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Predictores de remisión precoz y tardía en hipoparatiroidismo posquirúrgico transitorio

Sara Mera Carreiro[1], Aurelio López Guerra[2], Laura Ávila Antón[1], Beatriz Ugalde-Abiega[3], Paola Parra Ramírez[4], María Martín-Fuentes[5], Noelia Sánchez-Maroto García[1], Ana M. Humanes-Navarro[6], Isabel Huguet[7]

[1]Department of Endocrinology. Hospital Universitario Clínico San Carlos. Madrid, Spain. [2]Department of Endocrinology. Hospital General Universitario Gregorio Marañón. Madrid, Spain. [3]Department of Endocrinology. Hospital Universitario Ramón y Cajal. Madrid, Spain. [4]Department of Endocrinology. Hospital Universitario La Paz. Madrid, Spain. [5]Department of Endocrinology. Hospital Universitario Santa Cristina. Madrid, Spain. [6]Department of Preventive Medicine. Hospital Universitario Clínico San Carlos. Madrid, Spain. [7]Department of Endocrinology. Hospital Universitario Infanta Leonor. Madrid, Spain

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Correspondence: Isabel Huguet. Department of Endocrinology. Hospital Universitario Infanta Leonor. Avda. Gran Vía del Este, 80. Madrid, Spain
e-mail: ihm.huguet@gmail.com

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ABSTRACT

Purpose: to analyze predictors of early, intermediate, late remission of transitory hypoparathyroidism after total thyroidectomy.

Methods: multicenter retrospective observational study of individuals who developed postoperative transient hypoparathyroidism.

Results: 164 patients with postoperative transient hypoparathyroidism were analyzed. Thyroidectomy was performed in 56 % for benign pathology and 44 % for suspected malignancy. Hypoparathyroidism remission occurred early (< 3 months) in 47 % of patients, intermediate (3-6 months) in 23.7 %, and late (> 6 months) in 29.3 %. No differences were found between three groups regarding preoperative PTH levels, PTH at 24 hours after surgery, or the percentage of PTH decrease. However, we observed higher calcemia values at 24 hours after surgery, and higher calcemia and PTH levels at the first outpatient appointment (2 weeks after discharge) in patients with early remission of hypoparathyroidism. In patients with late remission of hypoparathyroidism, a history of surgery for malignancy, the presence of undetectable PTH levels and lower calcemia at 24 hours after surgery, and the need for intravenous calcium treatment were remarkable ($p < 0.05$). This group had lower PTH levels at first and second outpatient visits, and lower calcemia on the second visit ($p < 0.05$).

Conclusions: calcium and PTH levels measured two weeks after discharge can predict early recovery. Late remission was more frequent in patients undergoing thyroidectomy for suspected malignancy, those with undetectable PTH 24 hours after surgery, and those requiring intravenous calcium. Calcium levels 24 hours after

surgery could probably predict hypoparathyroidism remission time, but the absence of a unique protocol to guide management at hospitalization does not allow us to provide a robust conclusion.

Keywords: Hypocalcemia. Hypoparathyroidism. Thyroidectomy.

RESUMEN

Objetivo: analizar predictores de remisión temprana, intermedia y tardía del hipoparatiroidismo transitorio tras tiroidectomía total.

Pacientes y métodos: estudio observacional retrospectivo multicéntrico en pacientes que desarrollaron hipoparatiroidismo transitorio posquirúrgico.

Resultados: se analizaron 164 pacientes. La tiroidectomía se realizó en 56 % por patología benigna y 44 % por sospecha de malignidad. La remisión del hipoparatiroidismo fue temprana (< 3 meses) en 47 %, intermedia (3-6 meses) en 23,7 % y tardía (> 6 meses) en 29,3 %. No se encontraron diferencias entre los tres grupos en cuanto a niveles de PTH preoperatorios, PTH 24 horas de la cirugía o el porcentaje de disminución de PTH. Sin embargo, observamos mayores valores de calcemia 24 horas de la cirugía y mayores niveles de calcemia y PTH en primera consulta ambulatoria (2 semanas tras alta) en pacientes con remisión temprana. En los pacientes con remisión tardía, el antecedente de cirugía por neoplasia maligna, la presencia de niveles indetectables de PTH y calcemia más baja 24 horas posteriores a la cirugía, y la necesidad de tratamiento con calcio intravenoso fueron destacables ($p < 0,05$). Este grupo tuvo niveles más bajos de PTH en primera y segunda visita ambulatoria, y calcemia más baja en segunda visita ($p < 0,05$).

