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Research Article

Predictors and Risk Factors of Hypoparathyroidism After Total Thyroidectomy: A Prospective Study

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Received: April 22, 2021; **Published:** April 30, 2021

Abstract

Background: Hypoparathyroidism is a frequent complication of thyroid surgery, its incidence in the literature varies from 1.6% to more than 50% of cases. It is a major cause of prolonged hospital stays requiring long-term calcium supplementation for some patients and very close clinical and biological post-operative follow-up.

Purpose: The purpose of this study is to determine the prevalence of hypocalcaemia in thyroid surgery through our experience of ENT and CFC service at the Rabat specialty hospital and the predictive factors for its occurrence.

Materials and Methods: This is a prospective, analytical study of patients undergoing total thyroidectomy over a period from April 2016 and November 2018. This study was carried out within the ORL and CCF department at the Rabat specialty hospital in Morocco. Outcome measures were initial postoperative hypocalcemia defined as serum calcium below 2.0 mmol/l after total thyroidectomy within 48h and persistent hypocalcemia defined as serum calcium below 2.0 mmol/l above six months and/or the need for additional calcium and vitamin D supplementation.

Results: Initial postoperative hypocalcemia was present in 62 of 240 patients (25.83%) with 72 out of 240 patients (30%) developing symptoms. 21 patients (8.75%) had a persistent hypocalcemia above six months. In the binary logistic regression analysis, Central neck dissection (OR 2.2; CI95% 1.3 - 3.8), Prolonged surgery time > 189 minutes (OR 1.6; CI95% 1.1 - 2.1) and Malignant anatomopathological diagnosis (OR 1.5; CI95% 1.2 - 2.2) were associated with initial hypocalcemia while only central neck dissection was shown to be independently associated with persistent hypocalcemia (OR 12.32; CI95% 7.56 - 23.34).

Conclusion: Post thyroidectomy hypocalcemia constitutes a diagnostic and therapeutic emergency, and its prevalence remains high. Good knowledge of the predictive factors will allow any surgeon to avoid as much as possible the occurrence of hypoparathyroidism after thyroid surgery.

Keywords: *Hypoparathyroidism; Hypocalcemia; Total Thyroidectomy*

Introduction

Hypoparathyroidism is a frequent complication of thyroid surgery [1]. Its incidence in the literature varies from 1.6% to more than 50% [2]. This complication was described with high rates from the start of thyroid surgery, and was responsible for several deaths. This quickly led to modifying the operative technique by locating the parathyroid glands intraoperatively and by performing a vascular liga-

tion. It also benefited from progress in improving the technique by KOCHER in 1917. Since then, the risk has decreased but it persists and must always be announced [2,3].

Total post thyroidectomy hypocalcemia is defined by a level of calcemia less than 80 mg / l [4-7]. It can be asymptomatic, particularly if calcium levels are reduced slightly or symptomatic with typical manifestations ranging from paresthesias and muscle spasms to signs of Chvostek and Trousseau [3]. It is a major cause of prolonged hospital stays requiring for some patients long-term calcium supplementation and very close clinical and biological post-operative follow-up [2]. Therefore, we analysed a consecutive cohort of total thyroidectomies in order to identify further potential risk factors for the development and persistence of postoperative hypocalcemia after total thyroidectomy.

Materials and Methods

Study design

In this prospective observational study, between April 2016 and November 2018 we evaluated 240 patients submitted to total thyroidectomy in the otorhinolaryngology and head and neck surgery department at Specialties Hospital in Rabat, Morocco, who met the selection criteria described below. All patients were informed and made clear about the study. They all signed the Informed Consent Form.

Settings

The Specialties Hospital is a teaching hospital, which consists of 4 clinical services: otorhinolaryngology and head and neck surgery, neurology, neurosurgery, ophthalmology with a radiological and biological unit and an administrative service. The otorhinolaryngology department is the biggest in CHIS. It has the capacity of seventy beds. We practice otology, rhinology, oncology, and maxillofacial surgery. We have hearing and laryngological explorations and daily external consultations of about over than 50 per day.

