

ORIGINAL ARTICLE

Use of intranodular parathyroid hormone values obtained by fine needle aspiration as a predictive factor of postoperative hypoparathyroidism

Uso de los valores de hormona paratiroidea intranodular obtenidos por punción con aguja fina como factor predictivo de hipoparatiroidismo posoperatorio

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Abstract

Objective: To analyze if parathyroid hormone (PTH) washout levels can be considered a predictive factor of postoperative hypoparathyroidism and determine its importance relative to other features already known as intraoperative PTH, Ca and PTH preoperative, and others. **Method:** Of the 157 patients to whom a fine needle aspiration (FNA) biopsy with intranodular parathyroid hormone level measurement was performed (washout PTH) 37 who underwent surgery were studied. 15 variables were taken into account when selecting patients for this study: age, gender, evolution length, size, associated thyroid surgery, preoperative treatment with calcimimetics, presence of renal lithiasis, bone densitometry alterations, creatine clearance, preoperative calcium and PTH levels, PTH scores obtained by fine needle aspiration, intraoperative PTH decrease, postoperative calcium levels and tumor malignancy. We compare the nominal values, using the Chi squared or the exact Fisher test, where p < 0.05 was considered statistically significant and perform a logistic regression analysis. **Results:** The use of mimetics prior to surgery, the preoperative PTH level above 88 pg/dl, and postoperative calcium levels under 8.5 mg/dl were all independently significant variables in the univariant analysis (p < 0.05) in order to establish an early postoperative hypoparathyroidism. This factor must be taken into account during the study and follow-up to identify possible complications and establish an adequate treatment on time.

Key words: Parathyroid hormone. Postoperative hypoparathyroidism. Calcium Parathyroidectomy.

Resumen

Objetivo: Análisis de los valores de hormona paratiroidea (PTH) intranodular obtenidos por punción con aguja fina como factor predictivo de hipoparatiroidismo posoperatorio. **Método:** De los 157 pacientes a los que se realizó la medición de la PTH intranodular, se estudiaron 37 que fueron intervenidos quirúrgicamente, estableciendo 15 variables para analizar: edad,

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sexo, tiempo de evolución, tamaño, cirugía de tiroides asociada, tratamiento preoperatorio con calcimiméticos, litiasis renal, densitometría ósea, aclaramiento de creatinina, calcio y PTH preoperatorios, PTH determinada tras punción con aguja fina, descenso de la PTH intraoperatoria, calcio posoperatorio y malignidad de la tumoración. Estas se compararon con la prueba de ji al cuadrado o el test exacto de Fisher, siendo significativa una p < 0.05, construyéndose así un análisis de regresión logística. **Resultados:** El uso de calcimiméticos previo a la cirugía, la PTH preoperatoria > 88 pg/dl, el calcio preoperatorio > 12 mg/dl, los valores de PTH intranodular > 2700 pg/dl, el descenso de la PTH intraoperatoria a < 15 pg/dl y el calcio posoperatorio < 8,5 mg/dl fueron variables independientes significativas en el análisis univariante (p < 0.05) para la predicción del hipoparatiroidismo posoperatorio. **Conclusiones:** Los valores de PTH intranodular pueden predecir qué pacientes tienen mayor riesgo de sufrir un hipoparatiroidismo posoperatorio. Este factor debe tenerse en cuenta durante el estudio y el seguimiento de los pacientes para identificar precozmente posibles complicaciones.

Palabras clave: Hormona paratiroidea. Hipoparatiroidismo posoperatorio. Calcio. Paratiroidectomía.

Introduction

After surgical intervention of a patient with primary hyperparathyroidism there is a rapid decrease in calcium values due to a reactive imbalance between production and bone resorption that produces an increase in bone uptake. Clinical impact of this mechanism translates into the presence of paresthesias, neurological disorders and cardiac alterations¹. Postoperative hypoparathyroidism prevention must be early, and in addition to preserving the rest of the parathyroid glands, certain factors that can predict which patients are at greater risk of suffering this disturbance should be taken into account.

The measurement of intranodular parathyroid hormone (PTH) by fine needle aspiration is a novel technique with known benefits and risks, which is used for localization and differentiation of the parathyroid from the thyroid gland²⁻⁴. These values, associated with other factors, could predict the development of postoperative hypoparathyroidism and be a useful tool in current clinical practice. In this study, we will determine its importance in comparison with other already known characteristics, such as intraoperative PTH, and preoperative calcium or PTH, among others.

