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Postoperative hypocalcaemia predictors after total thyroidectomy

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Summary

Introduction and objective: Given the increasing number of thyroid surgeries, the incidence of post-surgical hypoparathyroidism is on the rise. The frequency of hypocalcaemia due to hypoparathyroidism after total thyroidectomy is highly variable according to the literature (0.3-68%). The primary objective of this study is to analyze the biochemical, surgical and demographic factors related to an increased risk of hypocalcaemia.

Methodology: This retrospective study encompasses 297 patients who underwent total thyroidectomy over a period of 8 years in a tertiary hospital. Demographic, clinical and biochemical data, both preoperative, intraoperative and postoperative, and their relationship with postoperative hypocalcaemia are analyzed.

Results: The rate of total hypocalcaemia was 40.2%, being transient in 26.1%.

Statistically significant variables were age ($p=0.04$), Graves' disease ($p=0.04$), carcinoma confirmed by pathology ($p=0.04$), two-stage thyroidectomy ($p=0.00$), the number of transplanted parathyroids ($p=0.00$) and pre- and post-operative PTH ($p=0.03$ and $p=0.00$) and the PTH gradient ($p=0.00$).

Conclusions: This study demonstrates that there are a series of risk factors intrinsic to the patient and to the surgical procedure capable of predicting the risk of hypocalcaemia after total thyroidectomy. Possibly, the optimization of the surgical technique could prevent the appearance of hypocalcaemia after total thyroidectomy in some cases, while in others, the identification of these factors post-op could allow early detection and effective treatment of these patients. In the present study, age, Graves' disease, and parathyroid autotransplantation were associated with postoperative hypocalcaemia. Thyroid carcinoma and two-stage thyroidectomy were protective factors.

Key words: total thyroidectomy, hypocalcaemia, hypoparathyroidism, risk factors.

INTRODUCTION

Total thyroidectomy is one of the most frequent cervical surgeries, with a growing incidence in recent decades due to the increase in diagnoses of thyroid disease¹⁻³. One of the thyroid surgery complications is hypocalcaemia due to iatrogenic hypoparathyroidism^{1,2,4-11}. This hypo-function may be due to direct mechanical or thermal damage, inadvertent devascularization or removal of the parathyroid glands, post-surgical edema or hemorrhagic complications^{1-4,8,9,12}. Both the direct damage, as well as the edema and devascularization, can be reversed over time. This explains why hypoparathyroidism is usually transient in most cases^{3,8,12}.

According to the latest data provided by the Spanish Thyroid Cancer Association (AECAT), 75% of cases of hypoparathyroidism in Spain occur as a result of total

thyroidectomy, affecting between 10,200 and 17,300 patients. This is the most frequent complication after a total thyroidectomy.

Its frequency varies greatly in the literature, from 0.3% to 68%^{2,7,10-15}. It is difficult to interpret and compare the results of the various studies due to the lack of international agreement. Recently, the SEORL-CCC, together with the SEEN, have reached a consensus where they provide more specific definitions, and also recommendations to reduce hypoparathyroidism¹⁶.

Given its high incidence, studying the predictive factors that help identify those patients with a high risk of postoperative hypocalcaemia assumes considerable importance. The main objective of this study is to analyze the biochemical, surgical and demographic factors related to an increased risk of immediate postoperative hypocalcaemia.



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MATERIAL AND METHODS

This retrospective study of 297 patients who underwent total thyroidectomy was carried out from January 2011 to December 2018 in a tertiary care hospital.

All patients who underwent total thyroidectomy were included, both in one and in two stages, and regardless of the reason for the indication. All were referred from the Endocrinology Service of the center itself after a complete study. In each of them, the usual protocol was performed by the ENT service: complete history, cervical palpation and laryngoscopy to assess the mobility of the vocal cords.

In this study, post-op hypocalcaemia was defined as serum calcium <8.5 mg/dL and/or appearance of symptoms typical of hypocalcaemia. Hypoparathyroidism is defined as the presence of hypocalcaemia with low or inadequately normal PTH levels. This is deemed permanent if this situation lasts more than 12 months.

Preoperative, intraoperative, and post-op demographic, clinical and biochemical data were collected from each patient through medical records. Data on the surgical reports were collected, including the number of surgeries performed (1 or 2 times), the number of observed and spared parathyroid glands and also the autotransplanted parathyroid glands, the presence of intrathoracic thyroid extension, and the association of other surgical procedures with the thyroidectomy, such as lymph node dissections.

Among the biochemical parameters collected, the following stand out: PTH, albumin-corrected calcium and preoperative vitamin D; postoperative phosphorus, albumin-corrected postoperative calcium at 6 and 24 hours, and postoperative PTH at 24 hours after total thyroidectomy. Finally, in terms of factors related to the patient and their disease, we include age, gender, Graves' disease or carcinoma confirmed by pathological anatomy.

