



Original Article

Relationship Between Parathormone Concentration During Surgery and the Post-Operative Outcome of Primary Hyperparathyroidism

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A B S T R A C T

Introduction: The relationship between the intra-operative concentration of parathyroid hormone (IOPTH) and the long-term outcome of patients intervened due to primary hyperparathyroidism (PHPT).

Patients and methods: A prospective observational study was performed with 120 patients. Three determinations were made of PTH in blood: baseline, when the diseased gland was located, and 10 minutes after its extirpation. The calcium, PTH and vitamin D (25-OH-D₃) levels were measured during follow up.

Results: A decrease in IOPTH >50% was observed in 96 (80%) patients, and the post-extirpation value returned to the normal range (Group I), in 18 (15%) a decrease of >50% but the final value remained higher than normal (Group II) and in 6 (5%) the decrease was <50% (Group III). Persistent PHPT was detected during follow up in 6 patients (5%): one in Group I (1%), 3 (16.7%) in II and 2 (33.3%) in group III ($P < .001$). The risk of persistent PHPT was higher in Group II (odds ratio: 19; 95% CI: 1.85-194) and in Group III (odds ratio: 47; 95% CI: 3.53-639). There were no cases of recurrent PHPT. A normal calcium with an increased PTH was detected in 20 patients of Group I (20.8%), 11 (61.1%) in II and 3 (50%) in III ($P < .001$). These patients had a lower concentration of post-operative vitamin D (17 ng/ml, range: 24; compared to 28 ng/ml, range: 21) ($P = .008$) and higher frequency of hypovitaminosis D (70.6% compared to 26.2%) ($P > .001$).

Conclusion: The risk of persistent PHPT is higher when the IOPTH decreases more than 50% but still remains high.

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Relación entre concentración intraoperatoria de parathormona y evolución postoperatoria del hiperparatiroidismo primario

R E S U M E N

Palabras clave:

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Introducción: Se analiza la relación entre la concentración intraoperatoria de parathormona (IOPTH) y la evolución a largo plazo de pacientes intervenidos por hiperparatiroidismo primario (HPTP).

Pacientes y métodos: Estudio prospectivo observacional que incluye 120 pacientes. Se realizaron tres determinaciones de PTH en sangre: basal, en el momento de localizar la glándula patológica y a los 10 minutos tras su extirpación. Se determinaron las concentraciones de calcio, PTH y vitamina D (25-OH-D₃) durante el seguimiento.

Resultados: En 96 (80%) pacientes se observó disminución de IOPTH > 50% y el valor postextirpación volvió al rango normal (Grupo I), en 18 (15%) disminución > 50% pero el valor final se mantuvo superior al nivel normal (Grupo II) y en 6 (5%) la disminución fue < 50% (Grupo III). Durante el seguimiento se detectó HPTP persistente en 6 pacientes (5%): uno en el Grupo I (1%), 3 (16,7%) en el II y 2 (33,3%) en el III ($p < 0,001$). El riesgo de HPTP persistente fue superior en el Grupo II (odds ratio: 19; IC 95%: 1,85-194) y en el III (odds ratio: 47; IC 95%: 3,53-639). No se observaron casos de HPTP recidivado. Se detectó calcemia normal con PTH elevada en 20 pacientes del Grupo I (20,8%), 11 (61,1%) en el II y 3 (50%) en el III ($p < 0,001$). Estos pacientes presentaron menor concentración de vitamina D postoperatoria (17 ng/ml, rango: 24; frente a 28 ng/ml, rango: 21) ($p = 0,008$) y mayor frecuencia de hipovitaminosis D (70,6% frente a 26,2%) ($p > 0,001$).

Conclusión: El riesgo de persistencia del HPTP es superior cuando la IOPTH disminuye más del 50% pero se mantiene en niveles elevados.

