoperative calcium levels are independent predictors for postoperative hypocalcemia. Moreover, female sex, lymph node dissection, and postoperative low parathyroid hormone levels are risk factors for that complication.

Keywords:
hypocalcemia, predictors, thyroidectomy

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Introduction

Thyroidectomy operations can be followed by many serious complications, including bleeding and vocal cord palsy. Nevertheless, hypocalcemia remains the most common encountered complication after thyroid surgery [1].

Postoperative hypocalcemia is mainly caused by secondary hypoparathyroidism, which occurs owing to damage, ischemia, or removal of one or more parathyroid glands during operation [2]. In addition, other mechanisms including calcitonin oversecretion from thyroid handling during surgery and hungry bone syndrome can contribute to this complication [3–5].

Although most of these cases develop temporary hypocalcemia that responds to treatment within days or weeks [6], ~1.3–3% of cases develop permanent calcium deficiency (when it fails to return to its normal levels 6 months after operation) [7].

Hypocalcemia may be asymptomatic if there is a mild decrease in serum calcium levels. Nevertheless, typical manifestations might develop, including muscle spasms, paresthesia, and Chvostek's and Trousseau's signs [2].

Multiple risk factors for this complication have been identified in the literature, including female sex [8,9], extent of thyroidectomy [8,10], surgeon experience [11], large-sized thyroid gland [12,13], retrosternal thyroid extension [14], central lymph node dissection [9,15], vitamin D deficiency [16], and the presence of parathyroid tissue on examining the excised surgical specimen [17].

It is crucial to identify risk factors for this postthyroidectomy complications, as this will enable surgeons to early identify patients at risk, leading to a significant decrease in postoperative morbidity, hospital stay, as well as unnecessary laboratory investigations, as prophylactic calcium supplementation will be commenced for such cases to prevent the occurrence of hypocalcemic manifestations [1].

Although multiple studies have discussed the issue of hypocalcemia after thyroid surgery, no previous reports

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have discussed these risk factors in the Egyptian Nile Delta region. Moreover, the reported risk factors in the literature could not be necessarily applied to all cases from different centers owing to different surgical technique and experience. This study was conducted to evaluate the risk factors for postoperative hypocalcemia following thyroid operations.

Patients and methods

This retrospective study was conducted at the General Surgery Department, Tanta University. The data of 200 consecutive cases that underwent thyroidectomy for benign and malignant causes between January 2017 and December 2019 were retrospectively reviewed. Conversely, cases with recurrent goiter, uncontrolled systemic comorbidities, low preoperative serum calcium (normal range, 8.0–10.4 mg/dl), or receiving preoperative calcium supplementation were excluded from the current study.

An informed written consent was obtained from all cases after complete explanation of the details and possible complications of the operation. Moreover, the study was approved by the local ethical committee of Tanta University.

During preparation, all cases were subjected to full history taking, general and local neck examination, and routine laboratory investigations (including thyroid profile, complete blood count, liver and renal function tests, serum calcium levels, and tumor markers if malignancy was suspected). In addition, neck ultrasonography and fine-needle aspiration cytology were ordered for all cases. Neck computed tomography or MRI was ordered in malignant cases for proper tumor staging.

All cases were subjected to either total or hemithyroidectomy operations via the standard technique by the same surgical team. The surgical experience of the surgical team was classified based on the previous thyroidectomy operations performed during the last 3 years as follows: A (>100 operations), B (30–100 operations), C (10–29 operations), and D (1–9 operations). Such classification was based on the study conducted by Sosa *et al.* [18].

The following data were collected: age, sex, systemic comorbidities, disease nature, preoperative calcium levels, operation type, need for neck lymph node dissection, operative time, surgeon experience, and postoperative calcium and parathyroid hormone levels.

Hypocalcemia was defined as a decrease of serum calcium below 8.0 mg/dl during the first 24 h after operation, or when the patient develops one of the characteristic features suggestive of hypocalcemia, including muscle spasms, paresthesia, and Chvostek's and Trousseau's signs.

According to calcium levels and clinical manifestations, the included cases were divided into two groups: normocalcemic group which included cases that did not develop hypocalcemia after operation, and the hypocalcemic group which included cases that developed either clinical or laboratory features of hypocalcemia following surgery.

Statistical analysis

Data were analyzed using IBM SPSS software package, version 22.0 (Statistical analysis was done using IBM SPSS statistics for windows, Version 23.0. Armonk, NY: IBM Corp). Qualitative data were described using number and percent. Quantitative data were presented as mean and SD after testing normality using Kolmogorov–Smirnov test. χ^2 test was used for comparison of two groups of qualitative data (Monte–Carlo test as correction for χ^2 test when more than 25% of cells have count <5 in tables). Student t test was used to compare two independent groups of parametric data. Univariate and multivariate logistic regression analyses were used to determine the dependent and independent risk factors for binary outcome variable (postoperative hypocalcemia). P value less than 0.05 was considered statistically significant.

