

Prognostic Factors for Definitive Hypoparathyroidism Following Total Thyroidectomy

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Introduction and objective: Hypocalcaemia, transient in most cases, is the main complication after thyroid gland surgery with regard to functional impairment of the parathyroid glands or other reversible factors. Sixty-seven patients who underwent thyroidectomy were evaluated to identify potential clinical, pathological and surgical factors that might be predictive for frank hypocalcaemia following total thyroidectomy.

Methods: Serum samples were taken preoperatively and postoperatively to measure total calcium levels. Patients' plasma calcium levels were recorded post-operatively along with such factors as age, gender, thyroid function, definitive pathology-based diagnosis, accidental removal and autotransplantation of parathyroid glands, re-intervention to identify risk factors for the development of definitive hypoparathyroidism (DH). All comparisons were made between patients with hypocalcaemia and normal levels of post-operative calcaemia.

Results: Transient acute hypocalcaemia was identified in 25 of 67 patients (43.3%). DH was identified in 8 (11%) patients.

Conclusions: Our study revealed that the only risk factor for DH was a calcium level of less than 7.5 mg/dL within the first 24 hours following surgery; this is a reliable, inexpensive and rapid parameter that is highly predictive of the onset of HD. No statistical significant associations were detected with other factors such as thyroid function, histology, accidental removal or autotransplantation of parathyroid glands, thus it is possible to state that careful manipulation of the parathyroid to preserve the periglandular vascularization is of vital importance to ensure correct post-operative functionality.

Key words: Hypoparathyroidism. Thyroidectomy. Complications.

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Factores pronósticos de hipoparatiroidismo definitivo tras tiroidectomía total

Introducción y objetivo: La hipocalcemia tras tiroidectomía total constituye la mayor complicación, en la mayoría de los casos, transitoria, en relación con un daño funcional de las paratiroides u otros factores reversibles. Se trata de un estudio sobre 67 pacientes sometidos a tiroidectomía total para identificar posibles factores clínicos, anatomopatológicos y quirúrgicos predictivos de hipocalcemia definitiva tras tiroidectomía total.

Métodos: Recogida de valores plasmáticos de calcio en el período postoperatorio y factores como edad, sexo, funcionalidad tiroidea, diagnóstico anatomopatológico definitivo, extirpación accidental de las paratiroides y su autotrasplante, reintervención para identificar factores de riesgo para el desarrollo de hipoparatiroidismo definitivo. Las comparaciones han sido efectuadas entre los pacientes con hipocalcemia y concentraciones normales de calcemia postoperatoria.

Resultados: La hipocalcemia aguda transitoria ha sido identificada en 25/67 pacientes (43,3%). El hipoparatiroidismo definitivo ha sido identificado en 8 (11%) pacientes.

Conclusiones: En nuestro estudio ha supuesto que una calcemia después de 24 h de la intervención quirúrgica inferior a 7,5 mg/dl sea un factor altamente pronóstico de hipoparatiroidismo definitivo; esta determinación es un parámetro fiable, económico, rápido y muy predictivo del desarrollo de hipoparatiroidismo definitivo. No se han encontrado asociaciones estadísticamente significativas con otros factores, como funcionalidad tiroidea, histología, extirpación accidental o autotrasplante de las paratiroides, así que podemos afirmar que una atenta manipulación de las paratiroides conservando cuidadosamente la vascularización glandular representa un factor de fundamental importancia para garantizar una normal funcionalidad paratiroidea postoperatoria.

Palabras clave: Hipoparatiroidismo. Tiroidectomía. Complicaciones.

Table 1. Clinical and Pathology Characteristics of Definitive Hypoparathyroidism Cases^a

Patient	Age	Gender	Thyroid Function	Histology
1	70	Female	Normal	Goitre
2	79	Female	Hyperthyroidism	Goitre
3	59	Female	Normal	Goitre
4	46	Female	Normal	pT1 papillary carcinoma
5	58	Male	Normal	Retrosternal goitre
6	47	Female	Normal	Goitre
7	46	Female	Normal	Follicular adenoma in goitre
8	30	Female	Hypothyroidism	Hürthle cell carcinoma in goitre

^aNo parathyroid glands were removed/re-implanted.

