

Predictive Factors for Postoperative Severe Hypocalcaemia after Parathyroidectomy for Primary Hyperparathyroidism

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Hypocalcaemia is a complication of parathyroidectomy. We retrospectively analyzed data on patients who underwent parathyroidectomy for primary hyperparathyroidism (pHPT) to identify predictive factors for severe postoperative hypocalcaemia. Since 2004 we performed 87 parathyroidectomies for pHPT. We divided the patients into two groups: subjects who presented with postoperative hypocalcaemia (group B) or otherwise (group A). We looked for a correlation between several variables and the incidence of postoperative hypocalcaemia. The median calcemia in group B (19 patients) was 6.9 mg/dL on the first postoperative day and 7.6 mg/dL on the third day. We observed hypocalcaemia related clinical symptoms in every patient. In all 19 cases the reduction of intraoperative parathyroid hormone above 85 per cent after parathyroidectomy was related to the development of severe postoperative hypocalcaemia ($P = 0.042$). We found that the reduction of intraoperative parathyroid hormone over 85 per cent after parathyroidectomy can be considered a reliable predictive factor of postoperative hypocalcaemia after parathyroidectomy for primary hyperparathyroidism.

PRIMARY HYPERPARATHYROIDISM (pHPT) is an increasingly common endocrine disorder with a higher incidence between the fifth and seventh decade of life.¹⁻⁹ In more than 70 per cent of cases it is due to single adenomas whereas in 10 to 20 per cent of cases it is caused by multiglandular disease, like double adenomas or hyperplasia,^{1, 2, 5, 10-14} and it is rarely secondary to parathyroid cancer.^{1, 2, 10, 11, 15, 16}

Over the years many different therapeutic approaches have been proposed to treat pHPT and, among all these, parathyroidectomy represents a mainstay in case of symptomatic pHPT, with a percentage of success over 95 per cent. It is also indicated in selected asymptomatic patients.¹⁷⁻²³ It has been demonstrated that patients who underwent parathyroidectomy have a lower risk of mortality, onset of cardiovascular complications, and even pHPT-related tumors than patients who were not operated.^{1, 2, 6, 24-30} However, parathyroidectomy can be followed by life-threatening perioperative complications such as severe hypocalcaemia.³¹⁻⁴⁴ The incidence of

transient postoperative hypocalcaemia rates from 0 per cent to 35 per cent,³⁶⁻⁴⁶ whereas a permanent hypocalcaemia occurs in 0 per cent to 3.8 per cent of cases.⁴⁵⁻⁴⁸

At present, no specific causes have been disclosed to explain the onset of postoperative hypocalcaemia that still remains a postparathyroidectomy multifactorial syndrome.^{36-39, 49} Moreover, this syndrome has an important role in the postoperative management of patients who underwent parathyroidectomy because in case of severe hypocalcaemia a longer clinical observation and hospital stay associated to a supplementation of calcium and Vitamin D are required. In this light, the identification of predictive factors for the development of postoperative hypocalcaemia would be beneficial; this would allow surgeons to select patient candidates for parathyroidectomy on an outpatient or a short-stay basis.^{36, 37, 39, 40, 44, 45, 47, 48}

This study aimed to identify possible predictive factors for the onset of postoperative hypocalcaemia after parathyroidectomy for pHPT.

Patients and Methods

We retrospectively analyzed the data of 87 patients undergoing surgery for pHPT between June 2004 and December 2009. For all these patients we considered

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gender, age, symptoms experienced, symptom-diagnosis latency, and any previous neck surgery. We recorded the data of perioperative laboratory tests, specifically serum concentration of calcium, parathyroid hormone (PTH), alkaline phosphatase (AP), creatinine, magnesium, potassium, bicarbonates, phosphates, albumin, and serum pH value. We evaluated the reduction in intraoperative PTH (i.o. PTH) expressed as a percentage defined using the following formula: $[(PTH \text{ at induction} - i.o. PTH \text{ after 10 minutes from the parathyroidectomy}) / PTH \text{ at induction}] \times 100$.