Conclusiones: los niveles de calcio y PTH medidos a las dos semanas del alta pueden predecir recuperación temprana. La remisión tardía fue más frecuente en los pacientes sometidos a tiroidectomía por

sospecha de neoplasia maligna, aquellos con PTH indetectable a las 24 horas poscirugía y aquellos que requirieron calcio intravenoso. Los niveles de calcio a las 24 horas posteriores a la cirugía probablemente podrían predecir el tiempo de remisión del hipoparatiroidismo, pero la ausencia de protocolo único para guiar el manejo en la hospitalización no nos permite proporcionar una conclusión sólida.

Palabras clave: Hipocalcemia. Hipoparatiroidismo. Tiroidectomía.

INTRODUCTION

Calcium homeostasis is a complex process mainly regulated by parathyroid hormone (PTH) and vitamin D, with PTH being the major regulator of calcemia (1,2). Hypoparathyroidism is a disorder of mineral metabolism characterized by hypocalcemia and absent or deficient production of PTH (3).

Surgical hypoparathyroidism occurs after inadvertent trauma, devascularization, or removal of the parathyroid glands during neck surgery. In fact, anterior neck surgery is the most common cause of acquired hypoparathyroidism, especially after bilateral thyroid surgery (4). Post-operative hypoparathyroidism can be transient or permanent. Permanent hypoparathyroidism is most commonly defined as the failure of the parathyroid gland to return to normal function 12 months after surgery (5). The ability to anticipate transient as opposed to permanent hypoparathyroidism after thyroidectomy requires further investigation. Also, since transient hypoparathyroidism requires frequent biochemical monitoring for tapering or discontinuation of calcium and calcitriol due to risk of hypercalcemia and potential kidney damage, the identification of predicting remission parameters is needed to improve follow-up (6,7).

Whereas several authors are putting their efforts into anticipating the development of postoperative hypocalcemia as accurate as possible, to our knowledge, predicting parameters of the time of recovery in transient hypoparathyroidism have not been studied. The aim of our study was to analyze predictors of early, intermediate, and late remission of hypoparathyroidism after total thyroidectomy through a retrospective, multicentric observational study.

MATERIALS AND METHODS

This retrospective analysis enrolled 164 patients over 18 years of age from different hospitals in the Community of Madrid (Spain) with experience in thyroid surgery, who underwent total thyroidectomy and developed transient hypoparathyroidism. Remission of hypoparathyroidism was defined as the discontinuation of substitutive treatment and was categorized as “early” (< 3 months), “intermediate” (3-6 months), or “late” (> 6 months after surgery). Indications for surgery were thyroidectomy for benign nodular pathology; thyroidectomy for Graves´ disease; thyroidectomy for malignant pathology; combined thyroid and parathyroid surgery; and re-intervention for thyroidectomy totalization. We included the combined thyroid and parathyroid surgery as a group, since the presence of previous hyperparathyroidism could modify the calcium metabolism after surgery due to probably hungry bone influence.

We included socio-demographic and clinical data (sex, age, presence of obesity, treatment with vitamin D or thiazide). Data regarding the surgical procedure, changes in parathyroid function, and the management of hypoparathyroidism were reviewed. Intact PTH, alkaline phosphatase, and vitamin D were assessed pre-surgery. PTH, calcemia (albumin-adjusted calcium), and phosphatemia were evaluated at 24, 48, and 72 hours, at the first out-patient visit after discharge, the second visit after discharge, and the visit of recovery. Since several hospitals were involved in the study, there was not a unique protocol of follow up: on average the first follow-up visit was performed at 2 weeks after discharge and the second visit at 4-8 weeks after discharge. The between visits between 4-8 weeks and the recovery were not recruited, but were performed according to physician's criteria under the guidance of the First International Conference on the Management of Hypoparathyroidism (3), which was the current guide at that point. We also included as treatment data the need for intravenous calcium or magnesium in the immediate postoperative period. Therapy at discharge included oral calcium carbonate and calcitriol, according to the physician´s clinical criteria, same as the treatment withdrawal.