INTRODUCTION

Hypocalcaemia following total thyroidectomy is the main complication that determines prolonged post-operative stay.¹⁻³ Post-operative hypoparathyroidism is a relatively common sequela that, in most cases, resolves spontaneously after a few days or weeks.^{3,4} The mechanism by which this occurs is the result of multiple factors, depending on the accidental removal of one or more parathyroid glands, or more often, of arterial or venous vascular injury to the parathyroid glands during surgery.⁴

The complication most detrimental to the patient is the development of definitive hypoparathyroidism. This retrospective study evaluates the possible clinical, pathological, and surgical factors predicting definitive hypocalcaemia following total thyroidectomy.³

METHODS

We have carried out a descriptive, retrospective, non-randomized study of 67 patients who underwent total thyroidectomy between January 2005, and December 2006. The serum calcium levels were measured during the post-operative period and at 4, 24, 48, 72, and 96 hours after the surgical procedure. Data were also collected on such factors as age, gender, thyroid function (hypofunctioning, hyperfunctioning, and normofunctioning), definitive pathology diagnosis (multinodular hyperplasia, adenoma, carcinoma), post-operative supplementary calcium and vitamin D therapy, accidental removal of one or more parathyroid glands and their autotransplant, further surgery and surgery associated with adenopathies in the neck.

The indication for surgical treatment was due to suspicion of malignancy following cytology of fine needle aspiration (FNA) in 22 cases, (4 cases of adenoma, 18 cases of carcinoma) and, in 45 cases, due to macrofollicular or microfollicular goitre. Most of the patients in this study presented normal thyroid function (48 patients, 71.64%); 12 cases (17.9%) had hyperthyroidism; and only 7 (10.44%) had hypothyroidism. In 4 cases, the histology study revealed parathyroid tissue

in the capsule and intraglandular thyroid tissue (only one parathyroid gland was accidentally removed) and in another 4 cases, a parathyroid was autotransplanted into the sternocleidomastoid muscle. We have evaluated the incidence of temporary and permanent hypoparathyroidism. The continuous variables were analyzed by considering confronted means using a variance analysis (Student *t* test and one way ANOVA). Discrete variables were evaluated using χ^2 . A logistic regression model was created to quantify the risk associated with each of the prognostic variables. A *P* value less than .05 was considered significant.

RESULTS

Temporary hypoparathyroidism (acute hypocalcaemia), defined as values of 7.5 mg/dL or less in the first 96 h following surgery, were identified in 25/67 patients (43.3%). Permanent hypoparathyroidism (plasma calcium values <7.5 mg/dL 6 months after total thyroidectomy) was found in only 8 patients (11.94%), all following a course of supplementary calcium and/or vitamin D therapy. In 5 cases, surgery was performed for goitre (1 with retrosternal spread); in 3 cases, it was due to suspicion of neoplasm following FNA (2 follicular adenomas, 1 papillary carcinoma). In the 8 cases of definitive hypoparathyroidism, the 4 parathyroid glands were identified macroscopically and conserved during surgery; there has been no case of a definitive pathology diagnosis of parathyroid tissue in the capsule or intraglandular area (Table 1).

Bearing in mind the time progression of plasma calcium concentrations during the post-operative period (Figure), patients with definitive hypoparathyroidism were seen to present calcaemia values at 24, 48, 72, and 96 h that were moderately lower than the group of patients with conserved parathyroid function 6 months after surgery, and such a difference is statistically significant (Student *t*, *P*<.05 in each analysis).

Using a logistic regression model, statistical analysis demonstrated that the 24-hour post-operative calcaemia concentration is fundamental to prognosis: calcaemia values

>7.5 mg/dL are highly favourable (odds ratio = 0.02; $P=0.037$) for not developing definitive hypoparathyroidism. Thus, values below this cut-off are a reliable prognostic indicator for developing this complication ($P<0.05$) (Table 2).

Accidental extirpation or autotransplant of a parathyroid gland (8 cases), a definitive pathology diagnosis of total thyroidectomy and thyroid function do not appear to be associated to a statistically significant degree with the development of temporary and/or definitive hypoparathyroidism ($P>0.05$).

DISCUSSION

Post-operative hypocalcaemia is, in most cases, the most common complication following total thyroidectomy^{4,6} (1.6%-50%)⁷ and is generally temporary and limited to the first weeks following surgery.¹⁻³

The incidence of definitive hypoparathyroidism varies, depending on the different case series, from 0.4% up to 13.8%⁸ and affects the patient's quality of life, determines a prolonged hospital stay and the need for lifetime calcium and/or vitamin D supplement therapy. Many of the studies conducted sought to identify the clinical, pathology and biochemical factors capable of predicting the development of definitive hypoparathyroidism.^{1,3,4,7-9}

The medical literature reports that malignant histology of the thyroid lesion, hyperthyroidism, accidental removal

