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Retrospective Study

Effect of calcium supplementation on severe hypocalcemia in patients with secondary hyperparathyroidism after total parathyroidectomy

Liu J *et al.* Calcium supplementation in SHPT after TPTX

Abstract

BACKGROUND

Severe hypocalcemia (SH) is a dreaded complication of total parathyroidectomy (TPTX) without auto-transplantation.

AIM

To compare conventional and preventive calcium supplementation (CS) regimens in terms of SH occurrence after TPTX.

METHODS

This retrospective study included patients who underwent TPTX between January 2015 and May 2018 at the China-Japan Friendship Hospital. From January 2015 to May 2016, conventional CS was performed in patients administered TPTX, with calcium amounts adjusted according to postoperative serum calcium levels. From October 2016 to May 2018, preventive CS was performed according to preoperative alkaline phosphatase (ALP) levels. The patients were defined as low-risk (ALP < 500 U/L) and high-risk (ALP > 500 U/L) for SH. All preoperative blood samples were collected in the fasting state on the day before surgery. Postoperative blood samples were obtained at 6-7 AM from the first postoperative day.

RESULTS

A total of 271 patients were included. They were 47.7 ± 11.1 years old, and 57.6% were male. Their body mass index (BMI) values were 22.9 ± 3.8 kg/m². There were no significant differences in sex, age, BMI, preoperative ALP, serum calcium, serum phosphorus, calcium-phosphorus ratio, and intact parathyroid hormone (iPTH) between the two CS groups. Compared with conventional CS, preventive CS led to lower occurrence rates of hypocalcemia within 48 h (46.0% *vs* 74.5%, $P < 0.001$) and SH (31.7% *vs* 64.1%, $P < 0.001$). Multivariable analysis showed that preoperative iPTH levels [odds ratio (OR) = 1.001, 95% confidence interval (CI): 1.000-1.001, $P = 0.009$],

preoperative ALP amounts (OR = 1.002, 95%CI: 1.001-1.003, $P = 0.002$), preoperative serum phosphorus levels (OR = 8.729, 95%CI: 1.518-50.216, $P = 0.015$) and preventive CS (OR = 0.132, 95%CI: 0.067-0.261, $P < 0.001$) were independently associated with SH. In patients with preoperative ALP ≥ 500 U/L, only preventive CS (OR = 0.147, 95%CI: 0.038-0.562, $P = 0.005$) was independently associated with SH.

CONCLUSION

This study suggests that preventive CS could reduce the occurrence of SH, indicating its critical value for hypocalcemia after TPTX.

Key Words: End-stage renal disease; Secondary hyperparathyroidism; Parathyroidectomy; Hypocalcemia; Calcium supplementation

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Core Tip: Compared with conventional calcium supplementation (CS), preventive CS led to lower occurrence rates of hypocalcemia within 48 h and severe hypocalcemia (SH). Multivariable analysis showed that preoperative intact parathyroid hormone levels, preoperative alkaline phosphatase (ALP) amounts, preoperative serum phosphorus levels, and preventive CS were independently associated with SH. In patients with preoperative ALP > 500 U/L, only preventive CS was independently associated with SH.

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INTRODUCTION

Secondary hyperparathyroidism (SHPT), a common complication of end-stage renal disease (ESRD), is characterized by the progressive hyperplasia of parathyroid glands and increased secretion of parathyroid hormones^[1,2]. After 3-10 and 20 years of

hemodialysis, respectively, 20% and 40% of patients require parathyroidectomy (PTX)^[3]. At present, subtotal and total PTX plus auto-transplantation are the standard procedures for the treatment of SHPT. In the context of dialysis, SHPT may recur; in this case, total PTX (TPTX) without auto-transplantation is an effective therapeutic option^[3]. However, postoperative hypocalcemia limits its clinical application^[4,5].

Despite monitoring serum calcium levels and adjusting the amounts of supplemented calcium and vitamin D, the incidence of hypocalcemia after TPTX remains high, *i.e.*, 72%-97%^[6]. Hypocalcemia occurs because of the abrupt withdrawal of parathyroid hormones, which results in a sharp increase of bone remineralization (hungry bone syndrome), depleting calcium from the circulation^[7-9]. The ensuing severe hypocalcemia (SH) is a critical condition that may result in convulsions, arrhythmias, and even sudden death. Therefore, the possible complications of hypocalcemia limit the clinical application of TPTX. Studies examined the prognostic factors of hypocalcemia after PTX^[10-13] but reported conflicting data because of different methods.