The autoanalyzer used to determine PTH levels was the Roche-Hitachi Cobas® 6000 Series system. The normal range for this test is between 15 and 65 pg/mL. Spectrophotometry was used to determine both serum calcium and vitamin D.

Data analysis was carried out with R software version 3.6.2. All variables were subjected to a normality test. The Student's t test compared continuous parametric variables, the Mann-Whitney U test for non-parametric continuous variables and the χ^2 test for proportions, considering a value of $p < 0.05$ as significant. The data are presented in percentages and averages with their respective standard deviations and ranges. For the analysis of the effect size based on differences between groups, Cohen's d and the Odds Ratio (OR) were used. To simplify the graphic presentation of the data, tables and histograms have been used. A table is shown with the risk factors analyzed (table 1).

RESULTS

This study included 297 patients who underwent total thyroidectomy, the vast majority being women (81.5%), with a mean age of 54.2 ± 14.2 years [17-90]. Forty-four patients underwent a two-stage total thyroidectomy, and in addition, 40 of them underwent cervical dissection. More than half of the procedures were performed for benign disease (64%), and of these, 32% with preoperative thyroid hyperfunction (52 with thyrotoxicosis and 43 with sub-clinical hyperthyroidism). Of the patients included in the present sample, 16 had a docu-

mented radiological image of intrathoracic goiter. Of those with diagnostic confirmation of cancer (33%), 92 cases corresponded to the differentiated subtype and 6 cases to medullary carcinoma.

Statistical analysis showed significant differences between hypocalcaemia and age ($p=0.04$), Graves' disease ($p=0.04$), carcinoma confirmed by pathology ($p=0.04$), thyroidectomy in two times ($p=0.00$), the number of transplanted parathyroids ($p=0.00$), preoperative and postoperative PTH at 24h ($p=0.03$ and $p=0.00$) and the PTH gradient ($p=0.00$). In contrast, no significant relationship was shown with gender ($p=0.22$), preoperative calcium level ($p=0.54$), preoperative vitamin D ($p=0.24$), goiter with intrathoracic extension ($p=0.61$), cervical lymph node dissection ($p=0.33$) or the number of parathyroid glands observed during surgery ($p=0.99$) (table 2).

A total of 187 complications related to thyroid surgery were recorded in 154 patients. With great difference, the most frequent complication was hypoparathyroidism with 65%.

40.2% of the patients who underwent total thyroidectomy developed hypocalcaemia in the postoperative period (figure 1). Of the patients with hypocalcaemia, 43 recovered their calcium levels in the first 3 months, 22 in the following 3 months, and finally 13 after the sixth month of follow-up. Therefore, the total number of patients with transient hypocalcemia was 78 cases (26.1%) and the remaining patients who did not recover after 12 months of follow-up were classified as permanent hypocalcemia with a total of 42 cases (14.1%). (figure 2). No case of hypocalcaemia could be attributed to hungry bone syndrome.

DISCUSSION

According to the latest data provided by the Spanish Thyroid Cancer Association (AECAT), 75% of cases of hypoparathyroidism in Spain occur as a result of total thyroidectomy, affecting between 10,200 and 17,300 patients. This is the most frequent complication after a total thyroidectomy.

No factor alone predicts post-total thyroidectomy hypocalcemia accurately. Rather, it is about several factors that interact with each other, with a high probability of jointly predicting hypocalcaemia. For this reason, there is a great discrepancy in the literature. Some authors propose as possible risk factors the fact of completing a total

Table 1. Risk factors analyzed in relation to hypocalcaemia

Biochemical factors	-Preoperative CA -Preoperative PTH -Preoperative vitamin D -Postoperative PTH -PTH gradient (% decrease)
Intraoperative factors	-Thyroidectomy in 1 or 2 stages -Lymph node emptying -Number of parathyroid glands observed -Number of autotransplanted parathyroids
Factors related to the patient and disease	-Age -Gender -Overactive thyroid -Goiter with intra-thoracic extension -Definitive AP diagnosis

Table 2. Summary of the statistical analysis of the factors in relation to immediate hypocalcaemia

