

ORIGINAL ARTICLE

# Optimal time for measurement of parathormone as a predictor of hypocalcemia in patients after total thyroidectomy

Tiempo óptimo para medición de paratohormona como predictor de hipocalcemia en pacientes posterior a tiroidectomía total

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## Abstract

**Introduction.** Hypocalcemia after total thyroidectomy is a common complication in thyroid surgery. Parathyroid hormone has been shown to be a reliable predictor for detecting patients with at high risk of significant hypocalcemia and the consequent need for calcium supplementation. The objective of this study was to determine the optimal time for measuring parathormone for this purpose.

**Methods.** Prospective study carried out in two level 3 institutions in Popayán, Colombia, between April 2016 and February 2018, in which levels of preoperative parathormone were measured at 0, 2, 4 and 12 hours postoperatively, and compared with the values obtained at 3 months of follow-up in patients undergoing total thyroidectomy. A parathormone value less than 10 pg/ml or a decrease greater than 80% with respect to the pre-surgical value was considered as risk groups and in need of calcium supplementation.

**Results.** Thirty-four operated patients were included. Taking as a threshold a value of less than 10 pg/ml, the measurement of parathormone at 4 hours was sensitive and specific (60% and 93.1%, respectively). For a decrease greater than 80% with respect to the presurgical value, the sensitivity was 60% and the specificity was 96.5%, presenting a positive predictive value of 75% and a negative predictive value of 93.3% ( $p < 0.001$ ).

**Discussion.** A decrease of more than 80% in the preoperative parathyroid hormone value measured at 4 hours after total thyroidectomy allows the identification of those patients at high risk of significant hypocalcaemia, who require early administration of calcium supplements, compared with the determination of the decrease at 0, 2 and 12 hours postoperatively.

**Keywords:** hypocalcemia; parathyroid hormone; calcium-regulating hormones and agents; thyroidectomy; postoperative complications; diagnosis.

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## Resumen

**Introducción.** La hipocalcemia posterior a tiroidectomía total es una complicación frecuente en la cirugía de tiroides. La hormona paratiroidea ha demostrado ser un predictor confiable para detectar los pacientes con alto riesgo de hipocalcemia significativa y la consecuente necesidad de administrar suplemento de calcio. El objetivo de este estudio fue determinar el tiempo óptimo de medición de la paratohormona para dicho fin.

**Métodos.** Estudio prospectivo realizado en dos instituciones de nivel III en Popayán, Colombia, entre abril de 2016 y febrero de 2018, en el cual se midieron niveles de paratohormona prequirúrgico, a las 0, 2, 4 y 12 horas del postoperatorio, y se compararon con los valores obtenidos a los 3 meses de seguimiento en pacientes sometidos a tiroidectomía total. Se consideró como grupos de riesgo y con necesidad de suplemento de calcio un valor de paratohormona menor de 10 pg/ml o una disminución mayor del 80 % con respecto al valor prequirúrgico.

**Resultados.** Se incluyeron 34 pacientes intervenidos. Tomando como umbral un valor menor de 10 pg/ml, la medición de paratohormona a las 4 horas fue sensible y específica (60 y 93,1 %, respectivamente). Para una disminución mayor del 80 % con respecto al valor prequirúrgico, la sensibilidad fue del 60 % y la especificidad del 96,5 %, presentando un valor predictivo positivo de 75 % y negativo del 93,3 %, con una  $p < 0,001$ .

**Discusión.** Una disminución mayor del 80 % del valor de paratohormona prequirúrgico medida a las 4 horas después de la tiroidectomía total permite identificar aquellos pacientes con alto riesgo de hipocalcemia significativa, que requieren administración temprana de suplementos de calcio, comparado con la determinación de la disminución a las 0, 2 y 12 horas postoperatorias.

**Palabras clave:** hipocalcemia; hormona paratiroidea; hormonas y agentes reguladores de calcio; tiroidectomía; complicaciones posoperatorias; diagnóstico.

