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NEPHROLOGY - ORIGINAL PAPER

Risk factors for severe hypocalcemia after parathyroidectomy in prevalent dialysis patients with secondary hyperparathyroidism

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Abstract
Purpose Hypocalcemia is one of the common complications after parathyroidectomy (PTX). Severe hypocalcemia (SH) can lead to tetany, cardiac arrhythmia and even sudden death. However, predictors for the development of SH in patients with secondary hyperparathyroidism demonstrated in some small-scale studies with a limited sample size remain inconclusive.
Methods A retrospective chart review of 420 consecutive dialysis patients who underwent PTX during a 12-year period was performed. We checked serum levels of calcium (Ca), phosphorus (P), alkaline phosphatase (ALP) and intact parathyroid hormone (iPTH) for three consecutive days postoperatively. SH was defined as the minimum values of serum calcium lower than 1.875 mmol/L (7.5 mg/dL) within 3 days after operation.
Results The mean (±SD) age of our study population was 53 ± 12 years, and more than half (57 %) were female. SH occurred in 37 % of the patients after PTX. Using a multivariate stepwise logistic regression analysis, lower preoperative levels of Ca (odds ratio 0.69, 95 % CI 0.60–0.79, $P < 0.001$), higher preoperative levels of iPTH (odds ratio 1.04, 95 % CI 1.00–1.07, $P = 0.048$), P (odds ratio 2.43, 95 % CI 1.49–3.95, $P < 0.001$) and ALP (odds ratio 1.08, 95 % CI 1.05–1.11, $P < 0.001$) were found to be independent predictors of occurrence of SH following PTX.
Conclusions The readily obtainable preoperative laboratory parameters including Ca, iPTH, P, and ALP will allow identification of a subgroup of patients who are at greater risk for the development of SH following PTX.

Keywords Alkaline phosphatase · Hypocalcemia · Parathyroidectomy · Parathyroid hormone · Phosphorus

Introduction

For dialysis patients with secondary hyperparathyroidism (HPT) refractory to medical treatments, surgical parathyroidectomy (PTX) is a solution to improve the chances of meeting the recommendations from current clinical practice guidelines for bone and mineral parameters in dialysis patients [1] and also to improve the mortality [2, 3]. However, PTX may cause more cases of hypocalcemia among patients with secondary HPT than among those with primary HPT [4], and the incidence of post-PTX hypocalcemia has been reported to be high (72–97 %) in dialysis populations [4, 5]. Severe hypocalcemia (SH) causes tetany, seizures, cardiac arrhythmias and possibly sudden death [4, 6, 7]. Although much progress had been made, there is little literature exploring the relationship between the clinical parameters and development of SH following PTX in dialysis patients [4, 5, 7]. Preoperative risk factors for hypocalcemia after PTX in dialysis patients also remain unclear. The aim of this analysis was thus to explore the potential clinical parameters associated with the occurrence of SH after PTX in dialysis patients with refractory secondary HPT. After establishment of these risk factors for SH, intensive clinical surveillance with aggressive medical treatment should be expected in the postoperative period.

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Methods

Patients and demographic data

From February 2001 to September 2012, 420 prevalent dialysis patients, including referred cases, had received surgical PTX at the Far Eastern Memorial Hospital (FEMH) in Taiwan. Their medical records were reviewed retrospectively. Baseline data, including age at surgery, gender, type of dialysis modality, dialysis vintage and presenting symptoms, were recorded. Laboratory parameters were analyzed, and postoperative medical treatments were extracted from the electronic database from the FEMH. Data concerning the operative findings and the histology of the parathyroid glands were obtained separately from the surgical notes and pathology reports. For the sake of generalization, we included all the participants in our analysis regardless of whether PTX was successful or not. This study was approved by the ethics review board of our hospital.

Surgical indication

In our hospital, medical treatments for secondary HPT include dietary phosphate restriction, calcium- or non-calcium-based phosphate binders, active vitamin D sterols and adequate dialysis. Calcimimetic agents were not used preoperatively in any of the participants. Patients with a failed medical treatment were referred to a surgeon for evaluation for surgical PTX, with indications for PTX including persistently elevated iPTH of greater than 500 ng/L, uncontrolled hypercalcemia with hyperphosphatemia or clinical symptoms of secondary HPT refractory to medical treatment. These symptoms included bone pain, pruritus, fracture, fatigue and calciphylaxis. Preoperative imaging studies including chest computed tomography and sestamibi parathyroid scan for secondary HPT were not routinely done, and the decision may depend upon surgeon's clinical judgments. However, imaging was mandatory before reoperative parathyroid surgery for persistent or recurrent HPT and routinely performed in our daily practice. The presenting symptoms were recorded from the medical charts at admission and from outpatient notes.