Quick i.o. PTH was determined using a solid-phase chemiluminescent immunometric assay (Immulite Analyser Turbo Intact PTH, Medical System, Genoa, Italy). All the blood samples were taken from peripheral veins. We also recorded the results of the histological examination, with particular reference to the weight of the parathyroid adenoma, postoperative calcaemia, the presence of any hypocalcaemia-induced clinical symptoms (paraesthesia, cramps, Chvostek sign, Trousseau sign), and the duration of the hospital stay.

We defined postoperative hypocalcaemia as a serum calcium level < 8 mg/dL in one measurement recorded within 4 days of the parathyroidectomy.⁵⁰ Severe hypocalcemia was defined as serum calcium levels below 7.5 mg/dL.

We looked for statistical correlation between the variables considered and the incidence of postoperative severe hypocalcaemia by splitting the subjects into two groups: patients who did not present postoperative severe hypocalcaemia (group A) and patients who experienced such complication (group B).

We scheduled follow-up with clinical and biochemical examinations 1 week and 1, 6, and 12 months after surgery. At each follow-up meeting we recorded serum calcium, Vitamin D, and PTH values, and vitamin D metabolic complications. The mean follow-up was 12.6 months (range 18.7–10.0 months) to identify the onset of any recurrent or persistent pHPT.

Statistical Analysis

Chi-squared or Fisher's exact tests were used when appropriate to compare categorical variables; logistic regression models were used in univariate and multivariate analyses to identify the factors related to postoperative severe hypocalcemia. For each analysis the following potential predictive variables were taken into account: age, gender, previous neck surgery (yes/no), preoperative serum calcium, PTH, AP, creatinine, magnesium, potassium, bicarbonates, phosphates, albumin concentration, the weight of the parathyroid adenoma, and the reduction of i.o. PTH.

Finally, Receiver Operating Characteristic (ROC) curves were constructed when appropriate. The level

of statistical significance was set at $P < 0.05$. All tests were two-sided. Statistical analysis was performed with statistical software for biomedical research (MedCalc[®] Software for Windows, Version 9.2.0.0, MedCalc Software, Mariakerke, Belgium).

Results

The median age of the patients studied (61 female and 26 male) was 63.9 years. Among all the 87 subjects, 68 (78.2%) did not present severe hypocalcemia after parathyroidectomy (group A), whereas 19 patients suffered from severe postoperative (PO) hypocalcemia with serum calcium level lower than 7.5 mg/dL. Table 1 indicates the characteristics of the two groups of patients considered.

Group A

The median age among group A (49 females and 19 males) was 62.3 years (range 29–78 years). Overall, the preoperative clinical manifestation of pHPT were: renal in 33 cases (48.5%); 18 patients (26.5%) had bone alterations, 8 patients (11.8%) suffered neurological and/or mental disorders, and 17.4 per cent of patients (12 cases) were asymptomatic. Symptom-diagnosis latency varied from 3 to 54 months. Eleven patients (16.2%) were on chronic therapy with diuretics and two patients (2.9%) were on calcium antagonists.

Preoperative hypercalcemia was present in all patients (100%), with median values of 13.1 mg/dL (range 10.1–19.8 mg/dL) and in 10 cases (14.7%) alkaline phosphatase was elevated. No patient had low albumin values or serum pH alterations. All patients (100%) had preoperative PTH values above the normal range: median value 410 (range 97–1450 pg/mL). A single parathyroidectomy was performed in 61 cases (89.7%).

The histological examination showed the presence of a parathyroid adenoma in all cases (100%). The median weight of the adenoma was 550 milligrams (range

TABLE 1. Characteristics of Patients Undergoing Parathyroidectomy for Primary Hyperparathyroidism According to the Presentation of Postoperative Hypocalcaemia (Group B) or Otherwise (Group A)

Variable	Group A	Group B
Mean age	62.3 years	66.4 years
F/M gender ratio	2.6	1.7
Preoperative Ca+	13.1 mg/dL	12.3 mg/dL
Ca+ 1st postoperative day	8.5 mg/dL	6.9 mg/dL
Ca+ 3rd postoperative day	8.7 mg/dL	7.6 mg/dL
Preoperative PTH	410 pg/mL	390 pg/mL
Change i.o. PTH % 10 minutes	77.0%	89.7%
Weight of the adenoma	550 grams	635 grams

Data are given as a median \pm standard deviation unless otherwise indicated.

