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# Serum PTH levels as a predictive factor of hypocalcaemia after total thyroidectomy

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*Introduction:* Postoperative parathyroid hormone (PTH) levels as a predictor of hypocalcaemia in patients subjected to total hyroidectomy is analyzed.
*Matherial and method:* Prospective study involving 67 patients who underwent total thyroidectomy due to a benign disease. Serum PTH and ionised calcium were measured 20 h after surgery. Sensitivity, specificity, and predictive values of PTH and ionised calcium levels were calculated to predict clinical and analytical hypocalcaemia.
*Results:* A total of 42 (62.7%) patients developed hypocalcaemia (ionised calciumo <0.95 mmol/L), but only 20 (29.9%) presented with symptoms. PTH concentration the day after surgery was significantly lower in the group that developed symptomatic hypocalcaemia (5.57 [6.4] pg/mL) than in the asymptomatic (21.5 [15.3] pg/mL) or normocalcaemic (26.8 [24.9] pg/mL) groups (*P*=.001). Taking the value of 13 pg/mL as a cut-off point of PTH levels, sensitivity, specificity, positive predictive value, and negative predictive value were 54%, 72%, 76%, and 48%, respectively. On the other hand, sensitivity for predicting symptomatic hypocalcaemia was 95% and specificity was 76%. The test showed a high incidence of false positives (11/30, 36%). Negative predictive value was 97% and positive predictive value was 65%. In multivariate analysis, PTH and ionised calcium were the only perioperative factors that showed an independent predictive value as risk indicators of symptomatic hypocalcaemia.
*Conclusions:* Normal PTH levels 20 h after surgery practically rule out the subsequent appearance of hypocalcaemia symptoms. On the other hand, low PTH levels are not necessarily associated to symptomatic hypocalcaemia due to the high number of false positives.



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## Determinación de paratirina en suero como factor predictivo de hipocalcemia tras tiroidectomía tota

*Palabras clave:*
Paratirina
Calcio iónico
Tiroidectomía total
Hipocalcemia

RESUMEN

*Introducción:* Se analiza el valor de la determinación postoperatoria de paratirina como indicador de riesgo de hipocalcemia tras tiroidectomía total.
*Material y método:* Estudio prospectivo de 67 pacientes sometidos a tiroidectomía total por enfermedad benigna. Se determinó la concentración de paratirina y calcio iónico a las 20 h de postoperatorio. Se calculó la sensibilidad, la especificidad, y los valores predictivos positivo (VPP) y negativo (VPN) de las concentraciones de paratirina y calcio iónico para predecir la aparición de hipocalcemia sintomática o no.
*Resultados:* Presentaron hipocalcemia (Ca iónico <0,95 mmol/l) 42 pacientes (62,7%) pacientes, pero únicamente 20 (29,9%) mostraron síntomas. La concentración de paratirina a las 20 h de la intervención fue inferior en el grupo con hipocalcemia sintomática (5,5 ±76,4 pg/ml) que en el grupo de hipocalcemia sin síntomas (21,5 ±15,3 pg/ml) y que entre los pacientes normocalcémicos (26,8 ±24,9 pg/ml) (p = 0,001). Con un punto de corte para la paratirina en 13 pg/ml, la sensibilidad, la especificidad, el VPP y el VPN de paratirina para predecir la aparición de hipocalcemia analítica fueron del 54, el 72, el 76 y el 48%, respectivamente. Por otro lado, la sensibilidad para predecir hipocalcemia sintomática fue del 95% y la especificidad, el 76%. El test presentó alta incidencia de falsos positivos (11/30) (36%). El VPN fue del 97% y el VPP, el 65%. Paratirina y calcio iónico en el análisis multivariable fueron los únicos factores con valor predictivo como indicadores de riesgo de hipocalcemia sintomática.
*Conclusiones:* Una concentración normal de paratirina a las 20 h de la intervención prácticamente descarta la aparición posterior de síntomas de hipocalcemia. Por contra, cifras de paratirina bajas no se acompañan necesariamente de síntomas debido al elevado número de falsos positivos.