Surgical procedures

All operations were performed by surgeons with expertise in PTX. The surgical strategy included cervical exploration over the frontal neck, midway between the cricoid cartilage and sternal notch in layers. All parathyroid glands were identified and examined to determine the nature of the lesion by the experienced hands of the surgeon. The choice between the two types of PTX, subtotal PTX and total PTX with autotransplantation, depended upon the decision of the primary care surgeon. For the former type, a piece of healthy parathyroid tissue (approximately 40 mg) was left in situ after removing the others with preserved bilateral recurrent laryngeal nerves. For the latter PTX, all the identified parathyroid glands were excised with the autotransplantation of a healthy one into the right sternothyroid muscle. Cervical thymectomy was not routinely performed and would be done only if fewer than four parathyroid glands were identified. All but five patients received the subtotal type of PTX.

Operative notes and pathological findings

All available operative notes and pathological reports of participants were reviewed. Perioperative histology is not routinely done in general practice. The volume of excised parathyroid glands was also recorded because it was not clear whether they were associated with hypocalcemia after surgery. We hypothesized that the ability of the surgeon to excise all of the abnormal parathyroid glands is associated with the successfulness of PTX and subsequent postoperative hypocalcemia. The final diagnosis of the pathological report was used to correct the numbers of identified parathyroid glands in the operative notes. For example, even if the surgeon found four parathyroid glands during the operation, the number of parathyroid glands was coded as "3" when one of the parathyroid glands was shown to be a lymph node or thyroid gland.

Laboratory data

Before the operation, the typically measured laboratory parameters were serum calcium (Ca), phosphorus (P), alkaline phosphatase (ALP) and intact parathyroid hormone (iPTH). After the operation, the above biochemical data were routinely checked for 3 consecutive days during the in-patient period. The first serum laboratory parameters were obtained in the morning of the first day after surgery. Laboratory parameters were extracted from the electronic laboratory database.

Postoperative medications

All patients underwent dialysis using dialysate containing 3.5 meq/L of calcium after PTX. Active vitamin D sterols in a dose of 0.25 μg once a day and calcium carbonate 500 mg twice a day were given routinely. The doses of medications were adjusted according to the clinical symptoms of hypocalcemia and the biochemical data. Intravenous calcium was restricted to patients who had hypocalcemia either with or without symptoms and depended on the decision of the primary care physicians. We collected data on the medications from the electronic in-patient medication database of our

hospital and recorded the amount, frequency and type of medications.

Definition of postoperative hypocalcemia

Severe hypocalcemia (SH) after surgery was defined as a minimum value of serum calcium level lower than 1.875 mmol/L (7.5 mg/dL) postoperatively within 3 days. A cutoff of 7.5 mg/dL was chosen because symptoms of hypocalcemia develop up to serum Ca < 7.5 mg/dL [4].

Assays

Biochemistry data were determined using a Hitachi 747 automatic analyzer in the routine clinical laboratory. Intact parathyroid hormone (iPTH) was measured on the Immulite autoanalyzer and a commercially available enzyme immunoassay (Diagnostic Products Corporation, Los Angeles, CA, USA).

Statistics

The statistical analysis was performed using SPSS 19.0 version (SPSS Inc., Chicago, IL, USA). Continuous data were presented as means ± standard deviations (SD) and categorical variables, as numbers or percentages. Student's *t* test was used to compare continuous variables and Chi-square test for categorical variables. The non-normally distributed continuous variables were presented as median and interquartile range (IQR) and compared using the Mann–Whitney *U* test. Variables included in the univariate analysis are age, gender, vintage, dialysis modality, presenting symptoms, recurrent case, duration of hospital stay, preoperative variables including iPTH, Ca, P, Ca × P and ALP, intravenous Ca usage and its dose in 7 days, identified 4 or more glands, numbers and volume of excised glands. Covariates in the univariate analysis that reached statistical significance or of initial interest were chosen for further multivariate analysis. The covariates of age, gender, dialysis vintage, dialysis modality, presenting

Table 1 Comparison of demographic and laboratory data between patients with and without postoperative hypocalcemia (Ca < 1.875 mmol/L)