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Introduction

The use of intraoperative parathyroid hormone (IOPTH) monitoring in the surgical treatment of primary hyperparathyroidism (PHPT) has increased over the last decade. The half-life of this hormone is 5 minutes, so the level of PTH during surgery gives an indication of the amount of hyperfunctioning tissue removed.¹⁻⁶

Since the introduction of this test, there have been differences of opinion over its use. IOPTH is a functional parameter, not a morphological one. It determines when the abnormal secretion of PTH stops as a result of removing the overactive gland. However, it does not identify those glands with a pathological increase in size but which are not hypersecreting while an intervention takes place.^{7,8} Moreover, the application of the technique is not uniform; there are variations in the programming of the samples and the criteria of therapeutic success. The University of Miami group has stated that the best clinical results are obtained when the IOPTH, from a sample taken 10 minutes after removing the pathological gland, decreases by more than 50% compared to the previous samples.^{2,3,9-12} Under those circumstances, there is a low incidence (1%) of false positives and false negatives (2.6%), and calcaemia is normalised at 6 months in 95%-98% of patients. However, other authors consider it necessary for the IOPTH to turn to the normal range, as otherwise the risk of recurrence remains high.^{5,8,13,14}

The aim of this study was to analyse the relationship between IOPTH concentration and the long-term evolution of

patients operated on for PHPT. Results obtained from patients whose PTH levels dropped by more than 50% and were within the normal range were compared with those whose PTH concentration decreased by more than 50%, but were above the normal limit.

Patients and Method

The results from 120 patients operated on for PHPT were analysed. They were selected from 176 patients with PHPT who underwent surgery consecutively in our hospital between January 2002 and January 2010. Patients with a follow-up of over 6 months and those who underwent an intraoperative PTH measurement were included. Three patients with familial multiple endocrine neoplasia and 53 whose IOPTH was not determined were not included in the study.

The series consisted of 95 women (79.2%) and 25 men (20.8%), with an average age of 56 years (range: 36-78). Of these, 105 (87.5%) had a single adenoma and 15 (12.5%) had multiglandular disease. It was the first surgery for 111 patients (92.5%), and for 9 (7.5%) was a re-operation due to persistent PHPT. Cervicotomy with bilateral exploration was performed in 64 patients, in 53 with selective access (in 9, it was extended to bilateral exploration) and sternotomy in 3 patients.

Study Protocol

The blood levels of calcium, PTH and vitamin D (25-OH-D₃) were determined before the intervention. During the

intervention, 3 samples were obtained from peripheral blood. The first was taken after performing the surgical incision, the second after identifying the pathological gland and the third 10 minutes after excision. To determine the intraoperative PTH, a rapid commercial test (Immulite Turbo Intact PTH, Siemens Healthcare Diagnostic, IL, USA) was performed, which relied on an immuno-chemiluminescence technique. Normal PTH values are within the 10-65 pg/ml range. Vitamin D was analysed by an electro-chemiluminescence immunoassay method (LiaisonR, DiaSorin, Saluggia, Italy); the lower normal limit is 20 ng/ml. Those operated upon were followed up as outpatients. The serum concentrations of PTH, calcium and vitamin D were determined 2 and 6 months after the intervention, and annually thereafter.

The IOPTH test was considered positive when the concentration of PTH in the post-removal sample decreased by more than 50% compared to the higher of the two previous samples. If this reduction was not seen, it was considered that not all hyperfunctioning tissue had been removed and surgical exploration continued. A satisfactory post-operative result was considered when the serum calcium was normal 6 months after surgery. It was considered persistent if both hypercalcaemia remained and PTH was elevated at 6 months. Recurrence was defined as the reappearance of hypercalcaemia with elevated PTH after a period of normocalcaemia of more than 6 months.

Clinical and laboratory data from these patients were collected prospectively and filed on a database. For this study, patients were divided into three groups according to the degree of decrease in the PTH in the post-removal sample: Group I (decrease in PTH concentration of more than 50% and values in the normal range), Group II (decrease of more than 50%, although with a value higher than the normal range), Group III (less than 50% decrease).

Statistical Analysis

The median and interquartile range of the continuous variables were used. For categorical variables, the number of measurements and percentages were used. The frequency

of persistent PHPT was calculated in each group. The PTH and vitamin D values did not follow a normal distribution (using the Kolmogorov test). Therefore, to compare results between the three groups of patients, non-parametric hypothesis testing was applied (Mann-Whitney, Kruskal-Wallis), and the chi-square test for categorised variables. The IOPTH performance was studied as an indicator of favourable post-operative evolution through the parameters of sensitivity, specificity and predictive values. The risk of persistence was determined by the odds ratio. A SPSS 15.0 for Windows software (SPSS Inc, Chicago, USA) was used for statistical analysis, with P values below .05 being considered as statistically significant.