Results

The mean age of the included cases was 42.67 and 43.94 years in the normocalcemic and hypocalcemic groups, respectively (P=0.548). Females represented 79.27 and 91.67% of cases in normocalcemic and hypocalcemic groups, respectively (P=0.045). No significant difference was detected between the two groups regarding the prevalence of diabetes or hypertension. Simple goiter was the commonest diagnosis in the normocalcemic group (39.63%), whereas malignancy was the commonest encountered diagnosis in the hypocalcemic group (44.44%). There was a significant difference between the two groups regarding the preoperative diagnosis.

Total thyroidectomy was the commonest performed procedure in both groups (78.66 and 91.67% of cases in normocalcemic and hypocalcemic groups, respectively; P=0.039). Lymph node dissection was more performed in the hypocalcemic group (30.3 vs. 13.41% in the normocalcemic group; P=0.001).

Operative time was not statistically different between the two groups (P=0.602).

Preoperative calcium levels were significantly lower in the hypocalcemic group (8.42 vs. 9.75 mg/dl in the normocalcemic group; P=0.015). Regarding surgeon experience, most cases in the normocalcemic group were performed by level A surgeons, whereas most cases in the other group were operated by level D surgeons (P=0.021). Postoperative parathyroid levels were significantly lower in the hypocalcemic group compared with the normocalcemic group (14.23 vs. 35.9 pg/ml; P<0.001). These data are illustrated in Table 1.

On univariate analysis, female sex, toxic goiter, malignancy, lymph node dissection, total thyroidectomy, level D surgeon experience, low preoperative calcium levels, and low postoperative parathyroid hormone levels were risk factors for hypocalcemia. On multivariate analysis, toxic goiter, malignancy, total thyroidectomy, level D surgical experience, along with preoperative calcium levels were independent predictors of postoperative hypocalcemia. Table 2 illustrates these data.

Discussion

Hypocalcemia is a common postoperative complication that may be encountered after thyroid operations, and it may be symptomatic or asymptomatic [19].

This study was conducted at Tanta University Hospitals, aiming to evaluate the risk factors for postoperative hypocalcemia after thyroidectomy. The data of 200 consecutive cases were retrospectively reviewed. Temporary hypocalcemia was detected in 36 (18%) cases, whereas it persisted for more than 6 months (permanent hypocalcemia) in only four (2%) cases (not shown in the results).

The incidence of hypocalcemia in our study comes in agreement with the incidence reported in the literature. Previous studies have reported that transient hypocalcemia was encountered in 6.9–49% of cases following thyroidectomy [20–23]. Moreover, permanent hypocalcemia was reported in less than 3% of cases after thyroidectomy [24] and that coincides with our results.

In our study, patients' age was not significantly different between the two groups (mean=42.67 and 43.94 years, respectively; P=0.548). Age was not a significant predictor of hypocalcemia (P=0.215).

Del Rio *et al.* [1] confirmed our findings regarding age, as there was no significant difference between the two groups (mean=54.01 and 55.03 in normocalcemic and

Table 1 Demographics, clinical, and operative characteristics of the study groups

Variables	Normocalcemic group (N=164)	Hypocalcemic group (N=36)	P value
Age	42.67±12.72)	43.94±12.01)	0.548
Sex			
Male	34 (20.73)	3 (8.33)	0.045*
Female	130 (79.27)	33 (91.67)	
Diabetes	42 (25.61)	10 (27.78)	0.654
Hypertension	51 (31.09)	12 (33.33)	0.693
Diagnosis			
Simple goiter	65 (39.63)	6 (16.67)	0.005*
Toxic goiter	41 (25)	13 (36.11)	
Thyroiditis	8 (4.87)	1 (2.78)	
Malignancy	50 (30.48)	16 (44.44)	
Operation type			
Hemithyroidectomy	35 (21.34)	3 (8.33)	0.039*
Total thyroidectomy	129 (78.66)	33 (91.67)	
Need for LND	22 (13.41)	10 (30.3)	0.001*
Operation time	105.22±14.58	106.68±13.81	0.602
Preoperative Ca levels (mg/dl)	9.75±1.01	8.42±0.27	0.015*
Surgeon experience			
A	49 (29.9)	6 (16.7)	0.021*
B	35(21.3)	9 (25)	
C	49 (29.9)	10(27.7)	
D	31 (18.9)	11 (30.6)	
Postoperative PTH levels (pg/ml)	35.9±6.48	14.23±2.77	<0.001*

Data are presented as mean±SD and *n* (%). LND, lymph node dissection; PTH, parathyroid hormone. *It denotes that this factor has statistically significant impact or effect as relation to *P* value result.