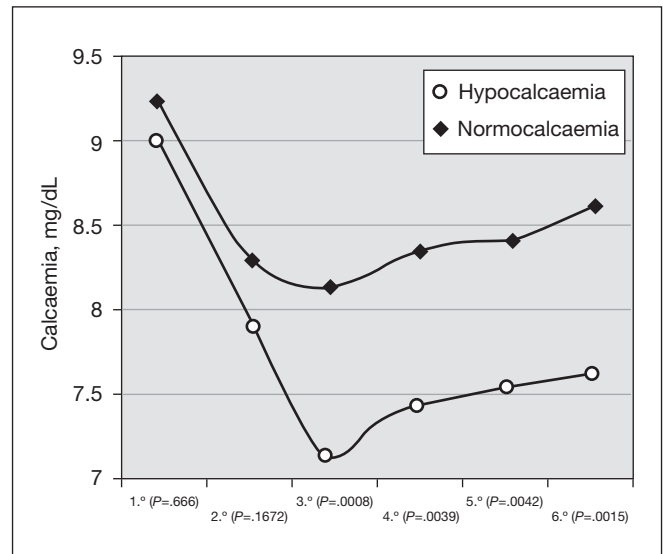


Figure. Post-operative calcaemia concentrations (Student *t* test). 1: post-operative calcaemia; 2: 4 h after surgery; 3: 24 h after surgery; 4: 48 h after surgery; 5: 72 h after surgery; 6: 96 h after surgery.

of the parathyroid glands, re-intervention and/or associated cervical dissection are directly related to the development of definitive hypoparathyroidism following thyroidectomy.^{1,4,8,10}

Table 2. Logistic Regression

	Comparison	OR (95% CI)	<i>r</i>	SE	Z	P
Pre-operative calcaemia	<9	1				
	>9 versus <9	0.3644 (0.0251-5.295)	-1.0096	1.3655	-0.7393	.4597
Post-operative calcaemia	<7.5	1				
	>7.5 versus <7.5	2.5531 (0.0699-93.2006)	0.9373	1.8355	0.5107	.6096
Calcaemia 24 h	<7.5	1				
	>7.5 versus <7.5	0.0205 (0.0005-0.7922)	-3.8894	1.8656	-2.0848	.0371
Calcaemia 48 h	<7.5	1				
	>7.5 versus <7.5	0.283 (0.0128-6.2702)	-1.2624	1.5808	-0.7986	.4245
Calcaemia 72 h	<7.5	1				
	>7.5 versus <7.5	2.7176 (0.0815-90.6033)	0.9997	1.7892	0.5588	.5763
Calcaemia 96 h	<7.5	1				
	>7.5 versus <7.5	0.5753 (0.0238-13.9105)	-0.5529	1.6253	-0.3402	.7337
Histology	Benign	1				
	Malignant versus benign	0.7906 (0.0116-53.6746)	-0.2349	2.152	-0.1092	.9131
	Goitre versus benign	0.1373 (0.0024-7.8524)	-1.9859	2.0647	-0.9618	.3361
Age	<40	1				
	>65 versus <40	3.0689 (0.0409-230.537)	1.1213	2.2037	0.5088	.6109
	40-65 versus <40	3.8638 (0.0669-223.1824)	1.3517	2.0696	0.6531	.5137

^aCI indicates confidence interval; OR, odds ratio; SE, standard error.

In our experience, no statistically significant associations have been found between the development of definitive hypoparathyroidism and the clinical factors cited above.

Parathyroid hormone (PTH) and low calcaemia and phosphoraemia values during the post-operative period have also been related with the development of definitive hypoparathyroidism in some studies.^{1,7,11-13}

In any case, there is no consensus with respect to the prognostic significance of these biological factors in predicting the development of definitive hypoparathyroidism.⁴

Our study indicates that calcaemia of less than 7.5 mg/dL 24 hours after surgery is a highly prognostic factor for definitive hypoparathyroidism, as reported in other case series.^{1,11,12} In contrast, in the experience of other authors, the evolution of calcaemia determined in the first 4 days following the intervention does not appear to provide enough information about the possible development of definitive hypoparathyroidism, whereas the prognostic value of intra-operative PTH concentrations is underscored in many articles,¹³⁻¹⁸ despite the high cost and complexity of the laboratory methods.⁷

In conclusion, we can state that the 24-hour post-operative calcaemia value is a reliable parameter and highly predictive of the development of definitive hypoparathyroidism and has the advantage of being an inexpensive, simple and fast biochemical test.

Taking into account the fact that we have been unable to detect any relationship between the incidence of definitive hypoparathyroidism and histology, accidental removal or autotransplant of the parathyroid glands our case series, we can state that careful handling of the parathyroid glands, meticulously conserving glandular vascularization, is a factor of supreme importance in guaranteeing normal post-operative parathyroid function.

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