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Utility of serum parathyroid hormone measurement as a predictor of postthyroidectomy hypocalcemia: A single-center observational study

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Abstract

Introduction: The prevalence of thyroid cancer ranges from 4 to 7%; in Ecuador, it reaches a rate of 16/per 100,000 inhabitants; in most cases, it requires surgical resolution associated with a complication rate of 2 to 15%, of which hypocalcemia represents at least 10.9%. This study aimed to evaluate the usefulness of measuring serum parathyroid hormone (PTH) as a predictor of hypocalcemia after thyroidectomy.

Methods: An analytical cross-sectional study of patients with thyroidectomy was carried out at the Metropolitan Hospital of Quito from January 2017 to December 2019. Demographic, clinical, surgical, and complication variables were analyzed. PTH's relationship with clinical or serological hypocalcemia or both was compared using PR, sensitivity, specificity, PPV, NPV, and LR. Other confounding variables were analyzed using multinomial logistic regression, comparing their ORs.

Results: A total of 212 records were included, 15.6% men and 84.4% women, with an average age of 52.1 years. The main indication for thyroidectomy was papillary carcinoma 123 (58.0%). Complications were 22.7%. A total of 48 patients developed hypocalcemia. PTH levels < 10 ng/l predicted hypocalcemia with a sensitivity of 0.55, specificity of 0.78, PPV of 43%, NPV of 85% and PR of 2.91 (95% CI 1.06 - 8.01).

Conclusions: PTH quantification of 10 ng/l or less helps predict clinical hypocalcemia in patients undergoing total thyroidectomy.

Keywords:

MESH: Parathyroid hormone; Hypocalcemia; Thyroidectomy.

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Introduction

At a global level, the complications of thyroid surgery reach 2 to 15%; among these, the most important are hypoparathyroidism at 10.9%, recurrent laryngeal nerve injury at 5.9%, or bleeding at 3% [1].

In a study carried out in Chile by Gac E et al. of total thyroidectomies performed for thyroid cancer, there was hypocalcemia in 23.7% of surgeries for papillary cancer and in 25% for follicular cancer [2].

In general, hypocalcemia presents acutely after hospital discharge in emergency services. Therefore, strategies have been developed for its early diagnosis, including subclinical measurement of total calcium, ionic calcium, and parathormone levels (PTH).

PTH measurement has been reported to help stratify patients into groups according to their risk of hypocalcemia using two cutoff points. This stratification has made it possible to adequately select 80% of candidates for early hospital discharge and 98% of those who need early calcium supplementation [3].

This study aimed to carry out a diagnostic test in a group of thyroidectomized patients with complications of hypocalcemia in whom parathyroid hormone was measured.

Materials and methods

Study design

This study is cross-sectional and analytical. The source is retrospective.

Scenery

The study was carried out in the Surgery Department of the Metropolitan Hospital of Quito, Ecuador. The study period was from January 1, 2017, to December 31, 2019.

Participants

Patients older than 17 years, undergoing thyroidectomy for any etiology who completed their postsurgical period at the study center and with a complete file for the investigation were included. Patients with previous partial or total thyroid surgery were excluded.

Variables

The study variables included sociodemographic characteristics: age, sex, reason for thyroidectomy, TI-RADS, Bethesda classification, length of hospitalization, surgical procedure, lymphatic resection, surgical time, histopathological diagnosis, number of parathyroid glands removed, parathormone, and total and ionic calcium. before and 12 hours after surgery, presence of bruising, recurrent laryngeal nerve lesions, reintervention, readmission, clinical hypocalcemia, and postsurgical complications with the Clavien Dindo scale.

Data sources/measurements

The source was indirect; the information was acquired from the review of the medical records of the GEMA ® hospital system of the Metropolitan Hospital. The selection of patients was digital, filtered in the IT department of the Metropolitan Hospital, among all the operating protocols between January 1, 2017, and December 31, 2019, and those containing the word "Thyroid" were selected. ", "Thyroid" or "Thyroidectomy" in the field "Performed Procedure"; Only medical records that met the inclusion and exclusion criteria were included.

