

Recommend a simple, sustained and sufficient perioperative calcium regulation therapy and analysis of related factors during perioperative period for secondary hyperparathyroidism

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Abstract

Background: Patients of secondary hyperparathyroidism (SHPT) with chronic renal failure treated by long-term dialysis have received surgical treatment. The severe complications, especially severe hypocalcemia, would endanger lives during perioperative treatment. Therefore, this study aims to recommend a simple, sustained and sufficient perioperative calcium regulation scheme, and analysis of preoperative related indicators, the patient's condition for a preliminary assessment, thus guiding the postoperative calcium regulation, to avoid the occurrence of serious complications.

Methods: We reviewed the clinical data of 136 patients with chronic renal failure in uremic stage, who received dialysis treatment for a long time and finally diagnosed as SHPT, from Jan 2017 to Dec 2019, were accepted different operations to treat hyperparathyroidism, were given corresponding calcium regulation therapy to avoid serious complications, and were divided into the observation group and the control group according to the mean time of postoperative calcium regulation time.

Results: According to the median time of adjusting the pump calcium ($7.67 + 2.823$)d, the patients were divided into two groups: the observation group (≤ 7 d) and the control group (> 7 d). Compared with the control group, the observation group were elder (54.01 ± 9.215 , $P < 0.01$), shorter preoperative dialysis time (5.05 ± 2.855 , $P < 0.01$), significant difference in operation mode ($P = 0.026$), positive preoperative oral calcium ($\chi^2 = 9.941$, $P = 0.002$), higher preoperative calcium value ($t = 4.795$, $P < 0.001$), lower preoperative Parathyroid Hormone (PTH) value ($t = 6.327$, $P < 0.001$), lower preoperative Alkaline phosphatase (ALP) value ($t = 3.527$, $P = 0.001$). Multivariate analysis showed that age, preoperative calcium value, preoperative PTH value and preoperative ALP value were independent risk factors for postoperative calcium regulation therapy. Those factors, Gender, preoperative dialysis mode, complications, preoperative Hemoglobin (HB) value, were not related to postoperative calcium regulation. There was no significant difference between the two groups ($P > 0.05$).

Conclusion: The simple, sustained and sufficient calcium regulation scheme can maintain a stable level of blood calcium in SHPT, and be able to avoid the occurrence of severe hypocalcemia and increase the curate. Especially for the younger, the lower preoperative serum calcium, the higher blood PTH and ALP, should lengthen the calcium pump time appropriately, until the right time and stop the medicine. This is more safe.

Background

Secondary hyperparathyroidism (SHPT) is a chronic compensatory clinical manifestation in which the parathyroid gland secretes excessive PTH under the stimulation of low blood calcium or high blood phosphorus for a long time under the condition of chronic renal insufficiency, intestinal malabsorption syndrome, vitamin D deficiency or resistance, in order to improve blood calcium and reduce blood phosphorus^[1]. In the early stage of SHPT, the level of serum calcium, phosphorus and PTH could be controlled within the target value range after medical treatment (such as phosphate binders, calcium mimics, etc.), and then the clinical symptoms could be relieved. For the late-stage refractory SHPT, more than 15% of the patients are in the state of high calcium, high phosphorus and high PTH, which increases the cardiovascular and cerebrovascular mortality and all-cause mortality seriously affecting the daily life of patients or even threatening their lives. Surgery has been widely embraced as an important clinical treatment. Various modes of operations are offered, such as subtotal parathyroidectomy (SPTX), total parathyroidectomy (tPTX), and total parathyroidectomy with autotransplantation (TPTX-AT)^[2-4]. However, the incidence of severe hypocalcaemia reaches 97% after these operations^[1]. Consequently, postoperative calcium regulation therapy is the most important treatment in the perioperative period^[5]. This study summarizes a simple, sustained and sufficient calcium pump therapy, that can maintain a stable level of blood calcium in dialytic CKD patients with SHPT, to avoid the occurrence of severe hypocalcemia and increase the cure rate. Analysis of preoperative related indicators, the patient's condition for a preliminary assessment, determine the preoperative body calcium deficiency, thus guiding the postoperative calcium regulation program, to a great extent to avoid the occurrence of serious complications.

