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Incidence and Predictive Factors of Post Thyroidectomy Hypocalcaemia

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Abstract

Background: Hypocalcaemia is a frequent complication of thyroidectomy. Although typically transient, it can lead to an increased length of hospitalization, readmission, and in rare cases be permanent with a lifetime supplementation of calcium.

Objective: The aim of this study was to determine the incidence of hypocalcaemia in patients undergoing different type of thyroidectomy for different pathologies, in order to determine which are the factors that could be used as predictive factors of post-operative, transient and permanent hypocalcaemia.

Materials and Methods: This retrospective study included 461 patients who had undergone thyroidectomy at the surgical department "A" in IbnSina Hospital between January 2007 to December 2018. The clinicopathologic, biological and surgical details of normocalcemic and hypocalcemic patients were compared.

Results: Out of the 461 patients 157 patients (34.1%) developed initial post- operative hypocalcaemia, 149 of them (32.3%) were found to have transient hypocalcaemia and 8 of them (1.7%) had permanent hypocalcaemia. Univariate analysis found female gender (p=0.009), preoperative hypocalcaemia (p=0.001), preoperative hyperthyroidism (0.029), bilateral intervention (p<0.01), bilateral central neck dissection (p=0.038) and inadvertent parathyroidectomy (p=0.018) to be significantly associated with transient hypocalcaemia. Multivariate analysis demonstrated that female gender (p=0.047 OR: 2.87 CI 95% [1.01-8.15]), preoperative hypocalcaemia (p=0.001 OR: 22.21 CI 95% [3.58-137.72]) and bilateral intervention (p=0.002 OR: 15.66 CI 95% [2.81-87.27]) were independent significant factors.In addition suspected lesion of the RLN during surgery was a significant factor for post-operative dysphonia on univariate analysis.

Conclusion: In conclusion female gender, preoperative hypocalcaemia and bilateral intervention increase the risk of developing transient hypocalcaemia. Preoperative evaluation of calcemia should be systematic and preoperative management of hypocalcaemia should be initiated in patients that are at high risk of developing hypocalcaemia after thyroidectomy.

Keywords: Thyroidectomy; Hypocalcemia; Post-thyroidectomy; Complications; Dysphonia

Introduction

Thyroidectomy is considered to be a common operative procedure in endocrine surgery. The most prevalent complications of thyroid surgery include hypocalcaemia and damage to the recurrent nerves. Hypocalcaemia occurs transiently in 20 to 30% of the time and it is permanent in 1 to 4 % of the time. Damage to the recurrent .laryngeal nerve resulting in dysphonia occurs transiently in 5 to 11% of operations and permanently in 1 to 3.5% of operations [1]. These complications cause a prolonged hospitalization but also increased cost of treatment [2]. And for patients who eventually develop permanent hypocalcaemia, a life time supplement of calcium.

Post thyroidectomy hypocalcaemia is due essentially to hypoparathyroidism. It is the result of direct injury, obstruction of venous drainage, devascularization, or inadvertent excision of the parathyroid gland [3]. However normal postoperative response to stress including hemodilution and antidiuretic secretion can also lowers total serum calcium levels [4,5]. Post operatative calcemia can either be asymptomatic if the calcium level is mildly reduced or symptomatic going from minor hypocalcemic signs to major complication resulting in hypocalcemic tetany.

Many endocrine surgeons are interested in predicting hypocalcaemia early to prevent serious complications and eventually begin treatment to hasten hospital discharge. The aim of this retrospective observational study was to determine the incidence of hypocalcaemia in patients undergoing thyroidectomy, and to determine which are the factors that could be used as predictive indicators of post-operative, transient or permanent hypocalcaemia.

Materials and Methods

From January 2007 to December 2018, 461 patients underwent thyroid surgery at the surgical Department "A" in Ibn Sina Hospital for different thyroid pathologies. A retrospective study was conducted from the medical dossiers of the patients and computerized data when available. A data collection form that we specifically designed for our study was used. Patients with concomitant parathyroid pathology and renal failure were not included in our series.

Patients were admitted to the department through referrals or transfers from the endocrinology department or during consultations. They underwent; Full medical interrogation, Physical examination, Biological tests (blood cell count, serum electrolyte levels, thyroid function test (TSH; Tyroid Stimulating Hormone), preoperative calcemia and phosphorus, calcitionin levels and thyroid antibody tests), medical imaging tests (Chest X-ray, cervical Ultra Sound (US), scintigraphy, cervical or mediastinum CT scan,). Fine Needle Aspiration Biopsy (FNAB) was performed for patients with suspicious thyroid nodules according to the BETSHEDA system [6,7].