The author reviewed the medical records individually; the information was collected in a data collection instrument formulated in the Google Forms® computer tool. A "spreadsheet" type document was obtained, which was analyzed again in search of tabulation errors.

Biases

To avoid possible interviewer, information, and memory biases, the principal investigator kept the data at all times with a guide and records approved in the research protocol. Observation and selection bias was avoided by applying the participant selection criteria. All the clinical and paraclinical variables of the period above were recorded. Two researchers independently analyzed each of the records in duplicate, and the variables were recorded in the database once their concordance was verified.

Study size

The sample was nonprobabilistic, a census where all possible cases were included during the study period with a confidence level of 95% and a 5% margin of error; the sample was 345 surveys.

Quantitative variables

Descriptive statistics were used. The results were expressed on a scale of means and standard deviation. Categorical data are presented in proportions.

Statistical analysis

First, a univariate descriptive analysis was performed, taking into account measures of central tendency and standard deviation for quantitative variables and frequencies and percentages for qualitative variables.

The results included the prevalence of the different thyroid pathologies and the etiology that indicated the surgery. In addition, postoperative morbidity rates, including hypoparathyroidism, recurrent laryngeal nerve injury, hematomas, reoperation, and readmission, were reported.

The correlation between PTH levels and clinical hypocalcemia determined by Chevostek and Trousseau signs, laboratory hypocalcemia determined by total and ionic calcium, prevalence ratios (PR), sensitivity, specificity, positive predictive value (PPV), negative predictive value, and likelihood ratios for a test (LR).

Other confounding variables for hypocalcemia and the different analytes to determine hypocalcemia were analyzed using multinomial logistic regression comparing their ORs.
The data were analyzed using the open-access statistical assistant developed
at the University of Amsterdam, JASP (Version 0.11.1).

Results

Participants

A total of 212 records were included (Figure 1).

General characteristics of the sample

A total of 212 papers were studied, 15.6% (33) men and 84.4% (179) women in a 1:5.4 ratio, with an average age of 56.8 ± 14.5 and 47.3 ± 13.6 years, respectively. A total of 107 cases (51.5%) registered their TI-RADS classification in the clinical record, TR 1: 1.4%, TR 2: 2.8%, TR 3: 16.0%, TR 4: 23.6%, and TR 5: 6.6%. A total of 131 cases (61.8%) registered the Bethesda classification in the clinical record: I: 0.5%, II: 3.3%, III: 2.8%, IV: 6.6%, V: 19.3%, and VI: 29.2%. A total of 80 patients (37.7%) had TI-RADS and Bethesda classifications recorded. The group had a hospital stay of 59 ± 27.7 hours. The surgical time was 142 ± 84.7 minutes. The most frequent preoperative diagnosis was papillary carcinoma in 58% of the cases (Table 1).

Central lymphatic resection was performed in 105 cases (49.5%), unilateral central and radical in 14 patients (6.6%), bilateral central and radical lymph node dissection in 2 cases (0.9%), unilateral lymphatic dissection in 1 case (0.5%) and without emptying in 90 patients (42.4%).

Figure 1. Classification flowchart of participating cases.