Results

According to the IOPTH evolution, 96 patients (80%) were in Group I, 18 (15%) in Group II and 6 (5%) in Group III. Table 1 shows the pre-operative clinical and laboratory data. In all three groups, the mean vitamin D concentration was below the normal value (20 ng/ml). Pre-operative PTH was significantly higher in patients with low vitamin D levels (217 pg/ml, range: 81) than in patients with normal vitamin D (139 pg/ml, range 96), $P=.029$.

The mean post-operative follow-up was 42 months (range: 6-103). During this period, the calcium and PTH concentrations returned to normal levels in 80 patients (66.6%); serum calcium was normal but PTH remained high in 34 (28%); and hyperparathyroidism persisted with hypercalcaemia and high PTH in 6 (5%), see Table 2. There were no cases of recurrent hyperparathyroidism.

When analysing the relationship between IOPTH and post-operative evolution, group I had a greater number of patients with normalised serum calcium and PTH (75 cases, 78%, $P<.001$), see Table 2. Group II patients had normal serum calcium and elevated PTH levels more frequently than in the other groups (11 patients, 61.1%, $P<.001$). Persistent PHPT was found in 1 patient from Group I (1%), 3 from Group II (16.7%) and 2 from Group III (33.3%). The risk of persistent PHPT

Table 1 – Pre-operative Clinical and Laboratory Data Classified According to the Evolution of the Intraoperative Parathyroid Hormone Concentration.

	Group I (n=96)	Group II (n=18)	Group III (n=6)	P
Calcium, mg/dl	11.2 (0.67)	11.2 (1.15)	10.95 (1.7)	.01
PTH, pg/ml	153 (90)	183 (155)	141 (64)	.04
Vitamin D,* ng/ml	17.5 (14)	17 (24)	11.5 (8)	.49
Number of patients with vitamin D <20 ng/ml	56	60	60	.28
Age	60 (62.5%)	10 (55.5%)	5 (83%)	.51
Sex				
Female	73 (76%)	16 (88%)	6 (100%)	
Male	23 (12%)	2 (12%)	0	.2
Number of glands				
Uniglandular (105)	86 (81.9)	15 (14.3%)	4 (3.8%)	.21
Multiglandular (15)	10 (66.6%)	3 (20%)	2 (13.4%)	
Median (interquartile range).				
*25-OH-D ₃ .				

Table 2 – Relationship Between Intraoperative Parathyroid Hormone Concentration and Post-Operative Evolution.

	Normal Calcaemia Normal PTH (n=80)	Normal Calcaemia High PTH (n=34)	High Calcaemia High PTH (n=6) (persistence)	P
Group I (n=96)	75 (78.1%)	20 (20.8%)	1 (1.1%)	
Group II (n=18)	4 (22.2%)	11 (61.1%)	3 (16.7%)	<.001
Group III (n=6)	1 (16.6%)	3 (50%)	2 (33.3%)	<.001
Chi-square test.				

Table 3 – Risk of Persistent Primary Hyperparathyroidism According to Final Parathormone Concentration.

	No. of Cases	Persistent PHPT	OR	CI 95%	P
Group I	96	1 (1%)	1		
Group II	18	3 (16.7%)	19	1.85-194.8	.02
Group III	6	2 (33.3%)	47.5	3.53-639.9	.001
CI 95% indicates confidence interval 95%; OR, odds ratio.					

was higher in Group II (odds ratio: 19; 95% CI: 1.8-194.8) and Group III (odds ratio: 47.5; 95% CI: 3.5-639), see Table 3.

Among the 9 patients operated on for persistent PHPT, 2 were diagnosed with mediastinal adenoma and surgical access was via medial sternotomy. In 7 cases, the location was cervical. In 1 of the mediastinal adenoma patients, the IOPTH reduced less than 50%. After surgery, serum calcium and PTH remained elevated. A new cervical adenoma was

subsequently found in a lower right location, so the patient was re-operated. In 6 patients, the IOPTH fell by more than 50% and turned to normal levels. After the intervention, all had normal calcaemia and serum PTH. In 2 cases, the IOPTH decreased by more than 50%, but did not return to the normal range; after surgery, they had normal serum calcium with 1 had transient elevation of PTH.

