EARLY TREATMENT OF POSTOPERATIVE HYPOCALCEMIA IN UREMIC PATIENTS WITH SECONDARY HYPERPARATHYROIDISM

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ABSTRACT

This study was to retrospectively analyze the clinical situations of hypocalcemia in uremic secondary hyperparathyroidism (SHPT) patients undergoing parathyroidectomy (PTX), and to summarize the early treatments of postoperative hypocalcemia (POH). Thirty-five uremic SHPT patients undergoing PTX within prior 3 years were retrospectively analyzed. In these patients, POH was found in 97.1% (34/35) of patients, and the duration of POH was 13±21.1 h. The preoperative serum alkaline phosphatase (ALP), intact parathyroid hormone (iPTH) and decline of intraoperative iPTH were positively related to the needed mean daily intake of calcium. Thus, to maintain normal serum calcium level in patients with POH (2.0 to 2.75 mmol / L), the mean daily intake of calcium within seven days after surgery should be 38.15±16.12 mg/kg. The levels of preoperative serum ALP and iPTH and degree of intraoperative iPTH reduction can be used to evaluate the severity of POH in these patients. Early and sufficient supplement of calcium and calcitriol are needed in patients at high risk, in order to avoid POH and mitigate symptoms.

Key words: postoperative hypocalcemia; secondary hyperparathyroidism; early treatment; calcium supplementation.

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Introduction

Secondary hyperparathyroidism (SHPT) is one of the most common complications in patients with chronic renal failure (CRF). SHPT can lead to high serum parathyroid hormone (PTH) level, causing bone dystrophy with high conversion. Ectopic calcification due to high PTH may cause damage to the cardiovascular system, centric and peripheral nervous system and skin, and also result in endocrine disorders and aggravation of anemia via antagonizing erythropoietin10. Thus, SHPT significantly compromises the quality of life and reduces the survival rate. Traditionally, measures have been taken to maintain the normal serum calcium and phosphorus and inhibit the PTH secretion so as to improve clinical symptoms15. However, surgery is still required when patients with severe hyperparathyroidism are unresponsive to pharmacotherapy, or unable to accept further treatments because of high phosphorus and hypercalcemia levels.

In recent years, increasing attention has been paid to the surgical treatment of SHPT. Hypocalcemia tends to occur after successful parathyroidectomy (PTX). Thus, it is imperative to develop measures for the prediction and treatment of POH.

Subjects and method

Subjects

Clinical data of 35 uremic patients who underwent PTX in our hospital from July 2009 to July 2013 were retrospectively reviewed. There were 14 males and 21 females with a mean age of 53.00±8.06 years (range: 35-59 years) and a mean dialysis duration of 108.00±51.63 months (range: 3-192 months; 34 patients in hemodialysis and 1 patient in peritoneal dialysis).

The causes of end-stage renal disease were chronic glomerulonephritis (n =21; 60%), hypertensive nephropathy (n=4; 11.4%), diabetes mellitus...
(n=2; 5.7%), chronic pyelonephritis (n=2; 5.7%), polycystic kidney (n=1; 2.9%) and unknown causes (n=5; 14.3%).

The study was approved by the Ethics Committee of our hospital. Data were acquired routinely from all the patients undergoing PTX.

Preoperative Preparation
All patients were treated with 1.25 mmol/L calcium the day before surgery. Calcitriol therapy was done preoperatively in all high-risk patients (age ≤ 45 years) [3].

Surgical Approach
Patients mainly underwent subtotal PTX (SPTX), and total PTX plus autotransplantation (TPTX + AT). Several patients underwent total PTX without autotransplantation (TPTX) when less than 4 parathyroids were found or the second surgery was performed.

Observation and Analysis
The clinical manifestations of POH, mean time to occurrence of POH, age, duration of dialysis, serum levels of preoperative parathyroid hormone, calcium, phosphorus, alkaline phosphatase (ALP), tartrate-resistant acid phosphatase 5b (TRACP5b) and 25-hydroxy-vitamin D (25-OH-VID), bone mineral density, parathyroid total volume (demonstrated by ultrasonography), surgical approach, weight of retentive parathyroid, pathological findings and iPTH detected 10 min after PTX were recorded. Serum calcium level and daily intake of calcium within 7 days after surgery were also recorded for analysis. The mean daily intake of calcium per body weight within 7 days after surgery was calculated and expressed as mmean.

The total intake of calcium (mg) = 90 mg × capacity of intravenous calcium gluconate (ml) × 10% + calcium in one tablet (mg) × number of tablets × 40%. mmean = total intake of calcium within 7 days (mg) ÷ 7 ÷ body weight.