## Introduction

Transient hypocalcemia after total thyroidectomy is the most frequent complication of thyroid surgery, being observed in 1.6 - 68% of the patients<sup>1-3</sup>. It is mostly due to vascular compromise and to a lesser extent to an inadvertent parathyroid resection<sup>4-8</sup>. Its clinic presentation varies in a wide range, from asymptomatic patients up to tetany and shock<sup>5,9-11</sup>. Given the uncertainty about the evolution of calcium levels after total thyroidectomy, patients require additional studies, which prolong their hospital stay, or supplements with calcium routinely.

Although hypocalcemia is usually transient, usually less than 6 months, in 1 - 10% of the cases can be permanent<sup>6,7,9,12</sup>. The identification of patients at risk of significant transient hypocalcemia results in a decrease of morbidity, costs and need

for prolonged hospital stay, avoiding the unnecessary administration of calcium supplements<sup>11</sup>. Hence, postoperative calcium levels, although they are important as a predictor of symptomatic hypocalcemia, they are only relevant after 24 to 48 hours<sup>9,13</sup>.

Parathyroid hormone (PTH), or parathormone, is regulated primarily by serum levels of ionized calcium and, once secreted, is rapidly removed from plasma, with an average lifetime of two to four minutes<sup>14,15</sup>. Based on the above, multiple studies support the measurement of PTH as a useful test for the detection of patients at high risk of hypocalcemia after thyroid surgery; however, there is heterogeneity on methods and the ideal timing for testing<sup>2,4,7,12,13,15-31</sup>.

The objective of this study was to determine the optimal time for PTH measurement as predic-

tor of hypocalcemia in patients undergoing total thyroidectomy.

## Methods

This was a prospective study of diagnostic testing that included patients greater of 18 years who underwent a total thyroidectomy at Hospital Universitario San José y Clínica La Estancia, institutions of level III in the city of Popayan, Colombia. Patients with previous alterations of PTH or calcium levels, parathyroid pathology, renal insufficiency or pharmacological treatments that interfere with the levels of calcium were excluded, as well as those who did not fulfill the samples requested for the study. Probabilistic sampling was applied for convenience.

The project was classified as low-risk and was approved by the institutional ethics committees, respecting and protecting the bioethics principles of the investigation in humans, following the Statement of Helsinki and the Resolution No. 008430 of 1993 of Colombia. Informed consent was obtained of all included patients and their data were treated according to Law 1581 of 2012 and Decree 1377 of 2013.

Information was collected on sociodemographic and clinical characteristics, ionized calcium levels were measured preoperatively and at 12 hours after the surgery, taking as normal values those between 1.12 - 1.33 mmol/L. PTH levels were measured in the preoperative period, at the closure of the surgical incision (0 hours), 2, 4 and 12 hours postsurgical, as well as a control sample at 3 months. The PTH analysis was processed in a LIAISON® N-TACT® PTH Gen 11 equipment by in vitro chemiluminescent immunoassay, taking as normal values between 22.2 - 108.9 pg/ml. In the same way the intraoperative findings, hospitalization, clinical manifestations of hypocalcemia and the need of calcium supplementation were documented, tracking it until the day after the surgical intervention.

The data obtained was analyzed using the SPSS version 25 statistical package. For description of the population were used measurements of central and dispersion trend of the quantitative vari-

ables, as well as frequencies and proportions in categorical variables. The population was divided in patients at high risk of hypocalcaemia, if the PTH was less than 10 pg/ml, or with a decrease greater than 80% with respect to the baseline level for every defined hour, and sensitivity, specificity and positive and negative predictive values (VPP and VPN), to determine the suitable time to take the test. The level of statistical significance was established at  $p < 0.05$ .

## Results

Forty-three patients were operated on during the period comprised between April 2016 and February 2018; of those 43, nine were excluded because did not comply with the required number of samples. At the end, 34 patients were included in the study. Average age was 47.7 years  $\pm$  16.9 (range: 19-83); 91.2% were women ( $n = 31$ ), the predominant ethnicity was mixed race 82.4% ( $n = 28$ ) and a 58.8% lived with a partner ( $n = 20$ ) (Table 1); 66% ( $n = 19$ ) of the patients had comorbidities, being those of the cardiovascular system the more frequent (23.5%), followed by the endocrine (20.6%).