The descriptive and statistical analysis was performed using the Statistical Package software for Social Sciences 24.0 (SPSS). Qualitative variables are presented with their frequency distribution. Quantitative variables are summarized with their mean. Quantitative variables showing an asymmetric distribution are summarized with the median. A comparison of socio-demographic, clinical, surgical, and laboratory data according to time of remission was performed. The association between qualitative variables was assessed with the chi-square χ^2 test or Fisher's exact test, if more than 25 % of the expected values were less than 5. For quantitative variables, means were compared using a two-tailed Student's t-test or the Mann-Whitney U test if quantitative variables did not conform to a normal distribution.

RESULTS

A total of 164 patients were included. There were 144 women (87.8 %) and 20 men (12.2 %) with a mean age of 51 years (range 18-89), with a mean vitamin D level of 23 mg/ml and 17.7 % having received previous vitamin D treatment. 5.5 % of patients were taking thiazides. Most patients (72, 43.9 %) underwent a total thyroidectomy for suspected malignancy; 61 (37.2 %) patients for benign nodular pathology and 21 (12 %) patients for Graves´ disease. Also, 6 (3.7 %) patients had combined thyroid and parathyroid surgery, whereas 4 (2.4 %) patients required a re-intervention for totalization of thyroidectomy (Table I).

Hypoparathyroidism remission was early in 47 % of patients, intermediate in 23.7 % and late in 29.3 %. There were no differences by sex, but we did find differences by age at surgery in the early (p = 0.02) and intermediate (p = 0.021) groups when comparing patients in these categories to the remaining patients. There were no differences in clinical parameters such as obesity, presence of low vitamin D, serum alkaline phosphatase, or previous treatment with vitamin D or thiazides before surgery. Malignant pathology was associated with late recovery in our study (p = 0.003). Regarding biochemical parameters, no differences were found between the three groups regarding preoperative PTH values (55, 52, and 53 pg/mL); PTH at 24 hours after surgery (10, 9, and 9.5 pg/mL), or in the median percentage of PTH decrease (82, 80.5, and 83 %).

As shown in table II; patients in the group of early remission hypoparathyroidism had significantly higher calcium levels 24 hours after surgery (8.4 mg/dL, p = 0.001), and only a small proportion of patients had undetectable PTH at 24 hours after surgery (6.6 %, p = 0.020) compared to other patients. In this group, only 9.2 % (p = 0.000) of patients required intravenous calcium and none required

magnesium. In addition, at the first visit, these patients had a mean calcemia of 9.3 mg/dL (p = 0.010) and a median PTH of 20 pg/mL (p = 0.039), indicating early resolution of hypoparathyroidism and allowing discontinuation of calcium and calcitriol treatment.

In contrast, in patients with late resolution of hypoparathyroidism, calcium levels 24 hours were lower 7.9mg/dL (p = 0.000) after surgery; and 25 % of these patients had undetectable PTH (p = 0.003). In the postoperative period, 43.8 % (p = 0.000) of patients required intravenous calcium and 6.3 % magnesium. Calcium levels were lower, especially at the second visit (8.8 mg/dL, p = 0.019), and PTH levels were lower at the first visit (12pg/mL, p = 0.000) remaining lower in the second visit (21pg/mL, p = 0.014). Related to surgical parameters, 60.4 % of patients in late remission (p = 0.012) underwent total thyroidectomy for malignant pathology. After a median of 11 months the remission of hypoparathyroidism occurred.

Due to several missing values, phosphorus levels were not analyzed.

When receiver operating characteristic (ROC) curve analysis were done, the only parameter with a proper area under the curve (AUC) was calcemia 24 hours following surgery. The AUC for detecting early hypoparathyroidism remission using calcemia 24 hours after surgery was 0.645, with the best cut off of 8.22 mg /dL (sensitivity, 56 %; specificity, 32 %, positive predictive value 0.6) (Figure 1)

DISCUSSION

Hypoparathyroidism is the most common complication of thyroidectomy. Its frequency, if transient, can reach up to 46 %, and, if permanent, up to 3 % in literature (8,9). Early prediction of postoperative hypocalcemia is critical to initiate treatment and avoid potentially life-threatening complications; however, this treatment must be closely monitored since resolution of hypoparathyroidism should be accompanied by a discontinuation of calcium and calcitriol to prevent hypercalcemia (10).

Type and extent of surgery, operative technique, surgeon expertise and cause of disease contribute to the risk of surgical hypoparathyroidism (11-13) and probably to the length of the recovery period. In our study, patients undergoing total thyroidectomy for malignant pathology had more frequently a later remission than those that had thyroidectomy for other causes, maybe due to a more aggressive approach. Because of the multicentric design of the study, we could not compare surgeon expertise as a predictor of time of remission.