The correlations of mmean with preoperative biochemical indicators, electrolytes, gland pathology and surgical approach were evaluated.

Statistical Analysis
Data with normal distribution were presented as mean (x) ± standard deviation (SD). The data with abnormal distribution were presented as median. Statistical analysis was performed using the statistical product and service solution (SPSS Inc., Version 17.0). The correlation was analyzed with multiple linear regression analysis when the dependent variables showed normal distribution or with rank correlation analysis when the dependent variables showed abnormal distribution. t test or t’ test was used for analysis between groups depending on homogeneity of variance. Levene method was employed to test the homogeneity of variance. t-test was used to analyze the data between two groups and using one-way ANOVA among multi-groups. A value of two-tailed P < 0.05 was considered statistically significant.

Results

Surgical Findings
SPTX was performed in 15 patients (42.9%), TPTX+AT in 12 (34.3%), and TPTX in 8 (22.9%). Pathological examination showed hyperplasia in 20 patients (57.1%), and adenoma in 15 (42.9%).

The success rate of surgery was 91.4% (32/35); the iPTH level in 1 patient decreased by 1/3 at 10 min after surgery, but returned to the pre-operative level 2 days after surgery. The iPTH level decreased by greater than 1/2 in 2 patients 10 min after surgery, and returned to the pre-operative level at 2 and 5 days after surgery, respectively.

Postoperative Hypocalcemia
POH was found in 34/35 patients (97.1%). The time to occurrence of POH was 13±21.1 h. The mean daily intake of calcium within 7 days after surgery was 38.15±16.12 mg/kg.

Factors affecting Postoperative Intake of Calcium
The preoperative serum ALP and iPTH and the decline of intraoperative iPTH were positively related to the needed mean daily intake of calcium within 7 days after surgery. There were no significant correlations of mean daily intake of calcium with the age, duration of dialysis, serum levels of preoperative PTH, calcium, phosphorus, TRACP5b and 25-hydroxy-vitamin D (25-OH-VID), BMD, parathyroid total volume, surgical approach, weight of retentive parathyroid, pathological type and iPTH tested 10 min after PTH (Table 1, Table 2, Table 3)
Discussion

Symptoms of Postoperative Hypocalcemia
Symptomatic hypocalcemia is rarely found, and about 1/3 to 1/2 of patients receiving PTX develop symptomatic hypocalcemia after surgery (4). Mild clinical symptoms included fatigue, headache, intestinal obstruction, malabsorption, and muscle spasm. When serum calcium decreases greatly, neuromuscular irritability will be present and manifests as numbness, paresthesia and muscle twitching. Although symptoms may resolve after calcium and active vitamin D supplement, some patients may still develop serious life-threatening symptoms, such as wheezing, seizures, arrhythmias, congestive heart failure and so on(6).

Hypocalcemia Situations
Postoperative hypocalcemia is the most common complication after PTX, and generalized as “hungry bone syndrome”. The incidence of hypocalcemia after PTX among patients with secondary HPT has been reported to be up to 95%(5,7). In our study, POH was diagnosed in 97.1% of patients.

Factors Related To Intake of Calcium
The mean daily intake of calcium per body weight within 7 days after surgery (mmean) was used to evaluate the severity of postoperative hypocalcemia. Results showed that the levels of preoperative ALP and iPTH and the decline of intraoperative iPTH were positively related to the needed mean daily intake.
This may be explained as that PTH is able to increase the serum calcium. Long-term high PTH not only strengthens the existing osteolytic activity of osteoclasts, but also promotes the production of osteoclasts. Once the bone tissues are dissolved, a large amount of calcium and phosphorus are released into the circulation. After PTX, osteoclasts disappear due to the absence of stimulation by high PTH. Osteoblasts become active and calcium enter the bone tissues rapidly, causing a significant calcium increase in the bone and calcium decrease in the blood. The ALP reflects the severity of renal osteodystrophy. Therefore, the higher the levels of preoperative ALP and iPTH, the greater the intraoperative change in iPTH is, and the more the supplied calcium after surgery is, in order to maintain the normal serum calcium level.

Investigators have found that patients with postoperative hypocalcemia tended to have higher preoperative ALP level. They also found patients with primary hyperparathyroidism were more likely to develop hypocalcemia when they had higher preoperative PTH level. However, Bland and his colleagues did not find any correlation between the iPTH level and postoperative serum calcium level in patients with SHPT.