## Introduction

Hypocalcaemia in hypoparathyroidism is a well-known complication of total thyroidectomy. It is usually mild and transitory (in up to 50% of cases) and is rarely serious or permanent (5%), but is always a matter of concern for the patient and surgeon.[1-4] Normally, it is not easy to predict in which patients this post-surgical complication will occur. Therefore, hospitalisation must be extended to monitor the concentrations of serum calcium or administer a systematic calcium supplement.[5,6] Due to the current tendency to reduce hospitalisation and costs, there is great interest in identifying perioperative factors that could provide reliable, predictive information on the risk of hypocalcaemia developing after total thyroidectomy. The aim is to administer individualised treatment at an early stage for patients with a high risk and allow the early, safe discharge of patients not at risk.

During recent years the determination of parathyrine has been introduced as adjuvant therapy in surgery of the parathyroid glands.[7] Consequently, the intraoperative measuring of parathyrine has been divulged in the removal of parathyroid adenoma.[8,9] However, the parathyrine determination could also be used in other surgical procedures in which the parathyroid gland function could be impaired.[7] Total parathyroidectomy may cause hypoparathyroidism following the inadvertent extirpation of the glands or damage to the blood-flow in the glands.[10] Recent studies have highlighted the role of parathyrine alone or combined with the determination of serum calcium as a predictive factor of hypocalcaemica after thyroidectomy.[11,12] It has been observed that patients developing hypocalcaemia after total thyroidectomy surgery show low concentrations of parathyrine[13-15] during the immediate post-surgical period. But this examination is not systematised and has not been divulged, and therefore its value in indicating the risk of hypocalcaemia after thyroidectomy is not well known.

The purpose of this study is to analyse the value of determining post-surgical parathyrine as an indicator of a risk of hypocalcaemia after total thyroidectomy.

## Material and method

A prospective clinical study was performed between February 2006 and December 2007. Sixty-seven patients were included on whom surgery had been practised consecutively, in all cases for total thyroidectomy due to a benign condition: 50 due to normofunctioning multinodular goitre and 17 due to Graves-Basedow's disease. The patients include 53 females (79%) and 14 males (21%), with an average (interval) age of 50 (28–76) years. Patients operated with concomitant parathyroidism were not included and neither were patients subjected to total thyroidectomy after a previous operation. In all the cases analysed, a total bilateral thyroidectomy was

performed. During the operation, no special effort was made to locate and identify all the parathyroid glands. In cases in which vascular problems were observed in any of the glands, an autologous transplant was performed in the homolateral sternocleidomastoid muscle. All the patients were operated on following their own decision in the morning surgical programme.

A blood sample was taken first thing on the morning after the operation (20 h after surgery) to determine serum parathyrine. For this purpose, a commercial kit was used based on the immunochemical luminescence technique and an automatic Modular E179 analyser (Roche Diagnostics, Indianapolis, United States). Normal parathyrine values were between 10 and 65 pg/mL. The lowest detection limit of the technique is 3 pg/mL.

Peripheral blood calcium levels were determined on the afternoon of the day of the operation (6 h after the operation), and on the morning of the next day (20 h after the operation) and on the second day, and the ionic calcium value was calculated. Normal ionic calcium values are 0.95–1.3 mmol/L. For calcium replacement, a previous-defined protocol was used in which a selective criterion was established. No calcium was added in cases of mild asymptomatic hypocalcaemia. Only the patients who developed symptoms of hypocalcaemia were treated. The Chvostek and Trousseau signs were evaluated together with the presence of symptoms 3 times a day from the operation to the date of discharge. In patients with hypocalcaemia, the serum calcium was determined every day until it became normal, at which time the patient was discharged. After discharge, appointments were arranged with the patients one week afterwards in the outpatients' clinic. The study required a post-surgical hospitalisation time of at least 2 days.

In each patient, the following predictive factors were recorded: age, gender, preoperative diagnosis, type of surgery, number of parathyroid glands identified, operating time, and final histological values.