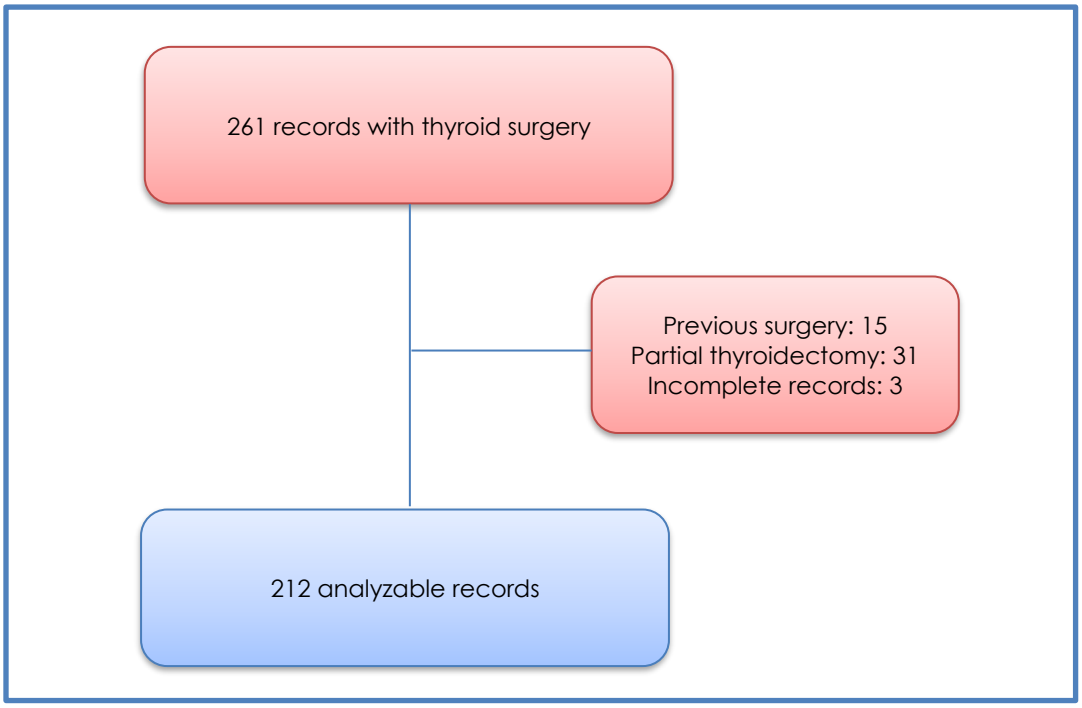

Table 1. Pre and postsurgical diagnoses of patients with thyroidectomy.

Diagnosis	Presurgical (n= 212)	Post surgical (n=212)
Papillary carcinoma	123 (58%)	153 (72.2%)
Thyroid adenoma	52 (24.5%)	11 (5.2%)
Multinodular goiter	26 (12.3%)	20 (9.4%)
Thyroiditis	5 (2.4%)	19 (9.0%)
Follicular carcinoma	4 (1.9%)	2 (0.9%)
Medullary carcinoma	1 (0.5%)	2 (0.9%)

Table 1. Pre and postsurgical diagnoses of patients with thyroidectomy.

Diagnosis	Presurgical (n= 212)	Post surgical (n=212)
Other	1 (0.5%)	5 (2.4%)

Complications and associated parathyroidectomy

After the histopathological analysis of the piece, 166 (78.3%) were found without parathyroid glands, 35 (16.5%) with one parathyroid gland, 9 (4.2%) with two parathyroid glands, 1 (0.5%) with three parathyroid glands and 1 (0.5%) with four parathyroid glands. There were 169 patients (79.7%) without complications, 7 patients (3.3%) with grade I complications, 32 patients (15.0%) with grade II complications, and 4 patients (1.9%) with grade IV complications on the Clavien–Dindo scale. The types of complications are presented in Table 2.

Table 2. Complications presented in patients with thyroidectomy.

Complication	Frequency (n= 212)	Percentage
Clinical hypocalcemia	31	14.6%
Readmission for hypocalcemia	8	3.8%
Bleeding or bruising	4	1.9%
Reoperation	4	1.9%
Laryngeal nerve injury	1	0.5%

Calcium and PTH

Total calcium, ionic calcium, and parathormone levels are presented in Table 3. Table 4 shows the prevalence of clinical and biochemical hypocalcemia. Table 5 offers the diagnostic tests.

Table 3. Serum tests for total calcium, ionic calcium, and parathormone.

Molecule		< 12 hours
Total calcium (n=109)	8.5 mg/dl or less	53 (48.6%)
	> 8.5 mg/dL	56 (51.4%)
Ionic calcium (n=73)	4 mg/dL or less	59 (80.8%)
	> 4.1 mg/dL	14 (19.2%)
PTH (n=48)	10 ng/l or less	14 (29.2%)
	Between 10.1 and 20 ng/l	15 (31.2%)
	> 20 ng/l	19 (39.6%)

Table 4. Prevalence of cases with hypocalcemia in patients with thyroidectomy.