Maintaining adequate calcium levels after TPTX is required to avoid hypocalcemia complications and hungry bone syndrome^[14]. Viaene *et al*^[15] showed that high preoperative parathyroid hormone levels and low calcium amounts are predictive of SH after TPTX^[15]. Previous studies have used alkaline phosphatase (ALP) levels to predict the level of calcium supplementation (CS), with apparent success in improving patient outcomes^[16,17]. Nevertheless, efficient tools for reducing or preventing SH after TPTX have not been reported.

Therefore, this study aimed to identify risk factors for SH and compare conventional and preventive CS regimens for their effects on SH occurrence after TPTX. We found that preventive CS reduces the occurrence of SH, indicating its critical value for hypocalcemia after TPTX.

MATERIALS AND METHODS

Study design and patients

This work was carried out in accordance with the Declaration of Helsinki (2000) by the World Medical Association. The current retrospective study was approved by the institutional review board of China-Japan Friendship Hospital (2019-SDZL-12). The requirement for written informed consent was waived due to the retrospective nature of this study. The records of patients who underwent TPTX between 01/2015 and 05/2018 were reviewed. The inclusion criteria were: (1) Age > 18 years, (2) ESRD complicated with SHPT; and (3) TPTX administration. The exclusion criteria were: (1) Severe complications before surgery; or (2) Incomplete medical records.

The diagnosis of SHPT was based on hypocalcemia or normocalcemia with elevated parathyroid hormone levels in patients with chronic kidney disease, vitamin D deficiency, or inadequate calcium intake or absorption^[18,19]. Hypocalcemia and SH were defined as total calcium corrected for albumin < 2 mmol/L and < 1.875 mmol/L, respectively.

TPTX

Indications for TPTX in patients with ESRD complicated with SHPT were: (1) Intact parathyroid hormone (iPTH) amounts exceeding 800 pg/mL before surgery; (2) Uncontrollable hypercalcemia with hyperphosphatemia or refractory PTH accompanied by clinical symptoms such as bone pain and itchiness; (3) Previous resistance to active vitamin D; and (4) Doppler ultrasound showing more than one parathyroid gland enlarged by over 1 cm, and abundant blood flow^[10]. Surgeries were performed by surgeons with > 10 years of experience. Under general anesthesia, the back of the cervical thyroid was explored to identify all four parathyroid glands, which were completely removed. The thymus was not routinely explored or removed. If less than four parathyroid glands were found, the thymus was explored, and the suspected parathyroid glands were removed.

The CS protocol

Between January 2015 and May 2016, conventional CS was performed in patients administered TPTX. The amounts of supplemented calcium were adjusted according to postoperative serum calcium levels.

The CS protocol in our hospital changed after October 2016 due to a significant number of patients developing hypocalcemia after surgery. From October 2016 to May 2018, preventive CS was performed in patients with ESRD complicated with SPTH administered TPTX. According to preoperative ALP levels, the patients were defined as low-risk (ALP < 500 U/L) and high-risk (ALP > 500 U/L) for SH. Low-risk cases received supplementation with 50 mL of 10% calcium gluconate daily, and the level of CS was adjusted according to daily serum calcium amounts. In high-risk patients, supplementation with 100 mL of 10% calcium gluconate was performed daily, with the level of CS also adjusted according to daily serum calcium amounts. In both the low- and high-risk groups, CS was started on the day of surgery.

Data collection

All preoperative blood samples were collected in the fasting state on the day before surgery. Postoperative blood samples were obtained at 6-7 AM from the first postoperative day (within 48 h after TPTX) to monitor daily blood calcium. Postoperative CS was administered at around 8 AM daily. Age, sex, body mass index (BMI), preoperative serum calcium amounts, serum phosphorus levels, calcium-phosphorus ratio, ALP amounts, and iPTH levels were recorded.

Statistical methods

Statistical analysis was performed with SPSS 21.0 (IBM, Armonk, New York, United States). Continuous data were presented as mean \pm SD and analyzed using Student's *t*-test. Categorical data were presented as numbers and percentages and analyzed using the chi-square test. Factors with $P < 0.10$ in univariable analysis were included in multivariable logistic regression analysis to determine risk factors for SH. $P < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics

A total of 271 patients administered TPTX with confirmed SHPT were included in this study. They were 47.7 ± 11.1 years old, and 57.6% were male. Their BMI values were 22.9 ± 3.8 kg/m². There were no significant differences in sex, age, BMI, preoperative ALP, serum calcium, serum phosphorus, calcium-phosphorus ratio, and iPTH between the two CS groups (Table 1).