The indication for total thyroidectomy was given by a malignant histology, obtained by biopsy in 61.8% ( $n = 21$ ), papillary carcinoma being the main cause. On the other hand, those patients whose histopathological biopsy report was not conclusive ( $n = 18$ ; 23.5%) were operated at the treating surgeon discretion.

In 79.4% ( $n = 27$ ) of patients, the procedure was total thyroidectomy, and in the remaining a unilateral or bilateral lymph node dissection was added (Table 2); 67.6% ( $n = 23$ ) did not present an extra-thyroid extension. In 55.9%, four parathyroid glands were preserved ( $n = 19$ ) and no autotransplantation was performed. The final histology reported malignant pathology in 61.8% ( $n = 21$ ), with a predominance of papillary carcinoma.

The mean hospital stay was 28 hours, with a median of 25 hours (range: 13-72).

Mild symptoms of hypocalcemia were present in two patients in the study, corresponding to the

**Table 1.** Sociodemographic and clinical characteristics of the study population.

Sociodemographic variables		n	%
Gender	Female	31	91,2
	Male	3	8,8
Age	Average	47,7	
	Standard deviation	16,9	
	Range	19-83	
Ethnicity	Mixed race	28	82,4
	Indigenous	3	8,8
	Black	3	8,8
Marital status	Married/Partner	20	58,8
	Single	10	29,4
	Divorced	2	5,9
	Widow	2	5,9
Origin	Rural	16	47,1
	Urban	18	52,9
Education level	None	4	11,8
	Primary	10	29,4
	High School	7	20,6
	Tertiary	9	26,5
	University	4	11,8
Clinical variables		n	%
Comorbidities	None	15	44,1
	Cardiovascular	8	23,5
	Endocrine	7	20,6
	Endocrine and cardiovascular	4	11,8
Presurgical diameter of the lesion	Less than 2 cm	10	35,7
	2-4 cm	10	35,7
	Greater than 4 cm	8	28,6
Presurgical pathology	Malignant	21	61,8
	No conclusive	8	23,5
	Benign	5	14,7
Final histology	Papilar neoplasia	19	55,8
	Follicular neoplasia	2	5,9
	Multinodular goiter	11	32,4
	Tiroiditis	2	5,9

5.9% of the cases (one of them presented low PTH levels from the surgery up to the latest control), and no severe hypocalcemic events requiring use of intravenous calcium were reported.

Ionized calcium and PTH levels and the percentage of decrease of PTH are shown in table 3. The frequency of levels of PTH lower than 22.2 pg/ml at 0, 2, 4 and 12 hours was 73.5% (n = 25), 67.6% (n = 23), 55.8% (n = 19), and 44.1% (n = 15), respectively. After few hours, PTH levels tended to normalize, but they were lower than those obtained in the follow-up at 3 months; however, they did not reach the values reported in the presurgical period such as presented in figure 1.

Six (17.6%) patients were discharged with calcium supplement, based on the results of PTH at 12 hours (lower than 10 pg/ml or a decrease higher than 80% compared to the presurgical value), or based on the presentation of hypocalcemia symptoms.

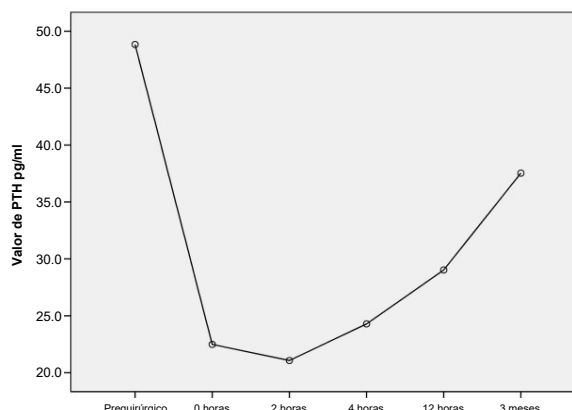
**Table 2.** Characteristics of the surgical procedures.