	Clinical and biochemical hypocalcemia				
	Cases No.=30	Controls n=18	OR	95%CI	*P*
PTH 10 ng/l or less	8 (26.6%)	6 (44.4%)	0.724	0.204 -2.592	0.623
PTH >10 ng/l	22 (73.3%)	12 (66.7%)			
	Clinical hypocalcemia				
	Cases N=11	Controls n=37	OR	95%CI	*P*

PTH 10 ng/l or less	6 (54.5%)	8 (21.6%)	4.35	1,050-18,003	0.0427
PTH >10 ng/l	5 (45.5%)	29 (78.4%)			

OR: odds ratio

Table 5. Diagnostic tests for clinical and biochemical hypocalcemia.

	S	AND	PPV	VPN	LR+	LR-	RR	95% CI	P
PTH <10 ng/l: diagnosis of clinical and biochemical hypocalcemia	27%	67%	57%	35%	0.82	1.09	0.88	0.53-1.48	0.623
PTH <10 ng/L: diagnosis of clinical hypocalcemia	55%	78%	43%	85%	2.5	0.58	2.91	1.06-8.01	0.043

S: sensitivity, E: specificity, PPV: positive predictive value, NPV: negative predictive value, LR: likelihood ratio, RR: relative risk.

Multivariate analysis

The only factor associated with a protective effect for the presence of clinical hypocalcemia was age (data presented in Table 6).

Table 6. Multivariate analysis for the presence of clinical hypocalcemia

	Estimation	SE	OR	Confidence interval		*P*
Age >40	-2.653	1.191	0.070	0.007	0.727	0.026
Lymphatic resection	0.527	1.274	1.694	0.139	20.585	0.679
Surgical time > 90 min.	0.740	0.941	2.095	0.331	13.247	0.432
Surgical time > 180 min.	-16.642	1864.971	5.924e -8	0,000	∞	0.993
Parathyroid removed	1.219	0.940	3.382	0.536	21.358	0.195
PTH 10 ng/l or less	0.883	0.834	2.418	0.472	12.399	0.290

SE: standard error. OR: odds ratio

Discussion

In this study, it affected men at 15.6% and women at 84.4% in a 1:5.4 ratio, consistent with that described internationally by Bray et al. 2018, who reported a ratio of 1:4-6 [4].

The average age of presentation of thyroid cancer was 56.9 ± 14.5 years and 47.3 ± 13.6 years in men and women, respectively; these data are below the mean for both sexes of 54.2 with a range 18 - 97 reported by Jasim et al.. 2020, in the United States [5]. The lower age of presentation in women was probably associated with the high prevalence of neoplastic thyroid disease in Ecuador.

In the reviewed medical records, the TI-RADS was recorded in 51.5% (107) and 61.8% (131) of Bethesda, while only 37.7% (80) of patients registered both presurgical predictors. It was worrying about finding these results because a regulated registry should have been carried out before surgical resolution since perhaps many of the missing data were known to the surgeon but not recorded in the clinical record.

Ultrasound in the study of thyroid nodules, when using scales such as ACR-TI-RADS, has a sensitivity of 84% and a specificity of 67%, and EU-TI-RADS has a sensitivity of 83.5% and a specificity of 84.3%. The use of these scales may suggest a fine needle aspiration puncture in mild cases [6].

The patients who underwent thyroidectomy in this group presented a presurgical ACR-TI-RADS risk of TR 1 1.4%, TR 2 2.8%, TR 3 16.0%, TR 4 23.6%, and TR 5 6.6%, similar to that reported by Jasim. et al., 2020, in the United States reached TR1 8.9%, TR2 15.8%, TR3 22.9%, TR4 36.4%, and TR5 16% [5]. Accounting for an adequate ultrasonographic screening system before the indication of a fine needle aspiration puncture.

The results of the fine needle aspiration puncture in the preoperative period were decisive when indicating surgery since in the study group, they reached I 0.5%, II 3.3%, III 2.8%, IV 6.6%, V 19.3%, and VI 29.2%.