Patients

The study included patients aged between 18 and 85 years old undergoing total thyroidectomy in our department. Resumption for thyroid totalization on the remaining lobe or stumps even if the initial procedure was performed in another center, patients who had an enlarged thyroidectomy secondary to Infiltration of the skin of the anterior cervical region and skin fistulizations and laryngeal involvement: Total thyroidectomy enlarged to the larynx.

The study excluded: Patients undergoing thyroid resection other than total thyroidectomy, Patients who have not benefited from postoperative calcium assessments, cases with uncontrolled hyper- or hypothyroidism, parathyroid disease, those who had undergone any type of dialytic procedure and those who were on medication which altered serum calcium concentrations.

Each surgery was performed by an experienced endocrine surgeon (Senior) or by a resident operating under supervision (Junior). The standard surgical technique involved capsular dissection of the thyroid gland with careful identification and conservation of the parathyroid glands, together with the recurrent laryngeal nerve. Reimplantation of a parathyroid gland was only performed if the gland was accidentally resected or judged to be devascularized.

Protocol

Hypocalcemic signs and symptoms including: Numbness of the extremities, facial paresthesias, muscular spasms and Chvostek's or Trousseau's signs were registered by a surgeon or a nurse twice a day from the day of surgery until discharge.

Postoperative biochemical hypocalcemia was defined as uncorrected serum calcium below 2.0 mmol/l within 48 hours [8,9]. Persistent hypocalcemia was defined as a serum calcium below 2.0 mmol/l and/or the need for supplementation with calcium and/or 1,25 OH vitamin D above 6 months after total thyroidectomy [9,10].

Oral calcium was routinely administered when a postoperative biochemical hypocalcemia below 2.0 mmol/l was proven. If clinical symptoms of hypocalcemia were present or did not improve over time. Oral 1, 25 OH vitamin D and if not sufficient intravenous calcium gluconate were added.

Patients with normal serum calcium concentrations were discharged on postoperative day 2 while in patients with significant hypocalcemia, serum calcium was measured daily until normalization was observed, so the patients were cleared for discharge. After discharge, patients were evaluated on an outpatient basis to control serum calcium on postoperative day 7. Supplementation therapy was gradually reduced based on serum calcium measurements on an outpatient basis.

Patients requiring treatment were followed weekly until normalization of their serum calcium concentrations after withdrawal of any supplementation therapy for > 1 week.

Data collection

The following general data were collected for sample characterization: gender, age (in years), BMI (Body mass index), personal and family history of thyroid disease (multinodular goiter, autoimmune thyroiditis, thyroid cancer), anatomopathological diagnosis (whether malignant or benign), and whether Cervical lymph node dissections included central neck dissection (CND) and CND combined or not with lateral neck dissection (LND). LND involved the usual method of removing lymph nodes from levels II to IV, sparing the internal jugular vein, spinal accessory nerve, and sternocleidomastoid muscle, surgery time (min) /The duration of the operation: was appreciated in minutes, the length of the post-operative stay: normal: less than or equal to 3 days, extended: length of stay exceeding 3 days.

Difficulties encountered during intervention: related to bleeding, related to location of recurrent nerve, of parathyroid glands or related to the fibrosis found during surgical resumption.

Statistical analysis

The statistical analysis was conducted with SPSS version 18.0 (SPSS, Chicago, IL, USA).

Descriptive analysis: Descriptive analysis of data was performed with frequency and percentages for qualitative variables and means and standard deviations for quantitative variables. Comparison of variables with symmetrical distribution was made using the Student's *t*-Test. Variables with asymmetric distribution were adjusted using a generalized linear model with gamma distribution followed by multiple comparisons.

Analytical analysis: The descriptive analysis of our population was followed by a univariate analysis based on the comparison of different characteristics in subjects with or without post total thyroidectomy hypocalcemia.