Once the surgical indication is set the patients who presented preoperative hyperthyroidism with low TSH levels (<0.5mUI/l) required a preoperative preparation as well as have their vocal cord function evaluated to make sure the patient is euthyroid before the surgical intervention [8].

All the procedures were peformed under general anesthesia. The surgical technique is a capsular dissection with vessel suture ligation of a thyroid lobe, which initiates as a hemithyroidectomy but can be extended to a total thyroidectomy if indicated. Detection and preservation of the recurrent laryngeal nerve Para Thyroid Glands (PTGs) was systematic during intervention, the ideal being 2 or more glands detected. In the event of accidental avulsion of a parathyroid gland or compromising its blood supply, the affected parathyroid gland will be removed and auto-transplanted the gland in the sternocleidomastoid muscle if viable [9].

After the surgical intervention patients undergo clinical and biological monitoring. Post operative serum calcium and phosphorus levels were analyzed on Day 1 (24h) and Day 2 (48h). Postoperative phosphate could also be assessed as a biochemical factor as it varies in parallel to post-operative calcemia [10].We consider as post thyroidectomy hypocalcaemia patients who presented calcemia level < 80 mg/l (<2 mmol/l), on one of the 2 consecutive dosages done on day1 and day 2 postoperatively. Post-operative replacement therapy was given upon observation of clinical hypocalcaemia symptoms no matter the calcium level or if calcium levels was below 70mg/l with or without clinical symptoms. All patients were monitored minimum up to 12 months after their surgery; we consider as transient hypocalcaemia, patients who presented calcemia level < 80 mg/l on 2 consecutive dosages at J1 and J2 postoperatively but eventually normalized their calcium levels before 12 months without the need of replacement therapy for at least 1 month. We considered permanent hypocalcaemia; the need to maintain calcium supplementation for more than 12 months after surgery [11]. As for statistical analysis, qualitative variables are represented by frequencies and percentages. Quantitative variables are represented in means +/- Standard Deviation (SD) or medians with Inter Quartile Ranges (IQR), the Kolmogorov-Smirnov test was used to assess the normality of the data distribution. Means were compared using the independent T test when the quantitative variables were independent and the paired sampled T test when they were dependent of a factor. Differences in frequencies between groups and statistical significance of the different factors were calculated using Fisher's exact test or CHI 2 [12]. Variables with p value< 0.2 were selected for use in the multivariate analyses. Multivariate analysis was performed by a multivariate binary logistic regression model by means of a forward stepwise method. Odds ratio and 95% CI for each variable and a p value<0.05 was considered statistically significant. To conduct this study we used SPSS (Statistical Package for the Social Sciences) version 13.0 2006 (IBM, Armonk, New York, USA).

Results

During the 12 year period 461 patients underwent surgical thyroid interventions at the surgical Department "A" in Ibn Sina Hospital, Rabat, for different thyroid pathologies. The patient's age varies from a minimum of 18 years old to a maximum of 88 years old, with a mean age of 48 years old (+/- 14.3 years) Women represent 89.2% (411 female patients) versus male patients who represent 10.8% (50 male patients).

In our series; 291 patients (63.1%) underwent thyroidectomy for Multi- nodular goiter, 62 patients (13.4%) for Solitary Nodule, 82 patients (17.8%) for thyroid cancer and 26 patients (5.6%) for Graves's disease. (Table1).

	N=461	**Transient**		**Permanent hypocalcemia**	
Variables	% (n)	hypocalcemia n=149 (32.3%)	P value	n=8 (1.7%)	P value
Age,years (mean +/- SD)	47.7 +/- 14.6	49.2 (+/-13.7)	0.234	39.6 (+/-9.8)	0.092
Gender			0.009		0.604
Male (%)	10.8%(50)	16% (8)		87.5% (7)	
Female (%)	89.2%(411)	34.3% (141)		12.5% (1)	
Antecedent of thyroid surgery			0.108		1
Yes	16.1% (74)	24.3% (18)		1.4% (1)	
No	83.9% (387)	33.9% (131)		1.8% (7)	
Hypertention			0.253		1

Yes	16.3% (75)	26.7% (20)		1.3% (1)	
No	83.7% (386)	33.4% (129)		1.8% (7)	
Diabetes			0.919		1
Yes	8.2% (38)	31.6% (12)		0% (0)	
No	91.8% (423)	32.4% (137)		1.9% (8)	
Diagnosis			0.164		0.37
Thyroid cancer	20.6% (82)	29.3% (24)		0 %(0)	
Other	79.4 % (317)	37.5% (125)		2.1% (8)	
Preoperative clinical symptoms			0.101		1
Symptomatic	87.6% (404)	33.7% (136)		1.7% (7)	
Asymptomatic	12.4% (57)	22.8% (13)		1.8% (1)	
Thyroid volume			0.261		1
>10 cm	4.9% (20)	20% (4)		0% (0)	
<10 cm	74.4% (306)	32.0% (98)		2.3% (7)	

Table 1: Patient and disease related Factors in relations with post thyroidectomy, transient and permanent hypocalcaemia

During admission 143 patients (31.0%) with TSH bellow 0.5mUI/l were considered to have hyperthyroidism and received preoperative treatment until euthyroid status was reached. In addition 14 (5%) patients presented preoperative hypocalcaemia (calcemic level <85mg/l) and 265 (95%) patients had normal calcemia level.