Likewise, the diagnostic value of fine needle aspiration puncture reached sensitivities from 92.2% to 96.9%, specificities from 81.7% to 96.2%, and PPVs from 73.8% to 94.4% [7]. The expertise of the interventional physician performing the needle aspiration puncture was associated with higher success rates and less morbidity [8].

The indications for thyroidectomy in the study group were as follows: multinodular goiter 26 (12.3%), follicular carcinoma 4 (1.9%), medullary carcinoma 1 (0.5%), papillary carcinoma 123 (58.0%), suspicious nodule 52 (24.5%), thyroiditis 5 (2.4%), and other 1 (0.5%). Regarding the comparison of presurgical and postsurgical diagnoses, it was striking that 24.5% (52) of the patients entered surgery as a suspicious nodule, and only in 5.2% (11) did this diagnosis remain as such. The rest of the patients were distributed among all groups with a predominance of papillary thyroid cancer that increased from 58% (123) to 72.2% (153) of the patients.

In contrast to those reported by Angell et al., 2019 in England, after studying the results of 20,001 thyroidectomies, malignancy was reported in 28% of patients, papillary carcinoma in 87.4%, follicular carcinoma in 5.9%, and medullary carcinoma in 0.9%[9]. Yilmaz et al. 2020 in Turkey in 2020 reported that the final histopathological results presented a malignancy at 22.1%, papillary carcinoma at 88.1%, follicular carcinoma at 5.6%, and medullary carcinoma at 3.5% [10].

Additionally, striking is the percentage of malignancy reached by the samples in our study, which is close to 70%, leaving the reports above 28% and 22.1% well below, data that accounted for the geographical distribution of thyroid cancer and the high prevalence of Ecuador.

Regarding the surgical characteristics of the thyroidectomies, the average surgical time was 142 ± 84.7 minutes; they reached a hospital stay of 59.0 ± 27.7 hours, and some form of lymphadenectomy was performed in 57.6% of the patients.

In the definitive histopathology reports, at least one parathyroid gland was found in 21.7% of the patients.

The complications presented in this investigation were 22.7%: bleeding or bruising 1.9%, laryngeal nerve injury 0.5%, reoperation 1.9%, clinical hypocalcemia 14.6%, and readmission for hypocalcemia 3.8%, similar to Palacios et al. 2018, has been reported in Ecuador, where hypoparathyroidism reaches 24.7%, cervical hematoma at 2.7%, lesions of the recurrent laryngeal nerve at 1.2% and, less frequently, lesions of the superior laryngeal nerve at 0.7% [11].

Complications were classified with the Clavien–Dindo scale, with 3.3% of patients having grade I complications, 32 (14.4%) patients having grade II complications, and 4 (1.65%) having grade IV complications; these figures are slightly higher than those reported by Latifi et al. 2019, in the United States, reported real difficulties in 2.8%, Clavien–Dindo 2 (1.7%), Clavien–Dindo 3 3 (0.6%), Clavien–Dindo 4 1 (0.2%), Clavien–Dindo 5 1 (0.2%), reoperation 3 (0.6%) [12].

These complications could be comparable if we subtract those due to hypocalcemia, which may be attributable to the implementation of protocols for its prevention in other centers.

For the prediction of hypocalcemia, total calcium was quantified before and after 12 hours of surgery in 128 (60.3%) and 109 (51.4%) patients, respectively, ionic calcium before 12 hours of surgery in 70 (41.4%), 12 hours after surgery in 73 (34.4%) patients and parathormone within 12 hours after surgery in 48 (22.6%). Because the quantification of the different calcium and PTH molecules is not protocolized, their titration was not homogeneous in the study group.

The utility of PTH levels less than ten ng/l to predict clinical or biochemical hypocalcemia was evaluated, obtaining a sensitivity of 0.27, specificity of 0.67, PPV of 57%, NPV of 35%, LR+ of 0.82 and LR- of 1.09. The RR was 0.88 (95% CI 0.53 - 1.48), as was the PR 0.88 (95% CI 0.53 - 1.48); neither was significant when comparing clinical and biochemical hypocalcemia.