In our study, younger patients showed a greater risk for hypocalcemia. Torer et al also emphasized that age was correlated with hypocalcemia. In their study, the younger patients were more likely to develop hypocalcemia when they had higher preoperative PTH level. In a recent study, Brown et al reported there is calcium receptor on the parathyroid cells. Because the receptor and signal transduction change after dialysis, calcium fails to effectively control the PTH secretion, resulting in excessive PTH secretion. That’s why long-term dialysis causes the rise of serum calcium and severe hungry bone syndrome.

In our study, mmean was higher among patients with higher preoperative serum calcium level. Investigators also suggested that high preoperative serum calcium level was predictive for the development of postoperative hypocalcemia. Our study also found that patients with bigger parathyroid needed more daily intake of calcium. This may be explained by the fact that bigger gland suggests a more serious hyperthyroidism. The volume of parathyroid reflects the severity of osteoporosis. However, in another study, Torer et al did not observe any correlation between mmean and parathyroid volume. They even identified that patients with small glands showed a higher risk for postoperative hypocalcemia.

Serum TRACP-5b has been used as bone resorption index with high specificity and sensitivity. TRACP-5b can reflect the number of osteoclasts. The increase in TRACP-5b suggests the enhanced osteoclast activity, which reflects the increased severity of osteoporosis. Therefore, patients with high preoperative TRACP-5b level relatively have more severe osteoporosis, and are more prone to develop POH. Vitamin D doesn’t directly reflect the activity of osteoblasts or osteoclasts, but can regulate the metabolism of calcium and phosphorus. 25-OH-VD significantly reduced in patients with osteoporosis. It has been reported that 25-OH-VD and TRACP-5b may provide guidance for the treatment of osteoporosis.

Our results showed that mmean was positively related to the TRACP-5b level while negatively correlated with 25-OH-VD level. However, there was no statistical significance in these correlations. The BMD directly reflects the degree of osteoporosis. We also found that the mmean was negatively associated with BMD, but without statistical significance.

Our results showed there was no significant difference between surgical approach and postoperative calcium supplement. Theoretically, patients require the largest amount of calcium after TPTX. Patients undergoing TPTX+AT needed more daily calcium intake than the patients receiving SPTX. This may be explained by the fact that TPTX may remove the blood supply from the original vessels and eliminate the innervation. Since autotransplants are denervated and nourished by a slowly sprouting capillary system arising from the surrounding tissues, the resurrection of glands is long-lasting. What’s more, not all the implanted glands can survive. However, some investigators emphasized that even an experienced surgeon is also difficult to estimate the accurate size of residual parathyroid after SPTX, particularly when the subtotally resected gland is exposed incompletely in order to preserve its blood supply, or when the gland is situated deep in an incisura of a thyroid lobe, resulting in more tissues being left in situ as compared to that after PTX + AT. Conversely, if the residual parathyroid is too small or its blood supply is significantly
destroyed, there will be a high incidence of hypocalcemia after SPTX than after PTX + AT, which caused the complicacy in comparison of these different surgical approaches\(^{(18)}\).

Adenomas are more functional than hyperplastic glands, and have greater inhibitory effect on the residual glands. When the adenomas removed, the PTH level will drop greatly. The PTH decreases significantly when compared with that after resection of hyperplastic glands\(^{(16)}\). It’s the reason why hypocalcemia is more likely to occur and postoperative calcium demand is greater after resection of adenomas. On the basis of available findings, Gasparri et al\(^{(17)}\) agreed on that postoperative calcium intake was higher after removal of adenomas than after resection of hyperplastic glands. However, our results did not show the correlation between pathological type and daily intake of calcium.

However, the correlations of above factors with daily intake of calcium were not observed in the present study. This might be explained as follows: the absorption rate of drugs differs among patients and the physicians’ judgment about the indications for calcium supplementation differs among patients. Furthermore, the sample size was small in our study. Thus, further studies with large sample size are required to confirm our findings.

**Postoperative Serum Calcium Test and Calcium Supplementation**

Postoperative calcium replacement therapy is important, because the remaining glandular tissue or transplanted gland can’t secrete enough parathyroid hormone within 3 weeks after surgery to meet the daily need, resulting in osteitis fibrosa cystica\(^{(18)}\). Even when the serum calcium rises to the normal level, the patients need intake of adequate vitamin D in order to prevent the recurrence of HPT and occurrence of adynamic bone disease.