The performance of IOPTH in predicting the development of normocalcaemia in the post-operative period is shown in Table 4. The sensitivity was 96% and specificity 33%. There were 4 false positives and 4 false negatives. The sensitivity among the 105 cases of uniglandular disease was 98%, with 1 false positive and 4 false negatives. The sensitivity for the 15 multiglandular cases was 83%, with 3 false positives and no false negatives. If the test had been considered positive when the IOPTH had fallen by more than 50% and the final level was found in the normal range, the IOPTH performance would have been: sensitivity 83%, specificity 83%, with 1 false positive and 19 false negatives (Table 4).

After surgery, 50 patients (41.6%) had low levels of vitamin D. Patients who developed normal serum calcium and elevated PTH levels had a lower post-operative vitamin D concentration (17 ng/ml; range: 24; $P=.008$) and a higher hypovitaminosis D frequency (70.6%), $P<.001$, see Table 5.

Table 4 – Prognostic Value of Intraoperative Parathyroid Hormone Concentration Tests on the Evolution of Calcaemia Positivity Criteria.

	IOPTH Decrease >50%	IOPTH Decrease >50%+IOPTH in Normal Range
Sensitivity	96% (110/114)	83% (95/114)
Specificity	33% (2/6)	83% (5/6)
PPV	96% (110/114)	98% (95/96)
NPV	33% (2/6)	20% (5/24)
False positives	3.5% (4/114)	1% (1/96)
False negatives	66.6% (4/6)	79.1% (19/24)
NPV indicates negative predictive value; PPV, positive predictive value.		

Discussion

The goal of PHPT treatment is to normalise calcium levels and, to do this, the hyperfunctioning tissue must be removed (in 85% of cases, it was due to a single adenoma). The appearance of locating techniques such as ultrasound, scintigraphy and IOPTH have led to safer surgical treatment.^{9,10}

The results from our study show a relationship between the final concentration of PTH and post-operative evolution. The frequency of persistent PHPT is significantly lower when both the IOPTH decreases more

Table 5 – Concentration of Vitamin D in the Post-Operative Period According to Hyperparathyroidism Evolution.

	Calcium and PTH - Normal	Calcium Normal and PTH high	Persistent PHPT	P
Vitamin D concentration ^a	28 (21)	17 (24)	13 (9)	.008 ^b
No. of patients with vitamin D <20 ng/ml	21/80 (26.2%)	24/34 (70.6%)	5/6 (83.3%)	<.001
Vitamin D (25-OH-D ₃): ng/ml.				
^a Median (interquartile range).				
^b Kruskal-Wallis test.				

than 50% and its value returns to the normal range. After surgery, calcaemia normalised in 78% of these patients, with frequency of persistent PHPT being only 1%. By contrast, those for whom the IOPTH decreased by more than 50%, but levels were higher than normal, showed a high frequency of persistent PHPT (16.7%) and the risk of persistence was 19 times higher (95% CI: 1.8-194). Although the number of patients in our series was small and the confidence intervals wide, the existence of statistical significance highlights the strength of the relationship. Theoretically, this data is an argument for requiring the IOPTH decrease to be within normal levels. It seems that the final value of the IOPTH is a better predictor of post-operative outcome after parathyroidectomy than the percentage decrease.

There is no agreement on the relationship between the long-term evolution of PHPT and the level of post-resection IOPTH. In a recent study by Carneiro-Pla et al¹⁵ of 341 patients, the percentage of persistent PHPT was similar in the group where the IOPTH decreased by more than 50% and was within the range of normal values (2% of persistent PHPT), and the group whose IOPTH decreased but did not return to normal levels (2.5% of persistent PHPT). In contrast, there are several publications^{13,14,16} that found a higher incidence of persistent PHPT among patients who did not regain normal IOPTH values, as in our study. These authors recommend reviewing the criteria for interpreting IOPTH, such that the PTH measured 10 minutes after resection of the adenoma should return to the normal range.