	All patients $N = 420$	Patients with postoperative hypocalcemia		*P* value
		Yes $N = 157$ (37 %)	No $N = 263$ (63 %)	
Age at surgery (years)	53 ± 12	52 ± 13	54 ± 11	0.06
Female (%)	57	61	54	0.19
Vintage of dialysis (years)	8.7 ± 5.2	8.0 ± 5.2	9.1 ± 5.1	0.04*
HD modality (%)	84	80	86	0.09
Presenting symptoms				
Pruritus (*n*)	27	9	18	0.65
Bone pain (*n*, %)	162 (39)	52 (33)	110 (42)	0.08
Fracture (*n*)	5	2	3	1.00[a]
Fatigue (*n*)	13	6	7	0.51
Recurrent case (*n*)	16	4	12	0.43
Duration of hospital stay (days)	4.3 ± 2.3	5.0 ± 3.0	4.0 ± 1.7	<0.001*
Preoperative variables				
Intact-PTH (ng/L)	1705 (1261, 2329)	2016 (1553, 2500)	1527 (1143, 2082)	<0.001*
Calcium (mmol/L)	2.7 (2.6, 2.9)	2.7 (2.5, 2.8)	2.8 (2.6, 2.9)	<0.001*
Phosphorus (mmol/L)	2.0 (1.6, 2.3)	2.0 (1.7, 2.4)	1.9 (1.6, 2.3)	0.03
Ca × P ($mmol^2/L^2$)	5.4 (4.4, 6.3)	5.5 (4.6, 6.3)	5.4 (4.2, 6.4)	0.45
ALP (U/L)	168 (117, 260)	241 (164, 411)	139 (105, 205)	<0.001*
Intravenous calcium usage in 7 days (%)	14	29	5	<0.001*
Elemental calcium dose in 7 days (meq)	31 ± 41	38 ± 44	8 ± 4	<0.001*
Identified ≥ 4 glands (%)	73	77	70	0.21
Numbers of excised glands	3.6 ± 0.8	3.7 ± 0.6	3.6 ± 0.8	0.11
Volume of excised glands (cm^3)	7.2 (3.9, 12.6)	6.7 (3.6, 12.4)	7.2 (4.0, 12.7)	0.56

HD hemodialysis, *PTH* parathyroid hormone, *Ca* calcium, *P* phosphorus, *ALP* alkaline phosphatase

* $P < 0.05$

[a] Performed using Fisher's exact test. For non-normally distributed continuous variables, values shown as median (1st, 3rd quartile); for normally distributed continuous variables, values shown as mean ± SD; for categorical variables, values shown as numbers or percentages

symptoms, preoperative laboratory parameters (such as Ca, P, iPTH and ALP) and the identification of more than four parathyroid glands were forced into a multivariate stepwise logistic regression analysis model for adjustment. A P value < 0.05 was considered significant.

Results

The baseline data of patient characteristics, their presenting symptoms, preoperative laboratory parameters and operative findings are shown in Table 1. A total of 157 patients (37 %) had SH after surgery. Patients who experienced hypocalcemia had the characteristics of shorter dialysis vintage, longer hospital stay and higher intravenous calcium requirement. Patients with hypocalcemia were also noted as having higher preoperative levels of serum iPTH, P, ALP, and lower Ca levels.

Patients with postoperative hypocalcemia had a lower baseline serum calcium level and a greater degree of calcium decline after surgery (Table 1; Fig. 1). In the multivariable logistic regression model (Table 2), the preoperative serum values of Ca, P, ALP and iPTH were independent predictors of SH after surgery.

Discussion

Our study reveals that more than one-third of the dialysis patients experienced SH following PTX. Patients who had lower serum Ca, higher serum P, ALP and iPTH levels before PTX were at a greater risk of developing SH postoperatively. Patients with any of these abnormal laboratory values should be monitored more closely and treated aggressively in the postoperative period to prevent SH.