Method

Retrospective, observational study with consecutive sampling carried out during the years 2007 and 2015 at the University Hospital of Gran Canaria, with 157 patients diagnosed with primary hyperparathyroidism who had intranodular PTH values measured by fine needle aspiration. All 37 patients who were operated on in this period were finally included in the study, with a minimum postoperative follow-up of 12 months, which ended in January 2017, with those who had postoperative hypoparathyroidism and which factors influenced on its appearance being identified.

All intervened patients diagnosed with primary hyperparathyroidism who had had intranodular PTH levels previously measured and only one gland resected were included in the study, while patients with multiglandular disease, with previous surgeries in another of the glands, with auto-transplant surgery and who did not comply with the data collection of all study variables were excluded.

Fifteen variables were established and studied: age, sex, disease evolution time, size, associated thyroid surgery, preoperative treatment with calcimimetics, presence of renal lithiasis, bone densitometry alterations (T-score < 2.5), creatinine clearance (< 60 mL/min), preoperative calcium and PTH, PTH values obtained by fine needle aspiration, intraoperative PTH decrease (10 minutes after excision), postoperative calcium (6 hours after excision) and tumor malignancy.

Quantitative variables were categorized in order to transform them into nominal with two homogeneous groups that were more comparable, which also prevented sample dispersion. As for age, a cutoff point of 50 years was chosen because it is one of the surgical intervention criteria in asymptomatic patients, and an age younger than this is related to a higher risk of malignancy. Large size nodules and long-time disease evolution are variables associated with an increase in the occurrence of postoperative hypoparathyroidism, and thus we decided on a large section size (2 cm) and longer waiting time for surgery (2 years). To decide a surgical attitude in asymptomatic patients with primary hyperparathyroidism there are defined values in bone densitometry and creatinine clearance, which were used to establish the cutoff point of these variables. Regarding PTH, normal values in our laboratory are 15 to 88 pg/dL, and thus we decided to study the latter figure as predictive factor. Albumin-corrected calcium normally ranges from 8.5 to 10.5 mg/dL, considering a clear increase of 1.5 mg/dL above the upper limit of normal and thus defining the 12 mg/dL described in our study variable. Intraoperative PTH decrease below 15 pg/dL and postoperative calcium decrease below 8.5 mg/dL are known predictive factors⁵, and hence we also decided to study them.

Intranodular PTH values obtained by fine needle aspiration are pathological when they are higher than 100 pg/dL, but had never been established as a hypoparathyroidism predictive variable; therefore, we decided to carry out multiple univariant analyses until obtaining a significant cutoff value at 2700 pg/dL.

In order to compare the nominal variables, contingency tables were created to use the chi-square test or Fisher's exact test, with a p-value < 0.05 being significant. When determining the variables that had a significant relationship with the presence of postoperative hypoparathyroidism, the generation of multiple multivariate analysis models was independently started, thus building a logistic regression analysis using the IBM[®] SPSS[®] Statistics program, v. 21.

Results

One-hundred and fifty-seven intranodular PTH value measurements were made by ultrasound-guided fine needle puncture. Thirty-seven patients underwent surgery, out of which 17 (46%) had later postoperative hypoparathyroidism, which was transient in all cases (< 12 months' evolution) and symptomatic only in 4 (24%), with mild paresthesias and muscle cramps, which were solved only with calcium and oral vitamin D.

The use of calcimimetics prior to surgery, preoperative PTH > 88 pg/dL, preoperative calcium > 12 mg/dL, intranodular PTH > 2700 pg/dL, intraoperative PTH decrease < 15 pg/dL and postoperative calcium < 8.5 mg/dl were significant independent variables in the univariate analysis (p < 0.05) for the prediction of postoperative hypoparathyroidism (Table 1); the rest of the variables were not statistically significant.

The multivariate analysis revealed that the use of calcimimetics prior to surgery, intraoperative PTH decrease < 15 pg/dL and intranodular PTH values > 2700 pg/dL are factors that increase the risk for the occurrence of postoperative hypoparathyroidism (Table 2).