Postoperative characteristics of the patients

In all patients, the hypocalcemia occurrence rate within 48 h after surgery was 61.3% (166/271), and serum calcium levels were lower than normal (< 2 mmol/L). Postoperative serum calcium levels within 48 h were higher in the preventive CS group compared with the conventional CS group (2.02 ± 0.32 vs 1.81 ± 0.32 mmol/L, $P < 0.001$). Meanwhile, the postoperative occurrence rates of hypocalcemia (46.0% vs 74.5%, $P < 0.001$), SH (31.7% vs 64.1%, $P < 0.001$) and critical hypocalcemia (4.0% vs 14.5%, $P = 0.003$) were lower in the preventive CS group (Table 2).

Risk factors for SH

Variables with $P < 0.1$ in univariate analysis (Table 3) were included in multivariate logistic regression analysis to determine risk factors for SH (Table 4). The results showed that preoperative iPTH levels [odds ratio (OR) = 1.001, 95% confidence interval (CI): 1.000-1.001, $P = 0.009$], preoperative ALP amounts (OR = 1.002, 95%CI: 1.001-1.003, $P = 0.002$), preoperative serum phosphorus levels (OR = 8.729, 95%CI: 1.518-50.216, $P = 0.015$) and the preventive CS regimen (OR = 0.132, 95%CI: 0.067-0.261, $P < 0.001$) were independently associated with SH.

Characteristics of the patients with preoperative ALP ≥ 500 U/L

In patients with ALP > 500 U/L, the occurrence rate of hypocalcemia within 48 h after surgery was 93.5% (72/77), and serum calcium levels were lower than control values (Table 5). Compared with the conventional CS group, the preventive CS group displayed higher postoperative serum calcium levels within 48 h (1.76 ± 0.22 vs 1.55 ± 0.17 mmol/L, $P < 0.001$) and lower occurrence rates of postoperative SH (62.9% vs 90.5%, $P = 0.005$) and critical hypocalcemia (8.6% vs 33.3%, $P = 0.012$).

Logistic regression analysis was performed to determine risk factors for SH in patients with preoperative ALP levels > 500 U/L (Table 6). As shown in Table 6, only the preventive CS regimen (OR = 0.147, 95%CI: 0.038-0.562, $P = 0.005$) was independently associated with SH.

DISCUSSION

SH is a dreaded complication of TPTX^[14], and tools for its prevention are scarce^[15-17]. This study aimed to identify risk factors for SH and to compare conventional and preventive CS regimens in terms of SH occurrence after TPTX. The results suggested that preventive CS could reduce the occurrence of SH, indicating its critical value for hypocalcemia after TPTX.

TPTX is an effective method for treating SHPT, but postoperative hypocalcemia occurs in 20%-85% of the treated patients^[11,20-22], which limits its clinical application. SH may lead to laryngeal stridor, spasms, arrhythmias, congestive heart failure, and tetany, which could be life-threatening in severe cases. In this study, the occurrence rate of hypocalcemia in patients administered conventional CS was 74.5% (108/145) within 48 h after surgery; meanwhile, the occurrence rates of SH and critical hypocalcemia were 64.1% (93/145) and 14.5% (21/145), respectively. These findings indicated that SH occurrence after surgery is very high with conventional CS.

Studies have reported the prognostic factors of hypocalcemia after PTX^[10-13], but surgical methods were different among those studies, which yielded conflicting findings. In addition, the effect of age on postoperative serum calcium amounts remains controversial^[10-13]. Furthermore, studies reported that older patients with SHPT are

more likely to develop postoperative hypocalcemia^[23,24]. The reason might be that such patients are prone to vitamin D deficiency and inadequate nutrition intake^[23,25,26]. Other studies suggested that younger age is a risk factor for postoperative hypocalcemia^[11,14,20,24]. Few reports considered the male gender as a risk factor for hypocalcemia after TPTX^[11]. Investigations revealed preoperative PTH levels to be an independent risk factor for SH; under excessive PTH stimulation, despite significant negative balance, bone formation and bone resorption are increased^[11,15]. Postoperatively, due to the rapid decline in PTH levels, reduced bone resorption and increased bone formation also occur rapidly, and hypocalcemia occurrence is consistent with such changes. ALP encompasses a group of isoenzymes that are mainly present in the liver and bones. High serum levels of ALP are characteristic of bone disease with enhanced osteogenic activity. In SHPT patients, both osteogenic and bone resorption activities are significantly increased^[23,27]. After PTX, osteoclast activity is significantly reduced, while osteoblast activity remains unchanged for a short time after surgery^[28,29]. The relative balance of bone metabolism is thus altered, inducing hypocalcemia. Therefore, high preoperative ALP levels may be an independent risk factor for SH after PTX^[11,30]. Nevertheless, these findings remain controversial in different reports^[11,13].