For our study we divided our patients into two groups; 1st group includes patients who underwent unilateral intervention (isthmo-lobectomy) which is 53 patients (11.5%). The 2nd group includes patients who underwent bilateral intervention (total thyroidectomy for 359 patients or iterative completion thyroidectomy for 49 patients) which is 408 patients (88.5%). During intervention 33 patients (7.2%) sustained inadvertent parathyroidectomy. In total 36 PTGs were injured, 35 PTGs that were considered viable were transplanted in the sternocleidomastoid muscle. Concerning the type neck dissection; 15 patients (32.6%) got a central neck dissection, 22 patients (47.8%) got a posterolateral neck dissection and 9 patients (19.6%) got both anterior and posterolateral dissection [13].

Senior surgeons performed 429 interventions (93.1%) and 32 interventions (6.9%) were performed by residents under supervision. In postoperative 149 patients (32.3%) developed transient hypocalcaemia and 8 patients (1.7%) developed permanent hypocalcaemia needing calcium supplementation indefinitely. In addition 25 patients (5.4%) presented post-operative dysphonia, and all 25 received steroid treatments, 10 received vocal cord rehabilitation treatment. The mean age of patients who developed transient hypocalcaemia is 49.2 +/-13.7 years versus 47.5 +/- 14.5 years with those who didn't , with p= 0.234. Transient hypocalcaemia was observed in 141 female patients (34.3%) versus 8 male patients (16%), with p =0.009. One hundred and forty seven patients (36.0%) that underwent bilateral intervention developed transient hypocalcaemia versus 2 patients (3.8%) that underwent unilateral intervention, with p<0.01.

Concerning preoperative biological factors; transient hypocalcaemia was observed in 57 patients (39.9%) who had preoperative hyperthyroidism versus 92 patients (29.5%) with normal TSH level, with p=0.029. Out of the 14 patients who presented pre operative hypocalcemia 11 (78.6%) of them developed post- operative hypocalcaemia versus 87 patients (32.8%) who developed post-operative hypocalcaemia without pre-operative hypocalcaemia, with p=0.001.

During intervention out of the 36 patients who sustained inadvertent parathyroidectomy transient hypocalcaemia was observed with 18 patients (50%) with incidental parathyroidectomy versus 131 patients (30.8%) without incidental parathyroidectomy, with p=0.018. And 17 patients (51.5%) with PTGs transplantation developed transient hypocalcaemia versus 132 patients (30.8%) who didn't have PTGs transplantation, with p=0,014.

Out of the 5 patients who are suspected to have lesion of a recurrent nerves 3 (60%) of them developed post-operative hypocalcaemia versus 154 patients (33.8%) out of the 456 patients who had no lesion of any of the recurrent nerves during surgery, with p= 0.343.

Concerning Neck dissection Transient hypocalcaemia was observed with 11 patients (50.0%) who got a bilateral neck dissection versus 5 patients (20.8%) who underwent unilateral neck dissections, with p= 0.038. Factors such as parathyroid incindentaloma ,surgical expertise, parathyroid glands detection, recurrent nerve detection and post thyroidectomy hematomas and hemorrhage that needed surgical re-intervention were also analyzed and were found to have no impact on the reccurence of post thyroidectomy hypocalcaemia (p>0.05).

A multivariate analysis logistic regression analysis identified three independent risk factor for transient hypocalcemia in patients who underwent thyroidectomy: female gender, preoperative hypocalcaemia and bilateralintervention. In addition women are more likely to have disease associated with a variety of hormones, such as menopausal syndrome, osteoporosis and vitamin D deficiency, which are possible confounding factors [76;77]. Furthermore a Moroccan study by Allali F on 415 women aged 24 to 77 years demonstrated that Vitamin D Deficiency (VDD) affects more than 90% of Moroccan women. However, preoperative vitamin D and preoperative bone mineral density were not measured in our study [14].

