Factors predictive of critical value of hypocalcemia after total parathyroidectomy without autotransplantation in patients with secondary hyperparathyroidism

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ABSTRACT

Background: Severe hypocalcemia is the most dangerous complication occurring after total parathyroidectomy without autotransplantation (TPTX) for secondary hyperparathyroidism (SHPT). We aim to identify the prevalence and potential risk factors of very severe hypocalcemia in patients with SHPT undergoing TPTX.

Methods: From April 2012 to August 2015, 157 patients with SHPT undergoing TPTX were reviewed. The critical value of hypocalcemia (CVH) was postoperative serum Ca\(^{2+}\) levels of ≤1.5 mmol/L.

Results: Univariate analysis showed that patients in the CVH group were significantly younger than those in the non-CVH group. Sex ratio was significantly different between the two groups. The CVH group had significantly higher levels of preoperative PTH and ALP. Male sex and preoperative levels of PTH and ALP were significant independent risk factors by logistic regression analysis.

Conclusions: Male sex, preoperative PTH and ALP were significantly associated with CVH in patients with SHPT undergoing TPTX.

Introduction

Secondary hyperparathyroidism (SHPT) is common in patients with chronic kidney disease, and can lead to severe complications such as metabolic bone disease, serious cardiovascular events, and ectopic calcification. Total parathyroidectomy without autotransplantation (TPTX), first reported by Ogg in 1967, has not been considered as a standard, but rather as an optional, therapy for SHPT. Its advantage is lower rate of recurrence compared with subtotal parathyroidectomy (SPTX) or total parathyroidectomy with autotransplantation (TPTX + AT). Therefore, some clinicians regard TPTX as a feasible strategy; however, there is a theoretical risk of severe hypocalcemia with TPTX. There are few studies regarding the risk factors for development of severe hypocalcemia after TPTX in patients with SHPT and how severe it is in clinical practice.

In our hospital, we use the critical value of hypocalcemia (CVH), defined as serum calcium levels of ≤1.5 mmol/L (6 mg/dL), which indicates a need for immediate management to avoid life-threatening consequences such as laryngeal stridor, seizure, cardiac arrhythmia, congestive heart failure, and tetany. Identification of predictive factors for CVH would allow less severe operation, more aggressive calcium supplementation, and intensive care monitoring during the perioperative period, thus helping to lower the rates of complications and mortality, shorten hospital stay, and reduce cost of therapy. Therefore, the aim of this study was to identify the prevalence and potential risk factors of CVH in patients with SHPT undergoing TPTX.

Methods

Consecutive patients with SHPT following parathyroidectomy (PTX) at the China-Japan Friendship Hospital between April 2012 and August 2015 were reviewed. In accordance with the Kidney Disease Outcomes Quality Initiative guidelines, parathyroidectomy was performed for patients with end-stage renal failure who had refractory SHPT and elevated levels of intact PTH (iPTH) (>800 pg/mL), hypercalcemia, hyperphosphatemia, renal osteodystrophy, calciphylaxis, pruritus, and failure to respond to medical therapy.

Preoperative localization workup included neck sonography and Tc-99m sestamibi scans. For TPTX, we...
resected all four (or more) parathyroid glands. We cut the thymus on one side if only one gland was found on that side or if there was a suspicious mass within the thymus.

Data were collected on age, sex, body mass index (BMI) (kg/m²), duration of dialysis, symptoms, follow-up, preoperative and postoperative serum calcium (Ca²⁺), phosphorus (P), alkaline phosphatase (ALP), intact parathyroid hormone (PTH), length of hospital stay; and hemodialysis time.

For serum PTH, an immunoradiometric assay (normal range 12–88 pg/mL) was used. Serum Ca²⁺, P, and ALP were determined by an autoanalyzer; reference values were 2.0–2.5 mmol/L for Ca²⁺, 0.81–1.78 mmol/L for P, and 40–150 U/L for ALP.

All preoperative blood samples were collected the day before surgery. Postoperative samples were measured in the morning on the first day after surgery (within 48 h of parathyroidectomy). Patients were divided into two groups based on the measured postoperative serum Ca²⁺ levels: ≤6 mg/dL (CVH group) or >6 mg/dL (non-CVH group). ALP increment was defined as the difference between the postoperative ALP and preoperative ALP.