	Normocalcaemia	Hypocalcaemia	P-value	Magnitude of the effect *
Age (years)	55.3	52.7	rl (p = 0.04)	r = 0.116 IC (0.002 – 0.227) p = 0.04
Graves disease	13 (40.6%)	19 (59.4%)	χ^2 (p = 0.04)	OR = 2.23 IC (1.05 – 4.70) p = 0.03
AP Diagnosis Thyroid Cancer	66 (61.7%)	32 (38.3%)	χ^2 (p = 0.04)	OR = 0.58 IC (0.35 – 0.96) p = 0.03
2-stage total thyroidectomy	39 (84.8%)	7 (15.2%)	χ^2 (p = 0.00)	OR = 0.22 IC (0.09 – 0.50) p = 0.00
Parathyroid autotransplantation	14 (31.1%)	31 (68.9%)	χ^2 (p = 0.00)	OR = 4.95 IC (2.37 – 10.32) p = 0.00
Preoperative PTH (pg/ml)	55.2	39.1	t (p = 0.03)	Cohen's d: 0.89 IC (0.01 – 1.77)
Postoperative PTH (pg/ml)	37.2	8.7	u (p = 0.00)	Cohen's d: 2.59 IC (2.19 – 2.99)
PTH gradient (%)	31.2	73.1	u (p = 0.00)	Cohen's d: -1.57 IC (-2.52 – -0.63)
Female gender	139 (57.4%)	103 (42.6%)	χ^2 (p = 0.22)	
Preoperative calcium	9.4	9.5	u (p = 0.54)	
Preoperative vitamin D	28.2	23.3	t (p = 0.24)	
Intrathoracic extension	8 (50%)	8 (50%)	χ^2 (p = 0.61)	
Lymph node dissection	27 (67.5%)	13 (32.5%)	χ^2 (p = 0.33)	
Parathyroid observed	2.5	2.5	u (p = 0.99)	

* OR calculated on the rate of overall postoperative hypocalcaemia.

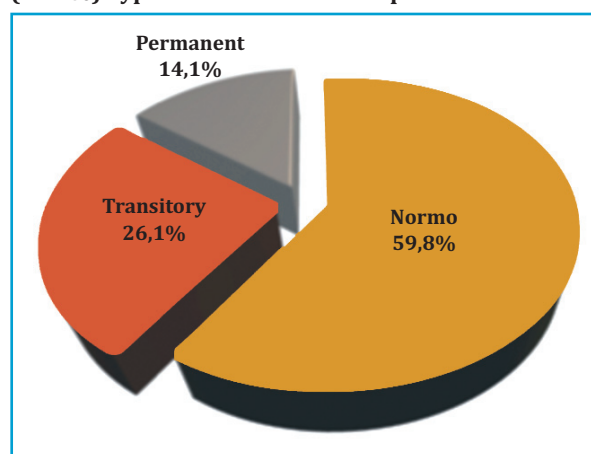
lr: linear regression; r: Pearson's correlation coefficient; t: T-Student test; u: Mann-Whitney U test; χ^2 : Chi² test.

thyroidectomy in a patient previously operated on a hemithyroidectomy, due to the distortion of the anatomy and the difficult recognition of the parathyroids^{14,17}.

The prevalence of transient hypocalcaemia, that is, when it lasts less than 6-12 months, ranges between 10% and 40%. The permanent one, present beyond 6-12 months, varies from 0.12% to 16.2%, according to the literature^{1,3,4,14,18}. Díez et al. published in 2019 a prevalence of hypoparathyroidism at discharge after total thyroidectomy of 48%, of which 52.5% recovered in the first 3-6 months¹². In the present study, the total hypocalcaemia rate was 40.2%, with 54.2% recovering parathyroid function in the first 6 months. Both the transitory (26.1%) and the permanent (14.1%) conform to what is described in the international literature. Thus, studying the predictive factors that help identify those patients with a high risk of post-op hypoparathyroidism is very importance.