The ratio between the parathyrine concentrations and ionic calcium levels was analysed, determined early on the morning after the operation, together with the postoperative evolution. Three types of patients were established: patients with symptoms of hypocalcaemia, patients with hypocalcaemia but without symptoms, and patients with normal calcaemia. The characteristics of each group were analysed and the averages and distribution of predictive factor frequencies ($\chi^2$) were compared. For the purpose of studying the postoperative parathyrine and ionic calcium values as predictive factors of analytical hypocalcaemia and symptomatic hypocalcaemia, the ROC (receiver operator characteristics) curves were determined and the areas below the curve were calculated. The value of the parathyrine concentration showing the greatest activity in the ROC curve was taken as the cut-off point. The sensitivity was calculated, as well as the specificity, negative predictive value (NPV), positive predictive value (PPV), and the general accuracy of the postoperative parathyrine determination. A logistical regression analyses was performed to determine the effect of each clinical prognostic and analytical factor with respect to the probability of developing hypocalcaemia. For the statistical analysis, the SPSS 10.0 software for Windows was used (SPSS Inc, Chicago, United States).

## Results

Of the 67 patients included in the study, 42 (62.7%) showed ionic calcium determinations during the postoperative period below normal values, but only 20 (29.9%) showed symptoms of hypocalcaemia. Among those with symptoms, in 16 cases the symptoms were minor (paraesthesia) with more severe symptoms in 4 (cramps, tetany). They were all treated for transitory symptoms, and after 2 months of follow-up the calcaemia had been normalised in all of them and none required calcium supplements. The group of patients developing hypocalcaemic symptoms showed no clinical preoperative or surgical differentiating characteristics (Table 1). The concentration of parathyrine on the day after the operation was significantly lower in the group with symptomatic hypocalcaemia (5.57 [6.4] pg/mL) than in the

**Table 1 – Patient Characteristics and Postoperative Evolution**

| | Symptomatic Hypocalcaemia (n=20) | Asymptomatic Hypocalcaemia (n=22) | Normal Calcaemia (n=25) | P |
|---|---|---|---|---|
| Gender | | | | |
| Male (n=14), n (%) | 4 (28.5) | 3 (21.4) | 7 (50) | |
| Female (n=53), n (%) | 16 (30.2) | 19 (35.8) | 18 (34) | .31 |
| Age, mean (SD), y | 51 (13) | 50 (7) | 49 (11) | .8 |
| Diagnosis | | | | |
| Multinodular goitre (n=50), n (%) | 15 (30) | 16 (32) | 19 (38) | |
| Graves-Basedow (n=17), n (%) | 5 (29.4) | 6 (35.3) | 6 (35.3) | .95 |
| Duration of surgery, min | 116 (21) | 113 (20) | 114 (21) | .89 |
| Parathyroids observed | 2.2 (1.2) | 2.6 (0.8) | 2.2 (1) | .38 |
| Parathyrine,[a] pg/mL | 5.57 (6.39) | 21.58 (15.3) | 26.8 (24.9) | .001 |
| Ionic calcium,[a] mmol/L | 0.86 (0.02) | 0.87 (0.02) | 1.03 (0.02) | <.001 |

[a]Determined early in the morning of the day after the operation.

asymptomatic hypocalcaemia group (21.5 [15.3] pg/mL) and among those with normal calcaemia (26.8 [24.9] pg/mL) (P<.001). Of the 6 cases in which an autologous parathyroid transplant was performed, 5 patients developed hypocalcaemia, but only 2 showed symptoms of hypocalcaemia.

There was a significant correlation between the serum ionic calcium and parathyrine values in each patient, determined early in the morning of the day after the operation ($r$=0.222; $P$<.001). Figure shows the ROC curve that reflects the ratio between sensitivity and specificity in detecting symptomatic hypocalcaemia during the postoperative period. The parathyrine value that showed the best ratio with the development of hypocalcaemia symptoms and, therefore, better capacity to predict its development was 13 pg/mL. The area below the curve shown for parathyrine was 896 (95% confidence interval [CI], 812–981), higher than that shown by the ionic calcium, 771 (95% CI, 658–883).