Statistical analyses were performed using SPSS software (version 17.0; SPSS Inc., Chicago, IL). Univariate analysis was performed using t-test for continuous data and χ² analysis for categorical data, followed by multivariate regression analysis. p < 0.05 was considered statistically significant.

Results

In total, 190 patients with SHPT who had undergone PTX were reviewed over a three-year period. Of these, 157 were shown postoperatively to have successful TPTX (when postoperative PTH levels were lower than normal level (88 pg/mL) and ≥4 parathyroids had been resected based on the pathological results). Of the entire TPTX group, 77% developed hypocalcemia with serum Ca²⁺ less than normal levels (2 mmol/L, 8 mg/dL) within 48 h of TPTX while 15.3% presented CVH with serum Ca²⁺ level ≤1.5 mmol/L (6 mg/L). Of the patients with CVH, 90% had no or only mild symptoms including weakness, headaches, numbness/parasthesias, and muscle cramps, and only 10% presented severe life-threatening symptoms, such as dyspnea and tetany.

The 157 patients with successful TPTX comprised 85 men (54%) and 72 women (46%) with a mean age of 47.32 ± 11.3 years (range 21–79 years), mean BMI of 22.6 ± 3.3 (range 16–32.3), and mean dialysis duration of 8.14 ± 3.9 years (range 1–27 years). Mean preoperative serum levels were 1831.1 ± 829.5 pg/mL (range 443–3741 pg/mL) for PTH, 2.6 ± 0.26 mmol/L (range 1.6–3.3 mmol/L) for Ca²⁺, 2.28 ± 0.5 mmol/L (range 0.86–3.79 mmol/L) for P, and 443.3 ± 396 U/L (range 61–2242 U/L) for ALP, with mean ALP increment being 24.1 U/L ± 160.8 (range 456 to 1243 U/L). Mean hospital stay was 8.03 ± 3.1 days (range 3–25 days). Mean hemodialysis time was 8.14 ± 4 years (range 1–27 years).

Univariate analysis (Table 1) showed that patients in the CVH group were significantly younger than those in the non-CVH group (40.3 ± 9.1 vs. 48.59 ± 11.1 years; p = 0.001). Sex ratio was significantly different in the two groups (21 men and 3 women vs. 64 men and 69 women; χ² p = 0.000). Preoperative PTH (2672.8 ± 715 vs. 1679.2 ± 756.4; p = 0.000) and ALP (777.8 ± 400.3 vs. 382.9 ± 365.3; p = 0.000) were significantly higher in the CVH group than in the non-CVH group. Preoperative P, ALP increment, hospital stay, BMI, duration of dialysis and hemodialysis time were not different between the two groups. Male sex and preoperative serum PTH and ALP levels were significant independent risk factors (p = 0.006, p = 0.018, p = 0.006, respectively) by logistic regression analysis (Table 2).

Discussion

Hypocalcemia has been reported to occur in 20–85% of patients with SHPT who have undergone PTX. SHPT predisposes to development of profound hypocalcemia, also referred to as “hungry bone syndrome” (HBS). HBS was first described in 1948 by Albright and Reifenstein in patients with prolonged hypocalcemia after PTX for primary hyperparathyroidism (PHPT). After abrupt
removal of high levels of PTH from circulation, there is a rapid shift of calcium to bone tissue, with a marked increase in bone remineralization. However, very severe hypocalcemia after TPTX is not well defined for SHPT. Some authors have reported predictors of postoperative hypocalcemia in patients with PHPT and SHPT, but the surgical strategy differed between these studies, including SPTX, TPTX + AT, and TPTX. To our knowledge, there are no published data about very severe postoperative hypocalcemia (Ca²⁺ ≤ 6 mg/dL) with SHPT after TPTX.

In our hospital, CVH is defined as a serum Ca²⁺ ≤ 1.5 mmol/L (6 mg/dL), indicating the possibility of life-threatening complications. Of the 157 patients we studied, 77% presented hypocalcemia in 48 h after TPTX, while 24 (15.3%) reached CVH. We routinely administered calcium infusions post-operatively as serum Ca²⁺ ≤ 1.8 mmol/L or with actual symptoms. Normally, cutting all the parathyroid without autotransplantation is a major operation and has been considered problematic in endocrine surgery. However, in our practice, we have found that only a small part of patients with SHPT develop severe hypocalcemia with life-threatening sequelae after TPTX, and we regard this surgery as a feasible treatment. The key point is to identify the risk factors for CVH in the early postoperative stage and place such patients on an aggressive program of perioperative calcium replacement to prevent severe hypocalcemia.