The quantitative variables with Gaussian distribution were compared by the Student test. Non-Gaussian quantitative variables were compared using the Man Whitney test. The qualitative variables were compared by the Chi-square test.

The significance level p was set at 0.05 (95% confidence interval). The above mentioned factors were all analyzed in a univariate logistic regression analysis if they were associated with transient postoperative biochemical hypocalcemia and persistent hypocalcemia. Factors identified as significant in a univariate logistic regression analysis were selected to perform a multiple logistic regression analysis.

Results

From the patients evaluated, 204 (85%) were females. Mean (± Standard Deviation) age of the sample was 49,58 (± 11,96) years. Malignancy by anatomopathological exam was found in 48 (20%) patients.

Initial postoperative biochemical hypocalcemia

Initial postoperative biochemical hypocalcemia was present in 62 (25.83%) patients.

54 (22.5%) showed minor symptoms of hypocalcemia (numbness of the extremities, facial paresthesias or muscular spasms). 18 (7,5%) showed Chvostek's or Trousseau's signs.

Treatment with oral calcium was necessary in 49 patients (20.42%), intravenous calcium in 20 patients (8,33%) and vitamin D in 21 patients (8,75%). Factors found on univariate analysis that significantly increased the risk of developing initial postoperative hypocalcemia were high BMI (p = 0,015), Central neck dissection (p = 0,00), Difficulties encountered during intervention (p = 0,013), longer operative time (p = 0,01), Extended days of post-operative stay (p = 0,02) and malignant anatomopathological diagnosis (p = 0,00) (Table 1).

Variables	Hypocalcemia		P
	Yes	No	
Age, years (mean ± SD)	51,41 ± (14,45)	48,94 ± (10,98)	0,08
Gender			
Male (%)	14 (38,9)	22 (61,1)	0,12
Female (%)	48 (23,5)	156 (76,5)	
BMI	29,41 ± 4,88	26,73 ± 5,78	0,015
Hormonal status			0,064
Euthyroid (%)	44 (21,8)	158 (78,2)	
Hypothyroid (%)	10 (45,5)	12 (54,5)	
Hyperthyroid (%)	8 (50)	8 (50)	
Central neck dissection			0,00
Yes	30 (65,2)	16 (34,8)	
No	32 (16,5)	162 (83,5)	
Educational type of surgery			0,081
Senior	42 (35)	78 (65)	
Junior	20 (16,7)	100 (83,5)	
Surgical intervention			0,013
Easy	16 (10,8)	132 (89,2)	
Difficult	46 (50)	46 (50)	
Surgery time (min)	135,16 (± 29,87)	112,80 (± 29)	0 ,01
Days of hospital stay			0,02
Normal	26 (13,68)	164 (86,31)	
Extended	36 (72)	14 (28)	
Pathology			0,00
Malignant	28 (60,9)	18 (39,1)	
Benign	32 (16,8)	158 (83,2)	

Table 1: *Clinicopathologic characteristics of the patients and factors that affecting to the development of initial postoperative hypocalcemia.*

These parameters were analyzed using a logistic regression model to determine the risk of initial post thyroidectomy hypocalcemia, and the estimated relative risk was calculated (Table 2). After logistic regression analysis, Central neck dissection (p = 0.001; odds ratio [OR] = 2.179 [range = 1.291-3.842]), Surgery time (p = 0.011; odds ratio [OR] = 1.649 [range = 1.118 - 2.198]) and malignant anatomopathological diagnosis (p = 0.025; odds ratio [OR] = 1.473 [range = 1.098 - 2.189]) were the significant factors that affected the development of transient hypocalcemia.