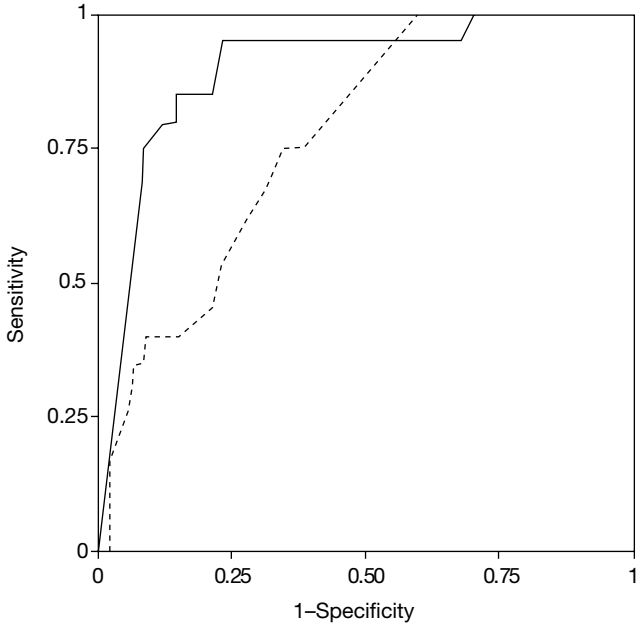


**Figure – ROC curve showing the ratio between sensitivity and specificity of parathyrine and ionic calcium in detecting symptomatic hypocalcaemia.**

**Table 2 – Calcaemia During the Postoperative Period Based on the Concentration of Parathyrine Determined 20 h After the Operation**

| Parathyrine | Hypocalcaemia | Normocalcaemia | Total |
|---|---|---|---|
| Low (<13 pg/mL) | 23 | 7 | 30 |
| Normal (≥13 pg/mL) | 19 | 18 | 37 |
| Total | 42 | 25 | |

P=.04. Diagnostic performance: sensitivity, 23/42 (54%); specificity, 18/25 (72%); positive predictive value, 23/30 (76%); negative predictive value, 18/37 (48%); general accuracy, 41/67 (61%).

**Table 3 – Symptoms of Hypocalcaemia During the Postoperative Period Based on the Concentration of Parathyrine Determined 20 h After the Operation**

| Parathyrine | With Symptoms | Without Symptoms | Total |
|---|---|---|---|
| Low (<13 pg/mL) | 19 | 11 | 30 |
| Normal) (≥13 pg/mL) | 1 | 36 | 37 |
| Total | 20 | 47 | |

P<.001. Diagnostic performance: sensitivity, 19/20 (95%); specificity, 36/47 (76%); positive predictive value, 19/30 (63%); negative predictive value, 36/37 (97%); general accuracy, 82.

**Table 4 – Symptoms of Hypocalcaemia During the Postoperative Period Based on the Concentration of Ionic Calcium Determined 20 h After Surgery**

| Ionic Calcium | With Symptoms | Without Symptoms | Total |
|---|---|---|---|
| Low (<0.95) | 18 | 24 | 42 |
| Normal (≥0.95) | 2 | 23 | 25 |
| Total | 20 | 47 | |

P=.002. Diagnostic performance: sensitivity, 18/20 (90%); specificity, 23/47 (48%); positive predictive value, 24/42 (42%); negative predictive value, 23/25 (92%); general accuracy, 41/67 (62%).

**Table 5 – Multivariable Analysis of Hypocalcaemic Risk Factors After Total Thyroidectomy**

| | OR | 95% CI | *P* |
|---|---|---|---|
| Gender | | | |
| Female | 1 | | |
| Male | 0.435 | 0.062–3.011 | .39 |
| Histological diagnosis | | | |
| Multinodular goitre | 1 | | |
| Graves-Basedow | 1.898 | 0.22–16.330 | .55 |
| Number of parathyroids | 0.524 | 0.22–1.23 | .14 |
| Operating time | 1.008 | 0.97–1.04 | .661 |
| Postoperative parathyrine | | | |
| Normal | 1 | | |
| Low | 112.59 | 8.99–1409.97 | .0002 |
| Postoperative ionic calcium | | | |
| Normal | 1 | | |
| Low | 13.68 | 1.117–167.52 | .04 |

CI indicates confidence interval; OR, odds ratio.

Table 2 classifies the patients based on their postoperative evolution (hypocalcaemia/normocalcaemia) and the concentrations of parathyrine 20 h after the operation.