Table 2 Univariate and multivariate analysis of predictors of postoperative hypocalcemia

Variables	Univariate analysis	Multivariate analysis		
		OR	95% CI for OR	*P* value
Age	0.215			
Female sex	0.012*	0.932	0.618–1.237	0.126
DM	0.236			
HTN	0.372			
Simple goiter	<0.001*	0.278	0.118–0.682	0.001*
Toxic goiter	0.009*	1.973	1.517–2.984	0.019*
Thyroiditis	0.246			
Malignancy	0.011*	2.150	1.844–3.006	0.017*
LND	0.036*	1.029	0.811–1.498	0.063
Hemithyroidectomy	0.011*	0.462	0.314–0.869	0.109
Total thyroidectomy	< 0.001*	1.824	1.273–2.982	0.003*
Operation time	0.289			
A	0.005*	0.317	0.211–0.764	0.031*
B	0.129			
C	0.089			
D	0.004*	2.147	1.874–3.119	0.015*
Preoperative Ca level	< 0.001*	3.263	2.187–4.293	0.001*
Postoperative PTH levels	0.021*	1.428	1.324–1.903	0.322

CI, confidence interval; DM, diabetes mellitus; HTN, hypertension; LND, lymph node dissection; OR, odds ratio; PTH, parathyroid hormone.*Statistically significant ($P<0.05$).

hypocalcemic groups, respectively; $P>0.05$). Although the mean age was higher than ours, it was not a significant risk factor for postoperative hypocalcemia.

On the contrary, another study reported that younger age was a significant risk factor for hypocalcemia after thyroidectomy. The mean age of the included cases was 50.89 and 48.0 years in the normocalcemic and hypocalcemic groups, respectively ($P<0.001$). Age was a significant predictor of hypocalcemia in that study, and this contradicts with our findings [25].

In our study, although female sex was predominant in both groups, its prevalence was significantly higher in the hypocalcemic group (91.67 vs. 79.27%; $P=0.045$). Female sex was a significant risk factor for hypocalcemia on univariate analysis ($P=0.012$).

Another study also reported that the prevalence of female sex was significantly higher in the hypocalcemic group ($P<0.001$). Females represented 73.72 and 88.17% of cases in the normocalcemic and hypocalcemic groups, respectively [1]. Other studies confirmed that finding [9,11,26].

The exact cause beyond that phenomenon is still under debate. This sex disparity could be attributed to the effect of sex hormones on parathyroid secretion, genetic differences, signaling pathway alternations, or anatomic differences [3]. Moreover, females tend to be more susceptible to vitamin D and calcium deficiency compared with males [27,28].

On the contrary, multiple studies have reported the insignificant effect of sex on the incidence of hypocalcemia [7,9,29].

In the current study, diabetes mellitus was not a significant risk factor for hypocalcemia ($P=0.236$). It was present in 25.61 and 27.78% of cases of normocalcemic and hypocalcemic groups, respectively.

Another study also reported no significant difference between the two groups regarding the prevalence of diabetes ($P>0.05$) [1].

On the contrary, other studies have confirmed the negative effect of diabetes on postoperative parathyroid function. This could be owing to microangiopathy and atherosclerosis associated with diabetes, which make parathyroids more vulnerable to ischemia in such cases [30,31].

In our study, hypertension was not a significant risk factor for postthyroidectomy hypocalcemia ($P=0.372$). It was present in 31.09 and 33.33% of cases in normocalcemic and hypocalcemic groups, respectively.

On the contrary, Del Rio *et al.* [1] reported that the prevalence of hypertension was significantly higher in the normocalcemic group (31.98 vs. 22.77% in the hypocalcemic group; $P<0.001$).

In the current study, toxic goiter was a significant risk factor for hypocalcemia on both univariate

and multivariate analyses (P=0.009 and 0.019, respectively). Toxic cases represented 25 and 36.11% of cases in normocalcemic and hypocalcemic groups, respectively. On the contrary, the presence of simple goiter was protective against that complication (odds ratio=0.118–0.682; P=0.001).

Although the mechanism behind that is still unclear, the larger gland size and more vascularity associated with thyrotoxicosis make the operation more difficult, and thus, more complications should be anticipated [30,32].

Conversely, Del Rio *et al.* [1] reported that the presence of hyperthyroidism was not significantly different between the two groups (P>0.05). It was present in 17.82 and 18.62% of cases in the normocalcemic and hypocalcemic groups, respectively.