360–1800 milligrams). The i.o. PTH level measured at the induction of anesthesia and 10 minutes from the parathyroidectomy revealed a median drop of 77 per cent (range 65–88%).

In the first and third postoperative days, none of the patients had median calcaemia values lower than normal range (8.5 mg/dL, range 8.3–9.0 mg/dL and 8.7 mg/dL, range 8.6–9.3 mg/dL, respectively) and none presented any clinical symptoms of hypocalcaemia. The pre and postoperative values of serum creatinine, phosphate, magnesium, potassium, bicarbonate, and pH were also found to be normal. No calcium and vitamin D supplies were administered. Median time for discharge was 3.5 days (range 3.0–4.5) and none of the patients presented persistent or recurrent pHPT at follow-up controls.

Group B

The median age in group B (12 females and 7 males) was 66.4 years (range 35–74 years). Nine patients out of the 19 presented preoperatively with renal symptoms; bone alterations were observed in five cases (26.3%) and 2 patients (16.7%) had neurological and/or mental disorders, whereas 3 patients were asymptomatic. Symptom-diagnosis latency varied from 3 to 48 months.

Two patients (10.5%) were on chronic therapy with diuretics, 1 patient (5.3%) was on angiotensin converting enzyme (ACE) inhibitors, and 1 patient (5.3%), digitalis therapy. Blood examinations revealed a median serum calcium value of 12.3 mg/dL (range 10.8–20 mg/dL), preoperative alkaline phosphatase was elevated in 3 patients (15.8%), and serum pH and albumin values were within the normal range. All patients had a preoperative PTH value above the normal range: median value 390 pg/mL (range 91–1600 pg/mL). None of the patients had had previous neck surgery. Sixteen patients (84.2%) underwent simple parathyroidectomy.

The histological response in all cases demonstrated the presence of an adenoma, with a median weight of 635 milligrams (range 400–1650 milligrams). The mean reduction in i.o. PTH was 89.7 per cent (range 86–97.5%).

The median serum calcium value on the first postoperative day was 6.9 mg/dL (range 6.3–7.4 mg/dL) and on the third postoperative day it was 7.6 mg/dL (range 6.8–7.8 mg/dL). The pre and postoperative values of serum creatinine, phosphate, magnesium, potassium, bicarbonate, and pH were within normal range.

All patients presented hypocalcaemia-related clinical symptoms, paraesthesia, cramps, Chvostek sign, and Trousseau sign, and were administered with parenteral and/or oral calcium and vitamin D until their calcaemia values normalized and the hypocalcaemia-related symptoms had disappeared. Patients were discharged when their serum calcium level was higher than 8 mg/dL. Median time to discharge was 5.5 days (range 6.0–

8.5 days). All patients had normal calcemia values 6 months from the procedure. None of the patients presented with persistent hypoparathyroidism or persistent or recurrent pHPT at each follow-up meeting.

Risk Factors For Postoperative Severe Hypocalcemia

At univariate analysis, only i.o. PTH reduction was found to be predictive of postoperative severe hypocalcemia. Conversely, preoperative serum PTH and calcium levels, as well as patients' gender, age, parathyroid adenoma weight, previous neck surgery, surgical approach, AP, creatinine, magnesium, potassium, bicarbonate, and albumin serum concentration were not significantly correlated to postoperative severe hypocalcemia.

Significantly, at multivariate analysis, the i.o. PTH reduction was confirmed as independent risk factor for postoperative severe hypocalcemia (Table 2).

The ROC-curve analysis for intraoperative reduction showed a significant area under the curve (Fig. 1). In particular, i.o. PTH reduction as high as 85 per cent was found to be the most reliable cut-off for postoperative severe hypocalcemia (odds ratio 93, 95% confidence interval 11 to 773, $P = 0.0001$).