Table 3 classifies the patients based on the parathyrine values and the development of hypocalcaemic symptoms.

Of the 37 patients with normal parathyrine values, 36 remained free from symptoms and 1 developed symptoms. Of the 30 with low parathyrine values, 11 remained free from symptoms and 19 developed symptoms of hypocalcaemia. False negatives were observed in 1 and false positives in 11. The sensitivity, specificity, PPV, and NPV of parathyrine <13 pg/mL for predicting the development of hypocalcaemic symptoms were 95%, 76%, 65%, and 97%, respectively. The general accuracy was 82%.

Table 4 shows the stratification of the patients based on the ionic calcium values determined 20 h after surgery and the development of hypocalcaemic symptoms during the postoperative period.

Table 5 shows the results of the multivariable analysis of the prognostical factors affecting the development of hypocalcaemic symptoms. Parathyrine and ionic calcium showed a significant separate predictive value.

## Discussion

Hypocalcaemia is a frequent complication after total thyroidectomy. The symptoms range from mild paraesthesia to cramps or tetany. In literature, its incidence fluctuates within a very wide range (from 1.7% to 68%).[1,4,5,11] This variability might reflect differences in criteria in defining it (asymptomatic hypocalcaemia or symptomatic hypocalcaemia) and the lack of uniformity in perioperative treatment with calcium. Hypocalcaemia usually develops within the first 48 hours of surgery, but the serum calcium concentration in many cases takes 72 h to stabilise.[1]

The incidence of hypocalcaemia in our study is high. We think this is due to the policy adopted for calcium replacement. No calcium supplements were systematically administered. We decided to administer calcium only when the hypocalcaemia developed with symptoms. We believe this guideline stimulates the functional recovery of the parathyroid tissue more rapidly and in the case of requiring treatment, the administration of calcium and/or vitamin D on an individual, controlled basis.

Although the incidence of hypocalcaemia after thyroidectomy depends on many factors, it appears to be confirmed that deterioration of the parathyroid function is the decisive factor. Direct surgical trauma or the devascularisation performed during the cervical examination deteriorates the function of the parathyroid glands.[10] It is also known that in the treatment of certain specific processes (Graves-Basedow, thyroid cancer, retrosternal goitre)[2,4,5] or in situations of a deficit in vitamin D, hypocalcaemia is detected more often.[16] However, it is impossible to predict the risk of a clinically-relevant hypocalcaemia developing for each individual patient.[7]

The deterioration in the function of the parathyroid glands during a cervical examination has a rapid effect on the serum parathyrine concentration. The half-life of the hormone is only 2–5 min, and so any aggression taking place produces a rapid fall in the serum concentration of parathyrine.[7,12] This fact has recently led some authors to investigate the use of the perioperative determination of parathyrine (using the traditional technique or the quick test) to identify patients with a risk of developing hypocalcaemia and hypoparathyroidism after total thyroidectomy.[1,6,11-20]

In the studies that have been published, there is an agreement that patients developing hypocalcaemia after thyroidectomy have a serum parathyrine concentration that is lower than those with calcaemia within the normal range.[12,17] However, there is no agreement as to whether perioperative determination of parathyrine furnishes relevant predictive information about each patients' individual risk of developing hypocalcaemia.

In our study, parathyrine determined 20 h after surgery was found to be within normal levels in 37 patients and was low in 30. The sensitivity of low levels of parathyrine in predicting the development of hypocalcaemia was 54% and specificity, 72%. However, the determining of parathyrine levels was more useful in predicting the development of hypocalcaemic symptoms. In this case, the sensitivity of parathyrine was 95% and specificity, 76%. Thirty-six of the 37 patients with normal parathyrine levels remained free from symptoms and 1 developed symptoms of hypocalcaemia. The predictive value of a negative test result (parathyrine >13 pg/mL without symptoms) was 97%. The normal parathyrine findings during the postoperative period practically rule out subsequent development of hypocalcaemic symptoms and so these patients could be discharged the day after the operation safely and without calcium treatment. By contrast, the obtaining of the value parathyrine <13 pg/mL does not necessarily imply the development of hypocalcaemic symptoms. Of the 30 patients with low parathyrine levels, 11 showed false positive (36%). The predictive value of a positive result for the test (PTH <13 pg/mL and development of symptoms) was 65%. These patients would require monitoring of the calcaemia and/or a calcium or vitamin D supplement.