We found the rate of post-operative and transient hypocalcaemia significantly higher among the group of patients undergoing bilateral interventions (p<0.001). This may seem to be an obvious result as during unilateral intervention, only one side is explored, thus only exposing 2 parathyroid glands whiles the contralateral remnant lobe remains intact. It is known that a single functioning gland is able to maintain calcium metabolism at normal values. As expected, our study demonstrated that preoperative hypocalcaemia is significantly correlated with post-operative hypocalcaemia and transient hypocalcaemia on both univariate (p=0.001) and multivariate (p=0.001) analysis.Thus patients with preoppertive hypocalcymia are 22.21 times more likely to develop transient hypocaleceam with a 95% Confidence interval of [3.58-137.72]. The same results were found in prior retrospective study of 349 patients undergoing thyroidectomy. This could be a result of preoperative vitamine difficency , which is often found in women . It is established that Calcium absorption is regulated primarily via parathyroid hormone and vitamin D. Vitamin D3 (cholecalciferol) is acquired via diet or photon-stimulated conversion of precursors in the skin. Activated vitamin D increases calcium absorption from the intestine. Thus Vitamin D deficiency is a known independent risk factor for post- thyroidectomy hypocalcaemia. Secondary hyperparathyroidism due to low calcium and vitamin D levels is thought to be the mechanism behind the increased risk of hypocalcaemia in patients with vitamin D deficiency. In Addition Hypomagnesemia or hypermagnesemia could also alter calcemia homeostasis , but was not assed in our study (Table 2).

Variables	N=461 % (n)	Transient Hypocal	P value	Permanent Hypocal	P value
Type of intervention			0		0.605
Bilateral	88.5% (408)	36.0% (147)		1.96% (8)	
Unilateral	11.5% (53)	3.8% (2)		0% (0)	
Bilateral intervention:			0.649		0.472
2 or more PTGs seen	92.4% (377)	36.3% (137)		1.9% (7)	
<2 PTGs seen	7.6% (31)	32.3% (10)		3.2% (1)	
Unilateral intervention:			0.375		
Both PTGs seen	79.2% (42)	2.4% (1)		0	
1 PTG seen	20.8% (11)	9.1% (1)		0	
Inadvertant parathyroidectomy			0.018		1
Yes	7.8% (36)	50% (18)		0% (0)	
No	92.2% (425)	30.8% (131)		1.9% (8)	
PTGs auto-implantation			0.014		1
Yes	7.2% (33)	51.5% (17)		0% (0)	
No	92.8% (428)	30.8% (132)		1.9% (8)	
Parathyroid incidentaloma			0.335		0.084
Yes	1.1% (5)	60% (3)		20% (1)	
No	98.9% (456)	32.0% (146)		1.5% (7)	
Suspected Lesion of the recurrent nerve			0.335		1
Lesion suspected	1.1% (5)	60% (3)		0% (0)	
No Lesion suspected	98.9% (456)	32.0% (146)		1.8% (8)	
Central neck dissection vs Postero-lateral neck dissection			0.829		
CND	52.2% (24)	33.3% (8)		0	
LND	47.8% (22)	36.4 (8)		0	
Bilateral neck dissection vs Unilateral dissection			0.038		
Bilateral ND	47.8% (22)	50% (11)		0	
Unilateral ND	52.2% (24)	20.8% (5)		0	
Surgical expertise			0.19		0.44
Residents	6.9% (32)	21.9% (7)	3.1% (1)		

Senior surgeon	93.1% (429)	33.1% (142)	1.6% (7)		

Table 2: Surgical Factors associated with transient and permanent hypocalcaemia

Conclusion

Overall, main conclusions were drawn from the present study: female gender, preoperative hypocalcaemia, and bilateral intervention are independent predictors of post-operative and transient hypocalcaemia. Additionally, in patients with preoperative hyperthyroidism, bilateral CND, 1st time thyroidectomy, and inadvertent thyroidectomy confers an increased risk of developing transient hypocalcaemia .We also confirmed that suspected lesion of the RLN is a risk factor for post-operative dysphonia. Based on our experience preoperative hypocalcaemia dosage should be systematic for all patients undergoing thyroidectomy and preoperative vitamin D evaluation for women should be considered. Perhaps preoperative calcium treatment and vitamin D supplementation for patients with risk factors may prevent post thyroidectomy hypocalcaemia, a prospective study need to be done to convey on the efficiency.

Declaration

Permissions

This is an original manuscript; it has not been published elsewhere. Our study has been approved by the appropriate ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Conflict of Interest

The authors have no financial or personal conflict of interest.

Ability of data and material

The data that support the findings of this study are available from the patient's registry qt the surgical department of Hospital Ibn Sina m but restrictions apply to the availability of these data, which were

used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the chief of surgery.

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