Allan et al. reported that advanced age was associated with postoperative hypocalcemia in patients with PHPT because such patients tend to have vitamin D deficiency and poorer nutritional intake. However, in the present study, we found that younger age correlated with severe postoperative hypocalcemia in patients with SHPT after TPTX, but only by univariate analysis, not by logistic regression analysis. The patients in the CVH group were younger than those in the non-CVH group (40.3 ± 9.1 vs. 48.59 ± 11.1 years; p = 0.001). Goldfarb et al. also identified younger age (≤ 45 years old) as the single preoperative risk factor significantly associated with the development of HBS in patients undergoing SPTX or TPTX for SHPT. It is generally agreed that bone remodeling, a complex homeostatic process during which bone undergoes a process of resorption and formation, continues throughout life. Bone formation reaches a peak during young adulthood (between 20 and 40 years of age). In other words, young people have stronger osteoblastic activity than old people. Advanced age is associated with acceleration in bone loss. Decline in sex hormones (testosterone, estrogen) with age may contribute to reduced bone formation. Increased bone formation occurred shortly after TPTX. We considered that as younger patients have greater bone formation ability than older patients, they are likely to be at higher risk of more severe hypocalcemia; however, age was not an independent risk factor in our study. Larger studies are needed to support this conclusion.

Few studies have considered sex as a risk factor of hypocalcemia in patients with SHPT after TPTX. However, our data showed that the sex ratio was significantly different between our two groups, both by univariate analysis and logistic regression analysis. There were 21 men and three women in the CVH group, and 64 men and 69 women in the non-CVH group (χ², p = 0.000). Men lose less cortical bone than women because the extent of endocortical resorption is less in men. In addition, compensatory subperiosteal cortical bone formation is greater in men than in women. As a result, male patients with SHPT undergoing TPTX have greater bone formation than women, so they also had more severe hypocalcemia than women.

In this series, preoperative PTH level was a significant independent risk factor both by univariate analysis and logistic regression analysis. Our data showed that preoperative PTH ranged from 443 to 3741 pg/mL (mean 1831.1 ± 829.5 pg/mL), while postoperative PTH ranged from 1 to 88 pg/mL. Preoperative PTH was a clear indicator of the severity of SHPT and bone disease. Under stimulation with excess PTH, bone formation and bone resorption are both increased despite a marked negative balance. Some authors have reported that PTH increases bone resorption and decreases bone formation; therefore, decreased bone resorption and increased bone formation would happen shortly after TPTX, and hypocalcemia would develop in line with this change after TPTX.

ALP is the term given to a group of isoenzymes found mainly in liver and bone. High levels of serum ALP are characteristic of bone disease with increased osteoblastic activity. In PHPT and SHPT, the activities of both bone formation and resorption are markedly raised. After PTX, osteoclast activity drops dramatically within 24 h after removal of functional adenoma, but osteoblast activity remains unchanged for a short time after surgery. The relative balance of bone metabolism is thus disturbed and postoperative hypocalcemia occurs. We found that, similar to previous reports, preoperative ALP was an independent risk factor of very severe hypocalcemia in patients with SHPT, while ALP increment was not different between the two groups, in contrast to Chandran’s finding. We believe that ALP increment does not have time to change significantly in the short measurement period after TPTX used in our
study, but it might show a stronger relationship with hypocalcemia over a longer time period.

One of the strengths of the study is that we prefer to use TPTX in preference to other surgical strategies where possible, so that the bias from the surgery is as low as possible. In addition, we collected all the clinical data in a very short time for 157 cases of TPTX because our hospital is one of the biggest centers for SHPT in China. Therefore, the time bias is very low as well. Thus, the low bias makes our results very reliable. There have been few previous studies attempting to predict CVH in patients with SHPT following TPTX, which is still a controversial surgical strategy. These identified risk factors for CVH should help increase the feasibility of TPTX. Furthermore, we look forward to finding more effective parameters to use as predictive factors in the future.

In conclusion, we confirm male sex and preoperative levels of PTH and ALP as preoperative risk factors for CVH. Patients with such risk factors should be given a more aggressive perioperative management protocol. We suggest that aggressive calcium infusion in the early postoperative stage after TPTX for high-risk patients is a useful method to prevent CVH.

Disclosure statement
The authors declare that they have no conflict of interest.

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