Procedure description		n	%
Type of surgery	Total thyroidectomy	27	79,4
	Total thyroidectomy plus lymphadenectomy	7	20,6
Type of incision	Standard transverse	25	73,5
	Enlarged transverse	9	26,5
Extra extension thyroid	No	23	67,6
	Yes	11	32,4
Lymphadenopathy	No	29	85,3
	Yes	5	14,7
Number of parathyroid preserved	2	4	11,8
	3	11	32,3
	4	19	55,9
Surgical time (minutes)	Average	106	
	Standard deviation	33	
	Range	70-180	
Hospital stay (hours)	Average	28,4	
	Standard	11,1	
	Range	13-72	

Using a PTH serum of 10 pg/ml as threshold to define the need of calcium supplements, sensitivity and specificity for each sample were calculated and are described in table 4. According to what was observed, the PTH taken at 4 hours it was more sensitive (60%) and with a higher negative predictive value (93.1%), while at 12 hours it was more specific (96.5%) and presented a higher positive predictive value (66.6%). The sample at 4 hours was statistically significant ( $p = 0.01$ ).

If a decrease greater than 80% of the baseline level was used as a reference for identification of patients at risk of hypocalcemia and decided the need for calcium supplements in the postoperative, the time considered more sensitive (60%), specific (96.5%), with higher positive predictive value (75%) and negative predictive value (93.3%), with a statistically significant difference ( $p < 0.001$ ), it was at 4 hours (Table 5).

Follow-up of patients included in the study lasted 3 months, at which time PTH levels were requested, observing a median of 29.0 pg/ml



**Figure 1.** Evolution of PTH levels in patients underwent total thyroidectomy.

(range: 14.5-100.2). Low levels of PTH were found in 14.7% ( $n = 5$ ) of the patients, two operated by benign pathology and three by malignant pathology, with a median PTH of 19.0 pg/ml, still requiring calcium and calcitriol supplements. No deaths were documented during the follow-up period.

**Tabla 3.** Niveles pre y postoperatorios de calcio, PTH y porcentaje de disminución de PTH

	Preoperative		PTH 0 hour		PTH 2 hours		PTH 4 hours		PTH 12 hours		PTH 3 months
	Calcium	PTH	Value	% decrease	Value	% decrease	Value	% decrease	Value	% decrease	Value
Average	1,22	48,83	22,48	55,47	21,66	56,25	24,29	51,34	29,02	41,09	37,53
Median	1,23	40,70	15,85	57,57	17,50	60,11	20,0	50,58	22,55	40,34	29,00
SD	0,04	24,11	22,06	25,27	20,07	25,77	19,31	21,46	20,41	24,33	19,92
Minimum	1,14	22,50	3,0	5,56	3,0	3,77	3,20	1,89	5,90	-26,51*	14,5
Maximum	1,32	108,0	102,0	93,52	102,0	93,52	104,0	90,06	104,6	85,95	100,2

\* Percentage in negative is because a patient presented a post-surgical value higher than the pre-surgical.

**Table 4.** Predictive value of PTH <10 pg/ml at 0,2,4 and 12 hours versus the presence of lower PTH levels at third postoperative month.

	PTH <10 pg/ml		PTH >10 pg/ml		Sensitivity	Specificity	PPV %	NPV %	p
	n	%	n	%					
PTH 0 hour	6	17,6	28	82,4	40%	86%	33,3	89,2	0,15
PTH 2 hours	8	23,5	26	76,5	40%	79%	25	88,4	0,34
PTH 4 hours	5	14,7	29	85,3	60%	93,1%	60	93,1	0,01*
PTH 12 hours	3	8,8	31	91,2	40%	96,5%	66,6	90	0,05*

\* Fisher's exact test was used.

## Discussion

This study, which sought to establish the optimal moment for PTH uptake as a predictor of transient postsurgical hypocalcemia in patients who underwent total thyroidectomy, had a population with an average age of 47.7 years, similar as described in the literature<sup>16-20,22-27,32</sup>; however, our patients had a symmetrical distribution for each of the decades, with only 20% between the 4<sup>th</sup> and the 5<sup>th</sup> decade, unlike what is described by the National Cancer Institute, which reports major incidents between the 4<sup>th</sup> and the 5<sup>th</sup> decade of life<sup>33</sup>, possibly due to our country demographic distribution.

The studied population was predominantly female, with a male-female ratio of 1:10, higher than the one reported for Colombia (1:8)<sup>33</sup>, and slightly higher than described by other authors<sup>2,13,28-30</sup>.