Variables	p	Odds Ratio (95% CI)
High BMI	0.395	1.412 [0.965 - 1.529]
Central neck dissection	0.001	2.179 [1.291 - 3.842]
Difficulties of surgical intervention	0.254	0.992 [0.989 - 1.002]
Longer surgery time	0.011	1.649 [1.118 - 2.198]
Extended days of hospital stay	0.170	1.241 [0.974 - 1.599]
Malignant anatomopathological diagnosis	0.025	1.473 [1.098 - 2.189]

Table 2: *Multivariate analysis of factors that affecting to the development of initial post-thyroidectomy hypocalcemia.*

Persistent hypocalcemia

Persistent biochemical hypocalcemia and/or supplementation with calcium and/or vitamin D was present in 21 (8.75%) patients. 14 patients of 21 had a biochemical normocalcemia under supplementation with calcium and/or vitamin D and 7 patients displayed a persistent biochemical hypocalcemia despite supplementation with calcium and/or vitamin D.

Factors found on univariate analysis that significantly increased the risk of developing persistent hypocalcemia were high BMI (p = 0,021), Central neck dissection (p = 0,031) and malignant anatomopathological diagnosis (p = 0,029) (Table 3).

Variables	Hypocalcemia		P
	Yes	No	
Age, years (mean ± SD)	52,12 (± 13,21)	45,64 (± 11,12)	0,08
Gender			
Male (%)	4 (33,33)	8 (66,66)	0,09
Female (%)	4 (17,39)	38 (82,60)	
BMI	30,11 (3,22)	24,34 (4,13)	0,021
Hormonal status			0,123
Euthyroid (%)	8 (16)	42 (84)	
Hypothyroid (%)	0 (0)	2 (100)	
Hyperthyroid (%)	0 (0)	2 (100)	
Central neck dissection			0,031
Yes	44 (91,66)	4 (8,33)	
No	4 (66,66)	2 (33,33)	
Educational type of surgery			0,135
Senior	3 (14,28)	18 (85,71)	
Junior	1 (16,66)	5 (83,33)	

Surgical intervention			0,082
Easy	4 (15,38)	22 (84,61)	
Difficult	4 (14,28)	24 (85,71)	
Surgery time (min)	146,32 (± 21,63)	123,80 (± 18,13)	0,13
Days of hospital stay			0,197
Normal	4 (9,52)	38 (90,47)	
Extended	4 (33,33)	8 (66,66)	
Pathology			0,029
Malignant	4 (8,33)	44 (91,66)	
Benign	4 (66,66)	2 (33,33)	

Table 3: *Clinicopathologic characteristics of the patients and factors that affecting to the development of permanent hypocalcemia.*

These parameters were analyzed using a logistic regression model to determine the risk of persistent post thyroidectomy hypocalcemia, in this case only central neck dissection was shown to be an independent factor associated with developing persistent hypocalcemia (p = 0.002; odds ratio [OR] = 12.32 [range = 7.56 - 23.34]) (Table 4).

Variables	p	Odds Ratio (95% CI)
High BMI	- 0.371	0.468 [0.325 - 0,876]
Central neck dissection	0.002	12.32 [7.56 - 23.34]
Malignant anatomopathological diagnosis	0.184	1.267 [0.671 - 2.497]

Table 4: *Multivariate analysis of variables associated with persistent post thyroidectomy hypocalcemia.*

Discussion

The present work analyzing 240 patients after total thyroidectomy shows that central neck dissection was the only factor independently associated with persistent hypocalcemia. Besides the known risk factors, malignant anatomopathological diagnosis, prolonged surgery time and central neck dissection were also associated with initial postoperative hypocalcemia prevalence. The rather high rate of persistent hypocalcemia in our study (8.75%) matches with a report from an UK registry, stating that approximately 7% of patients needed calcium or vitamin D supplementation six months after total thyroidectomy [11].