Discussion

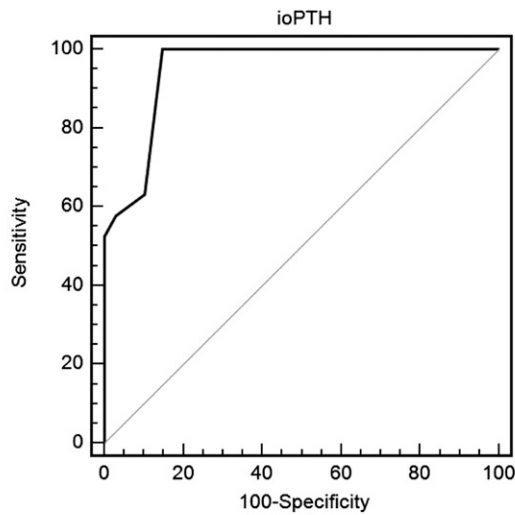
Postoperative hypocalcaemia is one of the most important and potentially most dangerous complications of

TABLE 2. Univariate and Multivariate Analyses of Risk Factors of Severe Postoperative Hypocalcemia

Independent Variables	Univariate Analysis P-value	Multivariate Analysis P-value
Preoperative serum PTH level	0.8	—
Preoperative serum calcium level	0.57	—
i.o. PTH level	<0.0001	0.042
Preoperative K ⁺ serum level	0.76	—
Preoperative Na ⁺ serum level	0.65	—
Preoperative PA serum level	0.55	—
Preoperative creatinine serum level	0.82	—
Preoperative Mg ⁺⁺ serum level	0.75	—
Preoperative albuminemia	0.45	—
Operative time	0.6	—
Surgical approach (unilateral/bilateral neck exploration)	0.44	—
Parathyroid adenoma weight	0.31	—
Gender	0.57	—
Age	0.45	—
Previous neck surgery	0.77	—

Of all the variables tested in univariate analysis, only those with P values ≤ 0.05 were entered into multivariate analyses in a stepwise manner until all variables remaining in the model were significant.

PA, alkaline phosphate.



Area under the ROC curve (AUC)	0.950
Standard Error	0.0357
95% Confidence Interval	0.880 to 0.985
z statistic	12.590
Significance level P (Area=0.5)	0.0001
For i.o.PTH drop > 85%	Sensitivity = 100% Specificity = 85.3%

FIG. 1. ROC-curve analysis. Variable: i.o. PTH drop. Outcome: severe postoperative hypocalcaemia.

parathyroidectomy, with a multifactorial pathogenesis.³⁶⁻⁵⁵ We considered severe hypocalcaemia as postoperative serum calcium level < 7.5 mg/dL. A possible cause of temporary or permanent symptomatic hypoparathyroidism is parathyroid gland damage, which can be caused by inadvertent removal of parathyroid tissue, but is more commonly caused by devascularization because the blood supply to the parathyroid glands from the inferior thyroid artery is limited and sensitive to surgical manipulation; other factors include direct trauma to the parathyroid gland causing haematoma.^{37, 38, 45, 51}

Many authors have reported a significant reduction in the incidence of postparathyroidectomy hypocalcaemia by performing a unilateral exploration in cases of pHPT.^{38, 52, 53, 55} Moreover the onset of hypocalcaemia could be dependent from calcitonin hypersecretion, due to thyroid manipulation, and perioperative calcium hemodilution.^{37, 49} The main mechanism is probably the inadequate parathyroid function caused by a slow or delayed functional recovery of the residual parathyroid tissue after hyper-functioning adenoma removal.^{46, 54} Post-parathyroidectomy hypocalcaemia can also be caused by a rapid recovery of calcium uptake by the skeleton (hungry bone syndrome).⁴⁵

Temporary hypocalcaemia has been reported to occur in 0 per cent to 35 per cent of patients after parathyroidectomy, whereas permanent hypoparathyroidism occurs after parathyroidectomy in 0 per cent to 3.8 per cent of cases.^{1, 36, 38, 43, 45, 46} In our experience the incidence of temporary postparathyroidectomy hypocalcaemia was 21.8 per cent (19/87 patients). Higher incidences of temporary and permanent hypocalcaemia (> 40%) are recorded in patients undergoing repeated surgery for persistent or recurrent pHPT.^{47, 48} A significant drop in calcium is often not evident until the third or fourth postoperative days.³⁷