The main indication for thyroidectomy was malignant pathology, being papillary carcinoma the most frequent histology, which coincides with the reports of AlQahtani<sup>27</sup>, Cayo<sup>22</sup> and Landry<sup>21</sup>, but different from most publications, where the main cause were benign pathologies<sup>7,11-13,16,18,19,25,28-30,32</sup>. The percentage of patients with hypocalcemia at 12 hours was near 25%, which is within the range reported in various studies<sup>4,7,11-13,19,20,22-27,29,31,32,34</sup>.

In the first classification method used in this study, with lower PTH values of 10 pg/ml, the levels at 4 hours had a sensitivity of 60% and specificity of 93%, with PPV of 60% and NPV of 93%, this being the time showing a statistically significant difference ( $p = 0.01$ ). In this regard, various authors<sup>19,25,26,29</sup> reported that the measurement of PTH between 10 - 12.5 pg/ml at 4 hours, presented a superior sensitivity and specificity

similar to our study, to predict postoperative hypocalcemia. The values are likely to be higher in these retrospective studies by the greater number of operated patients.

On the second method of estimating risk of hypocalcemia (decreased PTH greater than 80% of the baseline value), the measurement of PTH at 4 hours had a sensitivity of 60% and a specificity of 96.5%, with a PPV of 75% and NPV of 93.3%. These results are comparable with Del Rio study<sup>32</sup>, who found that a decrease of PTH greater than 80% has a sensitivity of 100% and specificity of 87%, possibly associated with similar research methodologies. The percentages are comparable to the reports published by Gupta<sup>30</sup> and Kala<sup>12</sup>, with sensitivity of 100% and 93% and specificity of 87% and 95%, respectively. Taking different cut off points of the percentage of decrease of PTH, others authors report lower rates of sensitivity and specificity<sup>28,29,31</sup> to detect the group at risk of postoperative hypocalcemia; however, the histopathology was predominantly benign, in comparison with our population in which the higher proportion of the interventions were performed by malignant histopathology.

Among the limitations of this study, it was found that loss of patients, in whom no samples were taken at the defined time, which affected the sample size, as well as the follow-up less than 6 months, to define whether the hypocalcemia was permanent. The strengths to highlight include the rigor on how the samples were taken, to compare both methods described and the use of PTH to predict the risk of hypocalcemia after total thyroidectomy in the county of Cauca, Colombia.

**Table 5.** Predictive value of a decrease in PTH greater than 80% at 0, 2, 4 and 12 hours versus the presence of lower PTH levels at third postoperative month

	PTH >80%		PTH <80%		Sensitivity	Specificity	PPV %	NPV %	P
	n	%	n	%					
PTH 0 horas	8	23,5	26	76,5	60%	82,7%	37,5	92,3	0,03
PTH 2 horas	7	20,6	27	79,4	60%	86,2%	42,8	92,5	0,01
PTH 4 horas	4	11,8	30	88,2	60%	96,5%	75	93,3	<0,001*
PTH 12 horas	2	5,9	32	94,1	20%	96,5%	50	87,5	0,27*

\* Fisher's exact test was used.

Despite the differences reported by the groups of authors, there is a general agreement on the utility of taking postoperative PTH to detect hypocalcemia after the total thyroidectomy. The results of this prospective study suggest that only one measurement of PTH lower than 10 pg/ml or a decrease of PTH higher than 80% of the baseline level, at 4 hours post-operative, allow to identify patients with high risk to develop hypocalcemia, and that the second method is superior to the first one. Based on these methods, a reduction in the morbidity associated to hypocalcemia and the early discharge of patients can be achieved, if is considered safe, with or without calcium or calcitriol supplementation.

### Compliance with ethical standards

**Informed consent:** Informed consent of all patients included in the study was obtained.

The Committees of Ethics of both institutions approved the study design and methodology.

**Conflict of interest:** The study authors declare no conflicts of interest.

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**Authors contribution:** Conception and design of the study, data acquisition, analysis and interpretation of data: Jenith Lagos, Jorge A. Herrera. Writing of the manuscript, critical revision: Daniela Lagos, Ángela Merchán- Galvis.

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