The evaluation of PTH levels less than ten ng/l about clinical hypocalcemia only has a sensitivity of 0.55, specificity of 0.78, PPV: 43%, NPV: 85%, LR+: 2.5, and LR-: 0.58. The RR was 2.91 (95% CI 1.06 - 8.01), and the PR was 2.91 (95% CI 1.06 - 8.01); both were significant. In the case of a PTH lower than ten ng/l, we accept the study hypothesis, validating PTH to predict clinical hypocalcemia.

Unlike Del Rio et. to the. 2011 [3], who found that the measurement of intact PTH has a PPV for postoperative hypocalcemia in 99% of cases, with reports reaching 100% sensitivity, 95% specificity, 33.33% false positive rate and diagnostic accuracy of 94.5% [3]. In this study, group, when evidencing a low level of PTH, calcium supplements were started, thus avoiding the development of hypocalcemia.

Palaces et. 2018, Ecuador reported that at 24 hours, the measurement of ionic calcium levels reached a sensitivity of 66%, a specificity of 84%, a positive predictive value of 75%, and a negative predictive value of 78%, data that were not comparable to this investigation [11].

Using logistic regression, the correlation determined by clinical signs, total calcium, or ionic calcium was evaluated, without finding significant results, probably due to the lack of quantification of these molecules in the entire group studied.

Possible confounding variables were studied using a logistic regression of the entire group studied between clinical hypocalcemia and the coefficients of age greater than 40 years, performing a lymphatic resection, surgical time greater than 90 minutes, surgical time greater than 180 minutes, the presence of parathyroids in the surgical piece and a PTH of 10 ng/l or less. Only ages under 40 showed an OR of 0.07 (CI 0.007 - 0.727), acting as a protective factor for hypocalcemia; the rest did not show a relationship with clinical hypocalcemia. However, it is worth mentioning that PTH levels were compared with hypocalcemia in the entire group and not only in those who measured this hormone, contrary to what was shown in the bivariate analysis.

Regarding the prediction of hypocalcemia, Mo et al. demonstrated that a decrease in PHT below 70% of the ordinal value predicts episodes of transient hypocalcemia with great certainty [13]. Chang et al., 2020 also showed that the measurement of intact PTH for the prediction of hypocalcemia four hours after surgery reached a sensitivity of 81.6% and specificity of 86.0% [14].

The possible limitations of the present study are due to the heterogeneity of the study group since the follow-up protocol for postoperative hypocalcemia is at the discretion of the surgeon, as well as in the patients in whom PTH was determined; this was obtained in a wide range when the recommendation is within 4 hours after surgery.

The low availability of PTH titration in Ecuador was also considered a limitation, which conditioned the use of research carried out in other countries, with the variation typical of the geographical distribution of thyroid cancer.

Conclusions

Early diagnosis of clinical hypocalcemia based on PTH measurement has a sensitivity of 55%, specificity of 78%, and a negative predictive value of 85%.

Nota del Editor
La Revista Oncología (Ecuador) permanece neutral con respecto a los reclamos jurisdiccionales en mapas publicados y afiliaciones institucionales.

Abbreviations

PTH: Parathormone.
E: specificity.
LR: likelihood ratio.
RR: relative risk.
S: Sensitivity.
PPV: positive predictive value.
NPV: negative predictive value.

Administrative information

Additional Files

None declared by the authors.

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Author contributions

Carlos Andrés Quinteros: Conceptualization, formal analysis, research, project administration, writing of the original draft.
Glenda Yamira Herrera Cevallos: Conceptualization, methodology, validation, visualization, writing - review and edition.
Kathy Alexandra Bustamante Paredes: methodology, validation, visualization.
All authors read and approved the final version of the manuscript.

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Availability of data and materials

Data are available upon request to the corresponding author. No other materials are reported.

Statements

Ethics committee approval

Not required for observational database studies.

Consent for publication

It is not required when images, resonances, or tomographic studies of specific patients are not published.

Conflicts of interest

The authors declare that they have no conflicts of competence or interest.

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