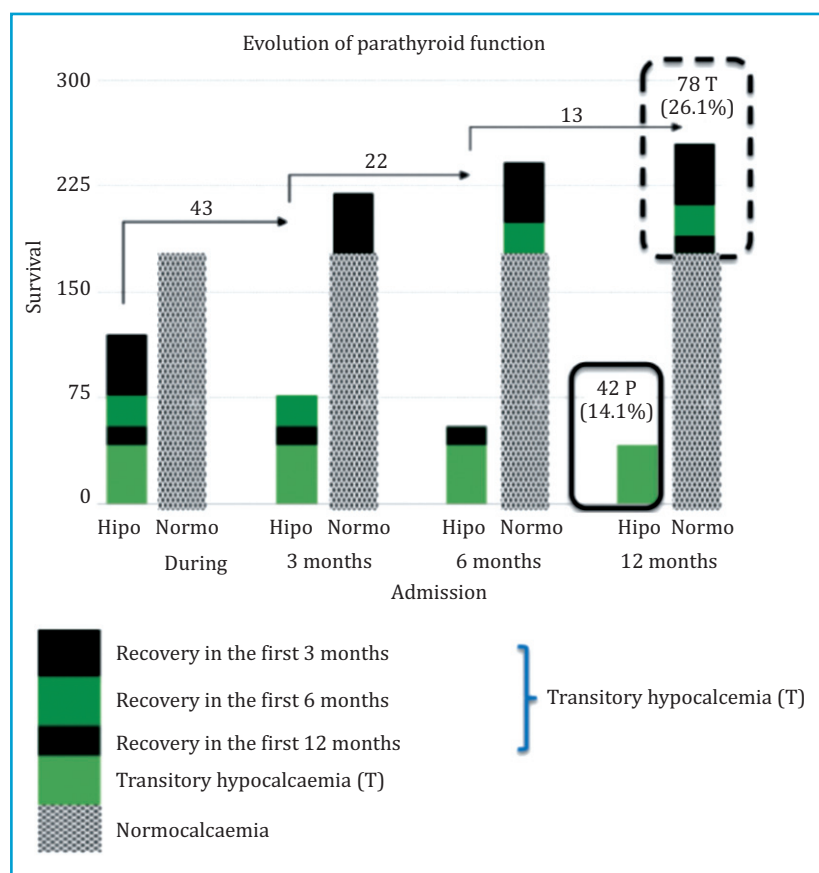
The average PTH at 24 hours was 24.6±17.9 pg/mL [3-78]. Patients with postoperative hypocalcaemia had lower mean PTH levels at 24h (8.7 pg/mL) compared to normocalcemic patients, who obtained a mean of 37.2 pg/mL (p=0.00). PTH has been extensively studied as a predictor of hypocalcaemia in the literature. Some studies propose the gradient or percentage of decrease in the PTH level from the preoperative to the postoperative period, while others propose a single intra-operative or postoperative PTH level some time after surgery. In the present study, the largest effect size is presented by postoperative PTH (Co-

Figure 1. Rates of permanent (14.1%) and transient (26.1%) hypocalcaemia in the sample



hen's d: 2.59), with the additional advantage of costing less, since it does not require preoperative PTH.

Regarding total hemi-thyroidectomy in a second stage, in the present study the relationship found is protective, so that those patients operated on in a single stage present a higher probability (4.55 times greater) of transient hypocalcaemia (p=0.00), coinciding with the study by Díez¹². There is no significant relationship bet-

Figure 2. Evolution of parathyroid function in 1 year of follow-up

54.2% of patients with hypocalcaemia recovered parathyroid function in the first 6 months.

ween total thyroidectomy in a second surgical time and permanent hypocalcaemia ($p=0.29$). This fact could be explained by the reversible parathyroid edema and de-vascularization caused by the surgery, allowing a second surgical time for recovery.

On the other hand, surgery for thyroid cancer^{17,19,20} or for Graves' disease^{17,20} and associated cervical dissection¹⁴ have also been proposed as possible risk factors. In contrast, other studies have not found a significant association¹¹. In the study by Díez et al., the presence of lymph node metastases was a negative predictor of parathyroid recovery in patients with thyroid cancer²¹.

In our study, a significant protective relationship with pathology-confirmed carcinoma is found, probably because

cases suspected of malignancy are handled by a more experienced surgical team. As for Graves' disease, there is a significant direct relationship, probably due to fibrosis due to thyroiditis, with these patients presenting 2.23 times more risk of hypocalcaemia. On the other hand, there is no significant relationship with lymph node drainage.

It is reasonable to think that the fact of preserving at least one parathyroid gland could maintain normal function, and even if it decreased, it could be a transient hypocalcaemia^{22,23}. In various studies, however, including the present study, it has not been possible to demonstrate significantly that the observation and preservation of more than two parathyroids prevents hypocalcaemia^{14,24}.

In some studies, autotransplantation of removed glands could reduce the incidence of hypocalcaemia¹¹. However, in the present study this association is inverse, so that in those patients who have autotransplanted one or more glands, they had a higher risk of hypocalcaemia at discharge (4.95 times more), but this relationship was not significant in terms of permanent hypocalcaemia. This concurs with other studies showing that parathyroid autotransplantation does not guarantee

recovery of parathyroid function^{7,12,18,24}.

CONCLUSIONS

Given the increasing number of thyroid surgeries worldwide, hypocalcaemia is assuming increasing importance and increasing the burden of disease in the population. A more precise understanding of the risk factors would help to better predict the risk of postoperative hypocalcaemia.

The factors directly related to postoperative hypocalcaemia were age, Graves' disease, number of transplanted parathyroids PTH preoperative and postoperative at 24 h and the PTH gradient; meanwhile the carcinoma confirmed by pathology and two-stage thyroidectomy were inversely related.



Conflict of interests: The authors declare no conflict of interest.

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