Several criteria have been described to interpret the IOPTH curve. The Miami criterion considered surgical success when PTH levels, 10 minutes after removing the adenoma, decreased by more than 50% compared to the higher value of the previous samples (at incision or pre-excision).¹² Having identified the pathological gland and before extraction, the second sample is to prevent the interference of theoretical PTH concentration peaks produced while handling the adenoma, which can prolong the IOPTH decay curve. The Vienna criterion requires post-removal IOPTH to decrease by more than 50% compared to the baseline sample.¹⁷ The Rome criteria require the IOPTH value to both reduce by 50% and be within the normal range.¹⁸ Carneiro-Pla¹² compared the results with six cure definitions in 341 patients. The best results were obtained with the Miami criterion, as it correctly predicted post-operative calcaemia in 329 patients and failed in only 12 cases (3 false positives and 9 false negatives). Using the other criteria, 2 of the 3 false positives could have been prevented, but the incidence of false negatives would have increased from 6% to 24%. Riss et al¹⁷ compared 3 criteria in 310 patients. The sensitivity of the Vienna and Miami criteria (92% and 98%, respectively) were higher than the criterion requiring a return to normal levels (70%). The latter and the Vienna provided greater specificity (89%), although with a greater number of false negatives. Similar results have been found from two other recent studies.^{18,19} We found an IOPTH reduction criteria of over 50% to within the normal range provides better predictive results and greater overall specificity, but considerably increases the number of false negatives.

In 4 of the 6 patients who developed persistent PHPT, the IOPTH gave a false positive. In the 4 cases, the IOPTH reduced by more than 50%, and 1 of them did so to within the normal range. In the post-operative period, they again presented hypercalcaemia and elevated PTH. The 4 patients were re-operated: a double adenoma was detected in 3 of them, and all the four glands were impaired in the other. In other words, the test failed in 4 of the 15 multiglandular cases. These data are consistent with previous publications, which indicate that the usefulness of the test decreases in multiglandular disease cases.^{7,20-22}

We have no previous analytical data for the 9 patients operated on for persistent adenoma. It would be interesting to compare the IOPTH in the first intervention with that of the re-operation.

Vitamin D plays an important role in calcium metabolism and PTH regulation, which was the reason for measuring the three factors in parallel. The results indicate that the solution for the interpretation of IOPTH may not be as clear as changing the cut-off level and requiring the recovery of normal IOPTH values. The vitamin D level must also be considered. The group of patients whose IOPTH decreased by more than 50% without reaching the normal range after the intervention, as well as developing persistent PHPT more often, also developed normal calcaemia with elevated PTH levels (HPTH) more frequently. These patients had lower vitamin D levels and increased frequency of hypovitaminosis D. The PTH normalised following treatment with vitamin D post-operatively and these patients are now cured. If we had followed up these patients, the indication to resume surgical exploration for a suspected pathological gland, which did not actually exist, would surely have extended the cervical dissection without finding anything pathologically important, leading to significant added morbidity. The IOPTH protocol probably needs to be modified to include the objectives of a 50% decrease and return to normal values. However, those patients with low vitamin D concentrations must also be treated with vitamin D.

The clinical significance of HPTH in patients operated on for hyperparathyroidism has been discussed. In our series, it was detected in 28% of patients, more frequently in Group II (61%) than in Group I (20.8%, $P=.001$). Other publications have reported 10%-30% of cases.^{5,9,12,15,16} Some authors consider it to be a mild and asymptomatic persistent PHPT.^{13,14} Our series had no cases of relapsed PHPT in these patients, so no association can be confirmed. However, a relationship with vitamin D deficiency was found. The association between hypovitaminosis D and PHPT has clear clinical implications. It is known that the severity and symptoms of PHPT are greater in patients with vitamin D deficiency.²³⁻²⁵ Also, the prevalence of hypovitaminosis D is higher in patients with HPTH in the general population.²³⁻²⁵ HPTH causes vitamin D deficiency due to consumption and hypovitaminosis D causes secondary HPT.²⁵

In conclusion, patients whose IOPTH decreases by more than 50%, but remains high, are at greater risk of persistent PHPT. Also, the occurrence of normocalcaemia and elevated PTH is frequent in this group, which is associated with hypovitaminosis D.

Conflict of Interest

The authors affirm that they have no conflict of interest.

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