PTH has been shown to be a useful tool in predicting post-operative hypoparathyroidism. Since calcium trends often require sampling over a period of 12 to 24 hours or longer, PTH seems to be a more reliable parameter (12). Several studies have attempted to validate different PTH thresholds and combinations of PTH and calcium, but the results have not been consistent (14-18). The percentage of decrease in PTH levels has also been used to predict hypocalcemia. In our series, the median decrease in PTH was of 84.9 %, similar to the decline reported by other authors in patients developing hypoparathyroidism. According to guidelines (19) post-surgical PTH can be used for predicting which patients will not develop permanent postsurgical hypoparathyroidism. The development of permanent hypoparathyroidism is unlikely when values of PTH are > 10 pg/mL 12-24 hours post-surgery, and therefore would be no long-term need for treatment with active vitamin D and calcium supplements above the recommended daily allowance. Also, according to Yao *et al* (20) 3-64 % of patients with PTH values < 10 pg/mL 12-24 hours post-surgery may still recover from temporary hypoparathyroidism. In our study mean level of PTH 24h after surgery was 9 pg/ml, and median level was 11 pg/ml, supporting guidelines assertion. We evaluated these parameters as predictors of time of recovery, but did not find significant differences between preoperative PTH, PTH at 24 hours after surgery or in the percentage of PTH decrease. The use of different PTH assays between centers could explain the lack of

significance, although it should not affect the percentage of decrease. We did find that higher levels of PTH and calcium in the first visit (2 weeks after surgery) could predict early remission of hypoparathyroidism while lower PTH levels were associated with late remission. Regarding calcemia at 24, 48 and 72 hours, the absence of a unique protocol to guide management at hospitalization could have influenced levels, mainly at 48 and 72 and probably in some cases at 24 hours. Our results suggest that calcemia at 24 hours after surgery could probably predict hypoparathyroidism remission time, since ROC analysis suggested that calcemia > 8.2mg/dL 24 hours after surgery is associated with early remission of hypoparathyroidism, and we also found differences between early and late groups, but we cannot provide a robust conclusion.

We also tried to analyze phosphorus levels, but there were considerable missing values, so the result was biased. Phosphate is raising interest when evaluating PTH function, not only to differentiate hungry bone disease from hypocalcemia due to hypoparathyroidism in the early postoperative period (21) but also as an indicator of the severity of PTH deficiency. In a study involving patients with PTH < 10 pg/mL on the first postoperative day, phosphorous concentration was found to be an independent factor influencing the return of PTH to normal levels in the first week after surgery (22). Since fibroblast growth factor 23 (FGF23) was not available in routine biochemical test in several hospitals, its value was not considered in this study. As far as we are aware, only one study has evaluated FGF23 in postsurgical hypoparathyroidism. In this study, the authors found a significant positive correlation between serum phosphate and FGF23 levels. Serum FGF23 was elevated in patients with hypoparathyroidism and hyperphosphatemia and normalized along with normalized phosphate levels after recovery of parathyroid function. The peak level of phosphate always preceded that of FGF23 by several days, suggesting that elevated phosphate is a

primary stimulus for release of FGF23 (23). This could explain the fact that phosphate changes appear to be slower than that of serum calcium, whose change is rapidly corrected within minutes.

The strength of this study lies in the multicenter recruitment of patients, the number of enrolled patients and the point that it represents real clinical practice involving second and third-level hospitals (Table III). Also, since our study is focused on transient hypoparathyroidism, we believe that our conclusions could help in understanding the recovery process of parathyroid function. On the other hand, regarding the weaknesses of our study we believe that evaluating a more homogeneous population could provide more precise data, but we aim to provide a general point of view and cover different settings. Also, we did not consider the effect that the treatment with Iodine-131 had in patients intervened for malignant pathology, which could be of interest since it has been described a prolonged recovery of parathyroid function of patients with thyroid cancer and treatment with Iodine-131 treatment after surgery (24). We also did not include data regarding lymph nodes dissection, which influences the extent of surgery.

To conclude, the definition of permanent hypoparathyroidism remains controversial. Since in most cases, parathyroid dysfunction after thyroidectomy resolves during few months after surgery, several authors consider that if parathyroid disfunction persists over 6 months (3), hypoparathyroidism should be considered as permanent. In our study almost 70 % of the patients had remission of hypoparathyroidism in the first 6 months (early 47 %, intermediate 23.7 %) but after that period, a significant percentage of patients recovered the parathyroid function (29.3 %), supporting the recommendation of the Second International Workshop for the Evaluation and Management of Hypoparathyroidism (19) to diagnose permanent hypoparathyroidism if the condition persists over 12 months after surgery.