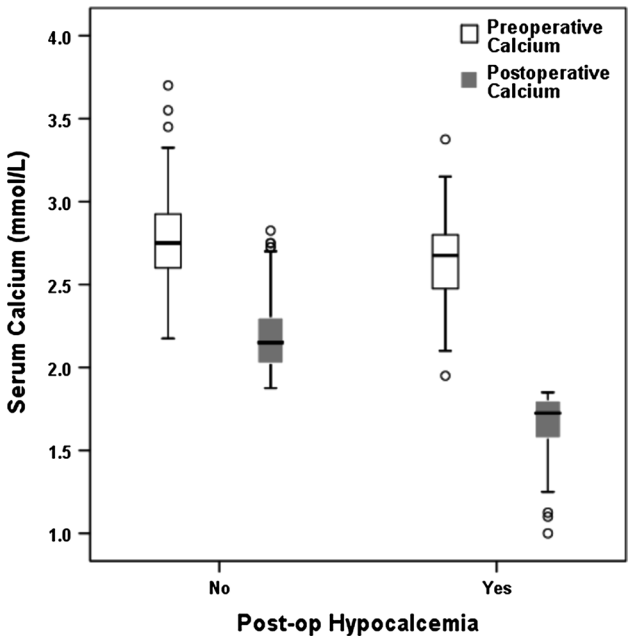

Fig. 1 Changes in serum levels of calcium in patients with or without post-op hypocalcemia

Table 2 Multivariate adjusted logistic regression analysis for the development of severe hypocalcemia (Ca < 1.875 mmol/L) after receiving parathyroidectomy

Variables[a]	Exp (β) (95 % CI)	P value
Intact-PTH (ng/L) (every increase of 100)	1.04 (1.00–1.07)	0.048
Calcium (mmol/L) (every increase of 0.1)	0.69 (0.60–0.79)	<0.001
Phosphorus (mmol/L)	2.43 (1.49–3.95)	<0.001
ALP (U/L) (every increase of 10)	1.08 (1.05–1.11)	<0.001

PTH parathyroid hormone, *ALP* alkaline phosphatase

[a] The adjusted covariates are age, gender, vintage, dialysis modality, presenting symptoms with bone pain and identified four or more glands during operation

Though the genesis of hypocalcemia after PTX may be multifactorial, some investigators have demonstrated the potential predictors by using a univariate analysis model in some small-scale studies with a limited sample size. In these studies [4, 5, 7, 8], young age, lower Ca, lower ALP, lower Hb, smaller adenoma, higher iPTH and subtotal type of PTX were potential predictors of postoperative hypocalcemia. In contrast to these studies, our study has a larger sample size and can therefore generate better statistical power to address this controversial issue. By using a multivariate analysis, we have identified the preoperative serum Ca, ALP, iPTH and P levels as independent predictors for the occurrence of SH following PTX. The finding that preoperative lower levels of Ca, higher ALP and iPTH predict post-PTX SH can be partially explained by a high baseline bone-remodeling status, a rapid shift of calcium from the circulation to the skeletal system due to hypoparathyroidism after PTX, and extensive remineralization of the skeleton [9].

Interestingly, our study identified a novel correlation between preoperative serum P level and SH following PTX. In an animal study [10], hyperphosphatemia was observed to stimulate nodular hyperplasia of the parathyroid glands and lead to highly elevated PTH levels. Since hyperparathyroidism causes excess bone resorption and worsens hyperphosphatemia [11], both hyperphosphatemia and hyperparathyroidism could possibly be engaged in a vicious cycle that results in a high bone-remodeling status. In our study population, 62 % of the patients had hyperphosphatemia

(>1.78 mmol/L), 67 % had high-serum ALP levels (>129 U/L), and 93 % had high iPTH (>800 ng/L) preoperatively, which indicates that our patients had high bone-remodeling status. In previous studies, for patients who had thyroidectomy [12], serum P was found to possibly predict temporary hypocalcemia after surgery; yet, serum P failed to predict early hypocalcemia following PTX in patients with primary HPT [13]. Therefore, further studies are needed to explore the association between serum P and post-PTX hypocalcemia in dialysis patients.

The major strength of our study is its comparably large sample size and fully adjusted model in the statistical analysis. However, our study nonetheless has a few limitations. First, given its retrospective design, not all data were available, and an indication bias for surgical treatment may have been present. Second, being a single-center study comprised predominantly of patients admitted to a tertiary medical center, the study's findings may not be generalizable to all other dialysis patients. Finally, measurement of ionized calcium is more complex and is not available in this study. Also, bone-specific ALP is not available either.

In conclusion, our results show that the preoperative serum Ca, P, ALP and iPTH levels were independent predictors for the occurrence of SH following PTX. These preoperative variables will allow physicians to identify dialysis patients who are at a greater risk of having SH after PTX and to both monitor and aggressively treat patients who have any of these factors in the postoperative period.

Conflict of interest The authors declare that they have no conflict of interest.

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