Methods

1. Materials

We reviewed the clinical data of 136 patients of SHPT, from Jinzhou Central Hospital and the Second Affiliated Hospital of Dalian Medical University, from Jan 2017 to Dec 2019, who received long treatment of dialysis for chronic renal failure in uremic stage.

Inclusion criteria: 1. SHPT in uremic stage of chronic renal failure diagnosed before operation; 2. Compliance with operation indications: 1) Patients with symptoms; 2) Abnormal calcium and phosphorus metabolism due to ineffective medicine treatment; 3) Preoperative PTH value > 800 pg/ml; 4) At least one parathyroid gland was > 1 cm in the diameter and the blood flow was abundant; which was consistent with

anyone of the above items; 5) There was no possibility of renal transplantation in the near future. Among them, 1) - 4) are necessary indications for surgical treatment. 3. There was no serious complication in the perioperative period.

Exclusion criteria: 1. Severe cardiopulmonary cerebral dysfunction, which resists general anesthesia and surgery. 2. Severe liver dysfunction, coagulation dysfunction.

The operation was performed by senior doctors. The patients and their families signed the informed consent related to the operation. The study has been granted an exemption from the Ethics Committee of the Second Affiliated Hospital of Dalian Medical University and Jinzhou Central Hospital Ethics Committee.

2. Surgical preparation

All indexes were improved after admission, such as routine blood parameters, blood coagulation, thyroid function, liver and kidney function, PTH, and ion series. Physical examinations were performed, which included thyroid and parathyroid ultrasound, neck computed tomography (CT), parathyroid MIBI and electronic laryngoscopy. Heparin-free dialysis was performed one day before the operation.

Catheterization of the subclavian vein was performed. The parathyroid gland grafted during autotransplantation was well organized, showed no obvious hyperplastic granules, and weighed approximately 30-60 mg. It had been cut into pieces with diameters of approximately 1 mm, and implanted into the quadriceps femoris of the left thigh of the patient. The cervical cavity was retained for drainage.

2. Postoperation

The details of the perioperative calcium regulation plan were recorded, the serum PTH and calcium value were detected, and the presence of any type of discomfort, such as numbness, convulsions of the hands or feet, headache, insomnia, acupuncture sensations in the lips, palpitation and agitation, was recorded. The details of the calcium regulation plan are described in the results.

3. The details of the calcium regulation plan

A total of 1 g of calcium gluconate was slowly injected before recovery from anaesthesia, and the dose was determined according to the recovery of patients' spontaneous respiration and the skeletal muscle strength. After recovery from anaesthesia, calcium gluconate was immediately pumped into the deep veins, and the initial speed was set at 1.0-1.5 g/h. After the operation, the observation indexes were measured according to the time axis, i.e. the operative day and the 1st, 2nd, 3rd, 5th, 7th, 10th and 15th day after the operation. The time node of calcium regulation was that the PTH value returned to the normal range and that the patients had symptoms of discomfort. The calcium gluconate concentration and pump speed were adjusted according to the results of relevant indicators. The patients were monitored for symptoms of discomfort during the process.

The arrangement of postoperative dialysis was made in accordance with routine dialysis before the operation, and heparin-free dialysis was recommended for the first time.

4. Observation index

Patients were divided into an observation group (≤ 7 days) and a control group (> 7 days), which is defined by the mean time of postoperative calcium regulation, and the calcium stop node was defined as the blood calcium index close to or exceeded the detection limit, and then change to oral-calcium which could maintain no symptoms. Each index was compared between the two groups, including age, sex, preoperative dialysis time, dialysis mode, complications, preoperative oral calcium levels, preoperative calcium levels, preoperative HB levels, PTH levels, ALP levels, and operation methods.