The results of our study coincide with most of the information published. Several series show that serum concentration of parathyrine below normal values during the postoperative period is a predictive factor for hypocalcaemia, with a sensitivity of 80%–90% and specificity of 80%–100%.[11,12,14,15,17] We agree that the usefulness of the test is higher for detecting symptomatic hypocalcaemia than for analytical hypocalcaemia.[17,19] In addition to this, as shown by our data, the main limitation of the test is the high number of false positives.[13,15,17] Indeed, in almost one third of patients with low parathyrine, no hypocalcaemia developed. We also coincide in that low parathyrine gave results that are similar to those given for calcaemia 24 h after the operation in predicting the development of analytical hypocalcaemia in the postoperative period, but are better than calcaemia 24 h after the operation in predicting the development of hypocalcaemic symptoms.[15,17]

There is no agreement about the time when the parathyrine must be determined. Some authors have used the quick determination test for parathyrine at the time of closing the skin.[12] This test is easy to apply, but its results do not affect surgical decisions. In addition to this, the parathyrine levels gradually fall and become stable 24 h after surgery,[7,11] and so a determination performed at an early stage might not be representative of the final result. Lombardi et al[11] compared

the results obtained after determining the concentration of parathyrine at different times: at the end of the surgical procedure and 2, 4, 6, 24, and 48 h afterwards. They found that a parathyrine >10 pg/mL measured 4 h afterwards or later was 100% sensitive and 100% specific for detecting symptomatic hypocalcaemia. According to these authors, the results of measuring on closing the skin and 2 h after surgery provide less concordance with the postoperative evolution. The group from Sydney University[21] compared the results obtained with the determinations made 4 and 24 h after surgery and found no significant differences between them. We think that if similar results are obtained between 4 and 24 h after surgery, the adopting of a specific time must be made in each centre, depending on availability and the existence of early discharge programmes.

Many endocrinal surgeons systematically administer oral calcium to their patients after discharging them the same day after surgery or 24 h after surgery. The determination of parathyrine would make it possible to evaluate the parathyroid function quickly and facilitate early discharge, while reducing the potential risk of developing hypocalcaemia.[22]

Recently, a study has been published by a group of Australian surgeons[23] that contains a series of recommendations on the use of determining parathyrine after total thyroidectomy. These are based on the results of four previous studies by the same authors. According to that publication, the obtaining of parathyrine values that are within the normal range predicts the maintenance of normocalcaemia with great accuracy during the postoperative period. The main clinical usefulness of the test would be to identify patients with a low risk of developing hypocalcaemia who could be discharged earlier in safety without requiring treatment. The identification of this group of patients would make it possible to select those who could be included in thyroid surgical programmes with short hospitalisation times. By contrast, a low parathyrine result would not allow the identification of patients with a high risk since in 16% of patients with low parathyrine levels, hypocalcaemia does not develop. According to these authors, patients with low parathyrine levels require the starting of treatment and monitoring of calcaemia. Those authors advise against early discharge and systematic treatment with calcium and/or vitamin D in all patients without first checking the parathyrine concentration. They think that although this practice could reduce the incidence of mild hypocalcaemia and facilitate early discharge, it could delay the diagnosis and appropriate treatment of hypoparathyroidism. In addition to this, it requires close monitoring of the calcaemia.

In a recent study, the preoperative determination of serum vitamin D provided additional information to that obtained by postoperative determination of parathyrine and allowed subgroups of patients with a risk of differentiated hypocalcaemia to be identified.[19] This is a line of research for the future.

The results of our study show that determination of parathyrine on the day following surgery is a useful test in forecasting the evolution of calcaemia during the postoperative stage. The usefulness of the test is higher for detecting symptomatic hypocalcaemia than analytical hypocalcaemia. The usefulness of low parathyrine values as an element for predicting hypocalcaemia is scarce, due to the high number of false positives. By contrast, the normal parathyrine finding practically rules out the subsequent development of symptoms of hypocalcaemia.

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