Few studies examined the prognostic factors of hypocalcemia after PTX. As shown above, by univariable analysis, age, preoperative iPTH amounts, ALP levels, serum phosphorus concentration, calcium phosphate product, and preventive CS were significantly associated with SH after surgery; however, only preoperative iPTH levels, preoperative ALP amount, preoperative serum phosphorus levels, and preventive CS independently predicted postoperative SH in multivariable analysis.

In this study, after preventive CS, the occurrence rates of postoperative hypocalcemia, SH, and critical hypocalcemia were all significantly decreased. The occurrence of SH was reduced from 64.1% to 31.7%, and that of critical hypocalcemia from 14.5% to 4.0%, with no life-threatening hypocalcemia. Based on the present findings, selective enforcement of preventive CS in patients with ALP \geq 500 could significantly reduce the occurrence rates of SH and critical hypocalcemia, easing the control hypocalcemia after

TPTX as a simple and feasible tool. In high-risk patients with ALP ≥ 500 U/L, the incidence rates of postoperative hypocalcemia were 97.6% and 88.6% in the conventional and preventive groups, respectively, indicating a slight but not statistically significant decrease. Nevertheless, the occurrence rates of SH and critical hypocalcemia were decreased significantly by the preventive CS regimen, from 90.5% and 33.3% to 62.9% and 8.6%, respectively. Although selective enforcement of preventive CS significantly improved the calcium status of patients at high risk of hypocalcemia, the incidence of life-threatening critical hypocalcemia remained as high as 8.6%, and further investigation is warranted to develop tools to reduce this rate. In addition, applying CS or selecting subtotal PTX or TPTX combined with auto-transplantation should be studied. However, although TPTX with auto-transplantation is a more rational therapy than TPTX, some patients decline auto-transplantation mostly because of high cost. Therefore, tools should be developed for preventing hypocalcemia in such individuals.

This study had some limitations. First, this was not a randomized trial, with differences in indications and periods for the two CS regimens. In addition, the study period was relatively short, and the sample size was small. Furthermore, as a single-center study in China, the results may not be suitable for other dialysis patients, as most patients in our center had an end-stage disease with severe symptoms and delayed surgical opportunities. Furthermore, postoperative iPTH levels were not assessed in this study, although they are more important than preoperative iPTH amounts, showing an association with SH^[31].

CONCLUSION

In conclusion, these findings suggest that preventive CS significantly reduces the occurrence rates of SH and critical hypocalcemia after TPTX for SHPT.

ARTICLE HIGHLIGHTS

Research background

Total parathyroidectomy (TPTX) without auto-transplantation is an effective therapeutic option for treating secondary hyperparathyroidism (SHPT). However, postoperative hypocalcemia limits its clinical application.

Research motivation

Identify risk factors for severe hypocalcemia (SH) after TPTX, and find efficient tools for reducing or preventing SH.

Research objectives

To identify risk factors for SH after TPTX and compare conventional and preventive calcium supplementation (CS) regimens for their effects on SH occurrence after TPTX.

Research methods

From January 2015 to May 2016, conventional CS was performed in patients administered TPTX, with calcium amounts adjusted according to postoperative serum calcium levels. From October 2016 to May 2018, preventive CS was performed according to preoperative alkaline phosphatase (ALP) levels. Continuous data were presented as mean \pm SD and analyzed by Student's *t*-test. Categorical data were presented as numbers and percentages and analyzed using the chi-square test. Factors with $P < 0.10$ in univariable analysis were included in multivariable logistic regression analysis to determine the risk factors for SH.

Research results

A total of 271 patients were included. Compared with conventional CS, preventive CS led to lower occurrence rates of hypocalcemia within 48 h (46.0% vs 74.5%, $P < 0.001$) and SH (31.7% vs 64.1%, $P < 0.001$). Multivariable analysis showed that preoperative iPTH levels [odds ratio (OR) = 1.001, 95% confidence interval (CI): 1.000-1.001, $P = 0.009$], preoperative ALP amounts (OR = 1.002, 95%CI: 1.001-1.003, $P = 0.002$), preoperative serum phosphorus levels (OR = 8.729, 95%CI: 1.518-50.216, $P = 0.015$) and

preventive CS (OR = 0.132, 95%CI: 0.067-0.261, $P < 0.001$) were independently associated with SH. In patients with preoperative ALP ≥ 500 U/L, only preventive CS (OR = 0.147, 95%CI: 0.038-0.562 $P = 0.005$) was independently associated with SH.

Research conclusions

Preventive CS is an efficient tool for reducing the occurrence of SH after TPTX.

Research perspectives

Preventive CS could reduce the occurrence of SH after TPTX, which might contribute to the clinical application of TPTX.

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