Discussion

Postoperative hypoparathyroidism is the most common complication that occurs in the clinical follow-up

Characteristic	teristic Postoperative hypoparathyroidism		р
	Present n (%)	Absent n (%)	
Number of cases	17 (46)	20 (54)	
Age (years) ≤ 50 > 50	9 (53) 8 (47)	7 (35) 13 (65)	< 0.272
Gender Females Males	12 (73) 5 (27)	13 (65) 7 (35)	< 0.717
Evolution time (years) ≤ 2 > 2	5 (27) 12 (73)	6 (30) 14 (70)	< 0.968
Tumor size (mm) < 20 ≥ 20	11 (65) 6 (35)	17 (85) 3 (15)	< 0.151
Associated thyroid surgery Yes No	5 (27) 12 (73)	5 (25) 15 (75)	< 0.763
Calcimimetic treatment Yes No	12 (73) 5 (27)	4 (20) 16 (80)	< 0.001
Nephrolithiasis Yes No	5 (27) 12 (73)	5 (25) 15 (75)	< 0.763
Bone mineral density, T-score < 2.5 > 2.5	7 (41) 10 (59)	6 (30) 14 (70)	< 0.477
Creatinine clearance (mL/min) ≥ 60 < 60	14 (82) 3 (18)	17 (85) 3 (15)	< 0.827
Preoperative PTH (pg/dL) ≥ 88 < 88	11 (65) 6 (35)	4 (20) 16 (80)	< 0.005
Preoperative calcium (mg/dL) ≥ 12 < 12	7 (41) 10 (59)	2 (10) 18 (90)	< 0.027
Intranodular PTH (pg/dL) ≥ 2700 < 2700	7 (41) 10 (59)	1 (5) 19 (95)	< 0.007
Intraoperative PTH (pg/dL) > 15 ≤ 15	10 (59) 7 (41)	19 (95) 1 (5)	< 0.007
Postoperative calcium (mg/dL) > 8.5 ≤ 8.5	13 (76) 4 (24)	20 (100) 0 (0)	< 0.021
Malignancy Yes No	3 (18) 14 (82)	1 (5) 19 (95)	< 0.216

PTH: Parathyroid hormone.

Table 2. Logistic regression analysis

Independent variable	OR (95% CI)	р
Calcimimetic treatment	4,67 (0,288-0,734)	< 0.001
Intranodular PTH \ge 2700 pg/dL	2,191 (0,023-0,667)	< 0.036
Intraoperative PTH \leq 15 pg/dL	3,174 (0,152-0,702)	< 0.003
Preoperative PTH \ge 88 pg/dL		< 0.585
Preoperative calcium \geq 12 mg/dL		< 0.218
Postoperative calcium ≤ 8.5 mg/dL		< 0.412

CI: confidence interval; OR: odds ratio

of patients after parathyroid surgery, and it is defined as a drop in PTH and onset of clinical manifestations related to calcium decline, such as paraesthesia, perioral dysesthesias, muscle spasms, myoclonus, weakness, headache and nausea, which can even be life-threatening for the patient^{5,6}. When it occurs in patients operated for primary hyperparathyroidism, it is usually related to previous gland hyperfunction, malfunction of the rest of the glands, alterations in the production and release of PTH, surgical manipulation, hungry bone syndrome and both tumor and patient characteristics⁵⁻⁸. Mean occurrence of this alteration varies according to the authors, but it ranges from 10 to 30% of cases^{5,9,10}, with a rate of 46% being observed in our department, which can be explained by the fact that our hospital concentrates its surgical activity in oncological conditions, with primary hyperparathyroidism surgical interventions being restricted only to patients with associated pathologies, complicated cases, with higher surgical technical difficulty, with suspicion of malignancy and with elevated anesthetic risk, who have to wait according to availability to be intervened, thus increasing the use of previous treatments, with longer time of hyperfunction of the affected gland. In the study, a follow-up of at least 12 months was carried out, and there were no cases of permanent hypoparathyroidism, given that we only included patients with single gland surgeries, with the rest being preserved.

There are many characteristics that can increase the risk for postoperative hypoparathyroidism, and although this work seeks the advantages of using the measurement of intranodular PTH, we also had to examine the rest of possible factors to compare its usefulness.

Age younger than 50 years is a factor to be taken into account when deciding a surgical attitude in

patients with asymptomatic hyperparathyroidism, given that it relates to an increased risk of malignancy and longer exposure time to the disease; when we examined it, we did not find any relationship with subsequent hypoparathyroidism occurrence¹¹. Creatinine clearance < 60 mL/min and a T-score < 2.5 in bone densitometry are parameters that decide surgical intervention of an asymptomatic patient and are related to the alterations attributed to a poorly controlled primary hyperparathyroidism; furthermore, prolonged alterations in bone turnover time lead to subsequent development of hungry bone syndrome with increased calcium uptake, which entails uncontrolled hypocalcemia¹¹⁻¹³. Nevertheless, in our study, these variables were not significant.