In our study, the serum calcium level was monitored once every 4-6 h within 48-72 h after surgery, and then twice daily until the calcium level was stable. But once hypocalcemia was found, the monitoring continued until the serum calcium level returned to normal and maintained stable without intravenous calcium gluconate supplement. We established central venous access for all patients to continuously provide intravenous calcium gluconate. According to the serum calcium level, the calcium was administered via a microinjection pump. Postoperative serum calcium level should be maintained at 2.0 mmol/L or a higher level to prevent muscle twitching and bone loss, as well as the clogging of internal leakage caused by hypocalcemia. However, the serum calcium level should not be maintained at higher level to avoid the influence on the survival of implanted glands (serum calcium may be maintained at slightly high level after SPTX and TPTX, but be less than 2.75 mmol/L). Oral calcium and vitamin D3 were administered within the first day after surgery. In our study, there were 300 mg of elemental calcium and 100 IU of vitamin D3 in each tablet and medication was done with three tablets thrice in the first day after surgery and then with an increment of 3 tablets every day. At the same time, the calcium intravenously administered decreased until oral medication was able to maintain the calcium level. The criteria for discharging were that the calcium level could be maintained stable with oral medication.

In our study, all the SHP patients were intravenously treated with 20 ml of 10% calcium gluconate after parathyroid adenectomy to reduce the risk for POH. All patients with hypocalcemia required 24-h infusion of calcium gluconate until the calcium level was stable. The speed of calcium administration was adjusted once every 4-6 h according to the serum calcium level, in order to maintain the serum calcium level at 2.0-2.75 mmol/L. To prevent hypercalcemia and ensure the timely treatment, the speed of calcium administration should be relatively slow at night. However, there is no consensus on the speed of calcium administration which is usually determined on the judgment of physicians. We summarized the methods of calcium supplementation. When the serum calcium level is below 1.6 mmol/L, the speed of calcium administration (10% gluconate) should be 10 ml/h; when the serum calcium level is 1.6-1.8 mmol/L, the speed be 7.5 ml/h; when the serum calcium level is 1.8-2.0 mmol/L, the speed be 5 ml/h; when the serum calcium level was above 2.0 mmol/L, the methods used for calcium administration depend on the specific conditions. If the serum calcium level is stable after intravenous calcium supplementation, the speed of calcium administration can be maintained; if the calcium level quickly rise, the intravenous calcium supplementation should be stopped, and oral calcium supplementation alone is used. Some, but not all, clinicians propose that the intravenous calcium administration can be discontinued once serum calcium level returns to above 2.0 mmol/L, and oral calcium alone is administered\(^{(19)}\).
However, we do not agree with this proposal, because the maintenance of normal calcium level requires the intravenous calcium supplement under most conditions, oral calcium supplementation often fails to meet the requirement for bone resorption, and absorption rate of oral calcium varies among patients.

There are some limitations in our study. First, it was a retrospective analysis and the sample size was small. In addition, data were collected for prospective outcomes and some other parameters that might be significant predictors of calcium intake were excluded. Moreover, some markers were not measured routinely before or after surgery, and calcium reagents changed in some patients. However, our results may provide evidence for the effective prevention and treatment of hypocalcemia. Investigators generally believe that an active intravenous calcium supplement is effective to relieve the symptoms of hypocalcemia. For some patients, the oral calcium and vitamin D supplementation are effective. On the other hand, when severe or symptomatic hypocalcemia occurs, intravenous calcium supplementation is often needed. Whether intravenous calcium supplementation should be used is determined by the severity of hypocalcemia. It usually takes 2 days for vitamin D supplement to increase intestinal calcium uptake. Therefore, we recommend preoperative vitamin D supplementation, even in patients with preoperative hypercalcemia. Furthermore, it is difficult to accurately adjust the calcium supplement due to the fluctuations of serum calcium no matter how frequently the test is performed, and patients always do not accept frequent testing. Therefore, it is necessary to use dynamic monitoring system to adjust the calcium supplementation according to the serum calcium level. In summary, postoperative hypocalcemia has a high incidence after PTX in uremic patients with SHPT. The serum levels of preoperative ALP and iPTH and the degree of intraoperative iPTH decline may help to assess the POH. Early detection of POH in high-risk patients will be helpful for the efficient calcium supplement. Finally, we recommend that the dynamic monitoring system may be used to detect the serum calcium level according to which the calcium supplementation is performed, which may improve the therapeutic efficacy.

Conclusions

To maintain normal serum calcium level in patients with POH (2.0 to 2.75 mmol/L), the mean daily intake of calcium within seven days after surgery should be 38.15±16.12 mg/kg. The levels of preoperative serum ALP and iPTH and degree of intraoperative iPTH reduction can be used to evaluate the severity of POH in these patients. Early and sufficient supplement of calcium and calcitriol are needed in patients at high risk, in order to avoid POH and mitigate symptoms.

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