5. Statistical methods

All data analysis was performed using SPSS 21.0 statistical software. The count data were measured by χ^2 tests, the normal distribution measurement data were described as $\bar{x} \pm s$, and the skewed distribution measurement data were described as the median M (range). Logistic Regression Analysis was used for single-factor analysis and multivariate analysis. The standard level α was 0.05, and the difference was statistically significant when $p < 0.05$.

Results

1. Single-factor analysis of postoperative calcium regulation by general data

A total of 136 patients were included in this study, 60 males and 76 females; 30 males and 38 females were included in the observation group, and 30 males and 38 females were included in the control group ($\chi^2 = 0.392$, $p = 0.332$). The mean age was (49.06 ± 12.259) years: the mean age of the observation group was (54.01 ± 9.215) years, and that of the control group was (44.10 ± 12.964) years ($p < 0.01$). The duration of preoperative dialysis was (5.05 ± 2.855) years in the observation group and (6.99 ± 3.436) years in the control group ($p < 0.01$). The dialysis methods included peritoneal dialysis and haemodialysis: there were 29 cases of peritoneal dialysis, and 39 cases of haemodialysis in the observation group, and there were 31 cases of peritoneal dialysis and 37 cases of haemodialysis in the control group ($p = 0.467$). With or without complication after the operation, there was no significant difference between the two groups ($p = 0.467$). Preoperative oral calcium: in the observation group 47 patients took calcium before the operation, and 21 patients did not take calcium; in the control group, 24 patients took calcium, and 44 patients did not take calcium ($\chi^2 = 9.941$, $p = 0.002$). Operation mode: in the observation group, 28 patients underwent SPTX, 19 patients underwent tPTX, and 21 patients underwent TPTX-AT; and in the control group, the numbers of patients were 33, 19, and 16, respectively ($p = 0.026$). The mean time of postoperative calcium regulation was (7.67 ± 2.823) days, which was the reason for dividing the patients into two groups of "7 days". See Table 1 for details.

2. Single-factor analysis and Multivariate analysis of the influence of preoperative indexes on

postoperative calcium regulation

The mean time of postoperative calcium regulation was (5.25 ± 1.164) days in the observation group and (10.09 ± 1.682) days in the control group ($t = 53.529$, $P < 0.001$). The preoperative HB value was (119.324 ± 22.59) g/l in the observation group and (111.84 ± 20.29) g/l in the control group ($t = 1.972$, $p = 0.053$). The preoperative calcium value was (2.55 ± 0.33) mmol/L in the observation group and was (2.32 ± 0.22) mmol/L in the control group ($t = 4.795$, $p < 0.001$). The preoperative PTH value was (1449.30 ± 711.70) ng/L in the observation group and was (2422.84 ± 1045.34) ng/L in the control group ($t = 6.327$, $p < 0.001$). The preoperative ALP value was (243.43 ± 257.73) U/L in the observation group and was (496.26 ± 518.84) U/L in the control group ($t = 3.527$, $p = 0.001$), as shown in Table 2.

The results of multivariate analysis showed that the age, preoperative calcium value, preoperative PTH value and preoperative ALP value were independent factors, as shown in Table 3.

Discussion

With the prolongation of dialysis (peritoneal dialysis or haemodialysis) treatment time for patients with chronic renal failure in the uremic stage, the risk of abnormal mineral bone metabolism in chronic kidney disease (CKD-MBD) increases. The results of the Dialysis Outcomes and Practice Pattern Study (DOPPS) showed that the incidence rate was 40-50%^[6]. The secondary changes in parathyroid function are caused by the abnormal metabolism of calcium and phosphorus, the lack of vitamin D, the decrease in its receptor sensitivity, and the increase in the balance point of calcium regulation in the body^[7]. As a safe and effective therapy, surgical treatment has been widely used in clinical practice, but serious postoperative complications have become the difficulty of perioperative treatment, especially hypocalcaemia, which has a probability of approximately 97%. Intravenous pumping of Portugal Calcium Gluconate is the main treatment for avoiding serious complications in the perioperative period^[8]. The purpose of this study is to come up with the safe and effective postoperative calcium regulation schemes, and to find that age, preoperative calcium value, PTH value, ALP value are closely related to them.