The presence of malignant thyroid lesion was a significant predictor for postoperative hypocalcemia on univariate and multivariate analyses (P=0.011 and 0.017, respectively) in our study. Malignant lesions were present in 30.48 and 44.44% of cases in normocalcemic and hypocalcemic groups, respectively.

In the presence of malignant thyroid disease, the posterior capsule should be removed to achieve radicality. Therefore, there is an increased risk for parathyroid injury [33–35]. Baldassarre *et al.* [25] have reported that malignant thyroid neoplasms are significant predictors of postoperative hypocalcemia (P<0.001).

In the current study, total thyroidectomy operation was a significant predictor of postoperative hypocalcemia (P<0.001 and 0.003 on univariate and multivariate analyses, respectively). It was performed in 78.66 and 91.67% of cases in normocalcemic and hypocalcemic groups, respectively.

Both thyroidectomy technique and extent are strongly linked to parathyroid edema, infraction, and even iatrogenic removal [20,26].

Wang *et al.* [19] reported that total thyroidectomy was a significant risk factor for postoperative hypocalcemia compared with lobectomy (P=0.001). Nevertheless, the same authors documented postoperative hypocalcemia and even hypoparathyroidism after lobectomy and combined lobectomy with isthmectomy, although limited thyroid resection operations like hemithyroidectomy do not include manipulation of the contralateral parathyroids.

In our study, lymph node dissection was a significant risk factor for hypocalcemia on univariate analysis (P=0.036). It was performed in 13.41 and 30.3% of cases in normocalcemic and hypocalcemic groups, respectively.

Other authors reported that thyroidectomy with either unilateral or bilateral neck dissection was a significant predictor for postoperative hypocalcemia (P<0.001) [25]. This agrees with our findings as more injury to parathyroids is expected with more extensive neck dissection.

Another series reported that hypocalcemia was more encountered in cases with total thyroidectomy with neck lymph node dissection compared with total thyroidectomy alone [36].

Operation time was not a significant risk factor for postoperative hypocalcemia (P=0.289). It had mean values of 105.22 and 106.68 min in normocalcemic and hypocalcemic groups, respectively.

Ma *et al.* [37] have reported that operative time was not a significant predictor neither for mild (P=0.828) nor severe hypocalcemia (P=0.875) after thyroid operations. This comes in line with our findings.

In the current study, low surgeon experience was a significant risk factor for postoperative hypocalcemia (P=0.004 and 0.015 on univariate and multivariate analyses, respectively). However, high experience was protective against that complication (odds ratio=0.211–0.764; P<0.05).

In a previous retrospective multicenter study, Sosa *et al.* [18] reported that surgeons with high expertise had the lowest complication rate in thyroid operations, and this agrees with our findings.Nevertheless, other authors reported thyroid surgery could be safely performed by residents or general surgeons if close supervision was ensured [38–40].

In the current study, low preoperative serum calcium was a significant risk factor for postoperative hypocalcemia on univariate and multivariate analyses (P<0.001 and 0.001, respectively). It had mean values of 9.75 and 8.42 mg/dl in normocalcemic and hypocalcemic groups, respectively.

Multiple previous studies have confirmed low preoperative calcium as a risk factor for transient postoperative hypocalcemia [9,41–43].

Nevertheless, another study reported no significant difference between the two groups regarding preoperative calcium levels ($P>0.05$). It had mean levels of 9.35 and 9.172 mg/dl in the normocalcemic and hypocalcemic groups, respectively [1].

In our study, low postoperative parathyroid hormone levels were a significant risk factor for hypocalcemia on univariate analysis ($P=0.021$). It had mean values of 35.9 and 14.23 pg/ml in the normocalcemic and hypocalcemic groups, respectively.

Islam *et al*. [44] have reported that postoperative parathyroid hormone levels can be used as a reliable predictor of postoperative hypocalcemia. Approximately 60% of cases whose parathyroid hormone level less than 23 ng/l developed early postoperative hypocalcemia. This coincides with our findings.

Conversely, Del Rio *et al*. [45] reported no significant correlation between postoperative parathyroid hormone levels and the development of hypocalcemia.

Our study has some limitations: first of all, it is a single-center study. Moreover, identification of parathyroid glands during surgery should have been reported. Therefore, more studies including more cases from multiple centers should be conducted in the future.

Conclusion

Based on our results, it is evident that toxic goiter, malignancy, total thyroidectomy, level D surgical experience, and preoperative calcium levels are independent predictors for postoperative hypocalcemia. In addition, female sex, lymph node dissection, and postoperative low parathyroid hormone levels are risk factors for that complication.

Cases expressing one of the previously mentioned parameters should have their calcium and parathyroid hormone closely monitored after surgery, and we also recommend prophylactic calcium and vitamin supplementation for such cases.

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Conflicts of interest

There are no conflicts of interest.

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