CND was significant on multivariate analysis of Initial postoperative and persistent biochemical hypocalcemia. This may mean that the CND itself was more likely to have damaged the, because the preserved contralateral parathyroid gland in patients who underwent unilateral CND in whom the ipsilateral parathyroid gland was sacrificed might have prevented the development of hypoparathyroidism. Sousa., *et al*. studied 333 patients and found that neck dissection was significantly predictive of hypocalcemia, but not definitive hypoparathyroidism [12]. This could be explained by the fact that during central lymph node dissection, the upper parathyroid gland could be left in place with satisfactory vascularization due to its fixed topography, however the lower parathyroid gland, which is located in the thyrothymic fat, could not always be preserved in situ during lymph node dissection. Hence, the interest of preserving upper parathyroid glands. In fact patients who require CND must be carefully selected and the current guidelines regarding CND might need to be adapted [13].

We found that an operative time exceeding 2 hours was a risk factor for developing initial post-thyroidectomy hypocalcemia. The mean operating time was also a risk factor for postoperative hypocalcemia in a study by Montana., *et al*. patients whose operating time

had exceeded 3 hours had a statistically greater risk of developing hypocalcemia unlike those whose operating time was less than 3 hours [14]. This would be explained by the fact that longer operative times implies a more complicated procedure, and central neck dissections implies a more involved surgeries as this procedure is commonly used for more advanced thyroid cancer [15]. However, a study by Ilker., *et al*. [16] didn't find any correlation between the prolonged operating time and the occurrence of post-operative hypocalcemia.

In our study, there is a statistically significant correlation between malignant histological results and the occurrence of transient post thyroidectomy hypocalcemia. In several studies, transient hypocalcemia was found when histological result is malignant in 13.6% to 19.3% of patients [17,18], it can even reach 75% of patients [19,20], while permanent hypocalcemia linked to definitive hypoparathyroidism after one year is noted in 3.3% to 5.8% of patients depending on the series [18-22].

Often, advanced thyroid cancer implies a more complicated procedure, and central neck dissections implies a more involved surgeries, therefore it is logical that in more involved, complicated procedures, there is an increased potential of parathyroid gland removal, which may lead to hypocalcemia [15].

In this study, we did not find a statistically significant relationship between patient's gender and the occurrence of post thyroidectomy hypocalcemia. However previous studies reported conflicting results with respect to female gender as a risk factor for post thyroidectomy hypocalcemia [23,24]. The difference may be secondary to the high frequency of vitamin D deficiency seen in women, especially during menopause. In a large study of a group of women with Graves' disease, Yamashita demonstrated that postoperative hypocalcemia was more common in patients with vitamin D levels < 10 ng/ml. In 2011 [25], Erbil had published similar results [26].

Postoperative parathormone (PTH) level is a better predictor of hypocalcemia than isolated calcemia [27,28]. For Wang., *et al*. if the postoperative PTH is higher than or equal to 5 pg/mL, no vitamin supplementation is necessary [29]. In a meta-analysis of four Australian studies, Grodski., *et al*. showed that undetectable PTH at the fourth postoperative hour was predictive of hypocalcemia with a sensitivity and specificity of 48.4% and 96.7% respectively [30]. However, its sensitivity and specificity depend on the chosen threshold value [31,32]. Taking into account the PTH decay rate improves these values. In a meta-analysis combining nine studies, Noordzij., *et al*. showed that a decrease of more than 65% in the concentration of PTH between its basal period and the sixth postoperative hour predicted hypocalcemia with sensitivity and specificity respectively of 96,4% and 91.4% [33]. These results have been confirmed by numerous studies including those recently published by Lecerf., *et al* [34]. Post-operative parathormone levels were therefore not assessed in this work to further differentiate the diagnosis of postoperative hypocalcemia as a valid conclusion was not possible due inconsistent determinations at varying time points.

Conclusion

Knowing which patients will experience a hypocalcemia will allow us to anticipate therapy in order to reduce symptoms and guarantee a timely and safe discharge.

Many studies have evaluated the possible risk factors for post-thyroidectomy hypocalcemia, some of which have been generally accepted. However, establishing these risk factors continues to be a challenge.

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