CONCLUSION

Two weeks after discharge, calcium and PTH levels can predict early recovery. Late remission was more frequent in individuals undergoing thyroidectomy for suspected malignancy, those with undetectable PTH at 24 hours after surgery, and those requiring intravenous calcium.

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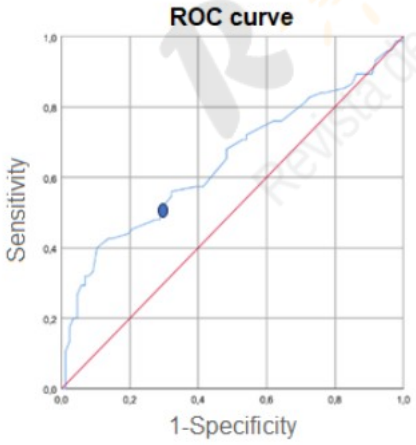

Figure 1. Receiver operating characteristic (ROC) curve analysis, calcemia at 24 hours.

Table I. Patient characteristics and indications for surgery

	Early	**Intermediate**	**Late**

	remission (*n* = 77)	**remission (*n* = 39)**	**remission (*n* = 48)**
Patient characteristics			
Patient age at surgery, mean ± SD	54 ± 15*	46 ± 14*	50 ± 15
Sex n (%)			
Male	9 (12)	4 (10)	7 (15)
Female	68 (88)	35 (90)	41 (85)
Indication for surgery n (%)			
Malignant pathology	30 (39)	13 (33)	29† (60)
Benign nodular pathology	33 (43)	15 (38)	13 (27)
Graves´disease	7 (9)	8 (21)	6 (3)
Combined thyroid and parathyroid surgery	5 (6)	1 (3)	0
Totalization of thyroidectomy	2 (3)	2 (5)	0

$^{*}p < 0.05$, $^{\dagger}p < 0.01$, $^{\ddagger}p < 0.001$

Table II. PTH levels, calcemia, alkaline phosphatase, vitamin D and post-surgery treatment

	Early remission (*n* = 77)	**Intermediate remission (*n* = 39)**	**Late remission (*n* = 48)**
PTH levels			
Preoperative (pg/ml)	55 (44-75)	52 (40-68)	53 (45-65)

Postoperative (pg/ml)	10 (5-12)	9 (7-12)	9.5 (5-13)
Median % of PTH decrease	82 (77-92)	80.5 (75-90)	85 (80-91)
Patients with undetectable postoperative PTH (%)	5 (6.6) *	4 (10.8)	12 (25) †
1st visit (pg/ml)	20 (12-34) *	19 (15-34)	12 (8-18) ǂ
2nd visit (pg/ml)	31.5 (20-48)	31.5 (18-41)	21 (12-34) *
Alcaline phosphatase (U/L)	*74.4 (63-88) **	71 (56-78)	68.1 (42-76) *
Vitamin D (pg/ml)	23 (14-30)	19 (16-25)	27.5 (20-36)
Calcemia (mg/dL)			
24 after surgery	8.4 ± 0.8 †	8.1 ± 0.7	7.9 ± 0.6 ǂ
48 after surgery	8.1 ± 0.9	8.2 ± 0.7	8.2 ± 0.6
72 after surgery	8.3 ± 0.8	8.6± 0.8	8.3 ± 0.7
1st visit	9.3 ± 0.7 *	9.1± 0.4	9.3 ± 0.5
2nd visit	9.2 ± 0.9	9.2± 0.4	8.8 ± 1.2*
Treatment			
Treatment with Ca iv (%)	7 (9.2) ǂ	9 (23.1)	21 (43.8) ǂ
Treatment with Mg (%)	0 (0)	2 (5.1)	3 (6.3)

$^{*}p < 0.05$, $^{\dagger}p < 0.01$, $^{\ddagger}p < 0.001$. Data are presented as mean± SD or median (IQ range) range depending on the type or the data distribution.

Table III. Number os patients included per hospital

Hospital	**Number of patients included *n*; (%)**
Clínico San Carlos	32 (23)
Gregorio Marañón	39 (27)
La Paz	18 (12)
Ramón y Cajal	27 (18)
Santa Cristina	15 (10)
Infanta Leonor	15 (10)