When a thyroid examination is carried out on the same surgical act of a parathyroid tumor exeresis, there is the risk, during mobilization, of causing excision, devascularization or trauma to the rest of the glands, which would increase the risk of subsequent hypoparathyroidism¹⁴⁻¹⁶; therefore, we decided to study this variable, which was not relevant in our patients. The highest number of hyperparathyroidism cases occurred in women, as in other studies^{5,8,10}, but this was not related to subsequent occurrence of hypoparathyroidism. High PTH values for a long time, as well as an increase in its production in the case of large adenomas or carcinomas, cause an adaptation of the calcium receptors to continuous hypercalcemia that is abruptly suppressed during surgery, which entails, in most patients, hypocalcemia as a reaction to this mechanism^{5,17}; however although these variables are important in clinical practice, in our study they were not significant.

Calcimimetics act on the calcium sensitive receptor located on the surface of the main cell of the parathyroid gland increasing its sensitivity, which reduces PTH concentrations. This reduction is associated with a parallel decrease of serum calcium concentrations^{18,19}. In our hospital, we use these drugs following the criteria of the European Medicines Agency guidelines²⁰ for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease on dialysis and for hypercalcemia reduction in patients with parathyroid carcinoma or primary hyperparathyroidism, in whom, according to their serum calcium values, parathyroidectomy would be indicated, especially when there is a long time to wait for surgical treatment, calcium values are considerably high or the patient has significant symptoms of hypercalcemia, with the medication being discontinued 24 hours before surgery. Although calcimimetics half-life is 6 hours, sometimes they can accumulate in tissues and maintain their effects up to 40 hours after discontinuation, which could explain their significant relationship with the presence of postoperative hypoparathyroidism in our patients¹⁸⁻²⁰. Based on these results, the need to discontinue this medication at least 2 days before the surgical intervention is proposed.

High preoperative PTH and calcium values are widely studied factors that are related to the presence of postoperative hypoparathyroidism⁵, which we confirmed with our study. Intraoperative PTH decreased values remain controversial, since in some studies a significant relationship was obtained with values lower than 10 pg/dL and in others below 15 pg/dL, and even predictive results have been obtained when the decrease is higher than 60% of PTH initial value²¹⁻²⁴. In our study, it was a decrease to values below 15 pg/dL which showed a significant relationship with the subsequent occurrence of hypoparathyroidism

After excision of the pathological gland, calcium may take 24 to 72 hours to descend, and values below normal at 6 hours of the excision should be a sign of alarm that should be taken into consideration to prevent probable hypocalcaemia²⁵; this relationship was significant in our study.

The measurement of intranodular PTH values obtained by ultrasound-guided fine needle aspiration is mainly used to locate the affected gland and confirm the parathyroid origin of the tumor. These values are variable, but when they are above 100 pg/dL they are considered pathological ^{26,27}. Performing multiple univariate analyses with the figures obtained in our different punctures, we found that values higher than 2700 pg/dL had a significant relationship with subsequent onset of hypoparathyroidism, both in the univariate and in the multivariate analysis. This relationship is probably explained by excessive hyperfunction of the gland, with high production of PTH, to which the body adapts, and when it is suppressed by surgical resection, reactive hypocalcemia occurs. The results of this measurement should be taken with caution, since it it is a small sample and there is no other study that has sought this relationship, which makes the comparison of our results with current literature difficult.

The measurement of PTH values might be a factor to be considered in the future since, associated with the rest of known variables, it could predict the occurrence of postoperative hypoparathyroidism, and allow the establishment of diagnosis and early treatment, which would decrease unfavorable clinical manifestations for these patients.

Conclusions

The use of calcimimetics prior to surgery, PTH and calcium values preoperative elevation, decrease in intraoperative PTH and low postoperative calcium values are known variables that, together with the measurement of PTH intranodular values, can predict which patients are at higher risk for suffering postoperative hypoparathyroidism. Therefore, PTH intranodular values are a useful tool in current clinical practice for obtaining better results and avoiding complications that prolong hospital stay and decrease the quality of life of our patients.

Conflict of interests

The authors of this work declare that they have no conflicts of interest.

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