Symptomatic hypocalcaemia plays an important role in delaying hospital discharge, and for this reason several surgeons advocate routine postoperative supplementation with calcium or vitamin D to facilitate early discharge.^{43, 49, 56} Several studies tried to identify factors that can predict the onset of postparathyroidectomy hypocalcaemia.^{36, 37, 39, 40, 43-45, 47, 48} Those patients who can be identified as being low risk for developing postoperative hypocalcaemia can conceivably be treated on an outpatient or short-stay basis, which would result in considerable reductions in health-care costs. Only selected cases require replacement therapy, and overtreatment may inhibit parathyroid function.^{36, 37, 39, 40, 43-45, 47, 48}

Multivariate analysis of clinical and biochemical data including patients' gender and age, symptoms, symptom-diagnosis latency, preoperative calcaemia, the preoperative PTH value and reduction in i.o. PTH, preoperative alkaline phosphatase, the weight of the gland removed, cardiac medications, and the type (mono or bilateral exploration) and duration of the surgical procedure have all been shown to be associated with the risk of postoperative hypocalcaemia.^{36, 37, 39, 40, 44, 45, 47, 48, 52-55} The demographic characteristics of our patients, their symptoms, and symptom-diagnosis latency were not related with the onset of postoperative hypocalcaemia, as reported in other studies.^{37, 39}

In contrast with the findings reported by Westerdahl et al.,³⁷ in our patients, postoperative symptomatic hypocalcaemia was not related with preoperative serum levels of calcitonin and alkaline phosphatase. Some authors^{36, 37} report that preoperative normocalcaemia was associated with an increased risk of postoperative hypocalcaemia. This was not confirmed in our study.

There is usually a discrete correlation between the mass of the adenoma and the amount of parathyroid hormone secreted.⁵⁷ By contrast the weight of the adenoma does not represent a predictive factor for the onset of postoperative hypocalcaemia, as reported in the literature³⁶ and by our experience.

Kald et al.³⁹ reported that a high preoperative PTH value (five times the upper limit of normal) represents a risk factor for the onset of postoperative hypocalcaemia

(41%), whereas only 6 per cent of patients with preoperative PTH values within normal range (<35 pmol/L) developed postparathyroidectomy hypocalcaemia. We did not observe statistically significant correlation between preoperative PTH values and the onset of postoperative hypocalcaemia.

The i.o. PTH assay has been widely used for predicting removal of hyperfunctioning parathyroid tissue.^{48, 58, 60} Although the pathogenesis of postoperative hypocalcaemia is multifactorial,^{36-39, 45, 46, 49, 52-55} impaired parathyroid function is likely the main contributing factor for clinical hypocalcaemia. Many studies have reported the utility of the quick i.o. PTH assay in predicting postthyroidectomy hypocalcaemia,^{45, 49, 50, 61} but its value in parathyroid surgery has not been well established.^{36, 44, 47, 48, 59} A significant reduction in i.o. PTH, higher than or equal to 80 per cent has been reported to represent a positive predictive value for identifying patients who develop postparathyroidectomy hypocalcaemia and who will require support treatment with postoperative calcium and vitamin D.^{36, 37, 44, 47, 48, 59}

In our experience, i.o. PTH reduction was found at multivariate analysis to be the only predicting factor for postoperative severe hypocalcaemia. Furthermore, ROC-curve analysis revealed that i.o. PTH reduction greater than 85 per cent is strongly and positively related to the development of severe postoperative hypocalcaemia, with odds ratio as high as 93. We did not record any other statistically significant relationship with the absolute values of i.o. PTH at induction and 10 minutes after parathyroidectomy.

Some studies comparing unilateral with bilateral cervical exploration found an increased incidence of hypocalcaemia and significantly lower postoperative calcium levels in patients undergoing bilateral exploration.^{38, 52, 53, 55} However, we did not find any relationship between the type of surgery performed (uni- or bilateral cervical exploration) associated with thyroid surgery and duration of the procedure with the onset of postoperative hypocalcaemia.

Conclusions

Our study showed that, among all the parameters analyzed, only reduction of i.o. PTH greater than 85 per cent after parathyroidectomy can be considered as a reliable factor for postoperative hypocalcaemia after parathyroidectomy for primary hyperparathyroidism. Therefore, the reduction in i.o. PTH, in addition to accurately predicting whether the surgical removal of parathyroid tissue was complete, can therefore identify patients at low risk for hypocalcaemia, thus promoting an early, safe discharge and helping to avoid expensive overtreatment with oral calcium and vitamin D analogue.

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