Continuous pumping of calcium after surgery can ensure the effective concentration of serum calcium and avoid fluctuations in blood calcium. It can alleviate the uncertainty of severe hypocalcaemia caused by the transient change in serum calcium, can greatly improve the safety level after surgery and can reduce the frequent test steps in patients of the continuous dynamic follow-up of blood calcium, parathyroid hormone and other indicators as well as the complicated links of postoperative treatment^[9-10]. Ensuring stability of the effective drug concentration of serum calcium is key to reducing the occurrence of severe hypocalcaemia after surgery, and is also the key point of perioperative treatment^[11]. This study showed that 10% Portugal Calcium Gluconate continuously pumped with a speed of 1.0-1.5 g/h (10-15 ml/h) after surgery could greatly guarantee the stability of serum calcium levels and avoid the occurrence of complications such as convulsion; it also did not lead to high levels of blood calcium, which can protect the heart and other important organs.

Because of the long-term dialysis leads to "bone hunger" or serious calcium deficiency in the body, a sufficient calcium regulation scheme can supplement the lost calcium in a short period of time, shorten the postoperative treatment time. The progress of "bone hunger" is related to the postoperative calcium treatment time and the total amount of calcium. While ensuring the maximum calcium regulation speed, shortening the calcium supplement time as much as possible is another key point for the occurrence of postoperative severe hypocalcaemia^[12]. It is very important for the adjustment of calcium, to evaluate "bone hunger" to the greatest extent before surgery and to evaluate the indexes affecting calcium metabolism in the perioperative period^[13-14]. The daily total supply of 24-36 g calcium gluconate can ensure the maintenance of a sufficient serum calcium concentration and the maximization of calcium accumulation. Excessive calcium

supplementation, such as calcium pump speed of > 1.5 g/h, will lead to high serum calcium. Therefore, the lethal risk caused by cardiac electrophysiology and brain meridian metabolism should not be underestimated.

The results of this study show that age is an independent risk factor for postoperative calcium regulation. The reason is that young patients need more calcium for their own growth^[15]. At the same time, systemic calcium loss is caused by repeated dialysis treatment, so the perioperative calcium demand is greater. Especially the age under (54.01±9.215) years, the degree of bone starvation is more serious, and the postoperative calcium demand is large. In the adjustment time of postoperative calcium pump, it is necessary to extend the time of calcium pump appropriately until the serum calcium is stable or gradually rises close to the upper limit of normal value, and then stop calcium pumping. However, some scholars believe that the absorption of calcium, calcitriol and other drugs in the gastrointestinal tracts of elderly patients is more serious, and hypocalcaemia is more likely to occur. Therefore, the correlation between age and hypocalcaemia needs more data to be confirmed^[15-16]. We should further collect and analyse relevant data. Blood calcium can directly reflect the quality of surgery and is closely related to the occurrence of postoperative symptoms^[17]. The key to avoiding severe symptoms is to maintain the stability of blood calcium after surgery. A rigorous and safe postoperative calcium regulation scheme is directly related to the prognosis of patients.

As the most important detection index in perioperative period, blood calcium can directly reflect the quality of operation, and is closely related to the occurrence of postoperative symptoms^[6]. The key to avoid severe symptoms, especially convulsion caused by hypocalcemia, is to maintain the stability of blood calcium after operation. A rigorous and safe postoperative calcium regulation scheme is directly related to the prognosis of patients. This study confirms that preoperative calcemia value is an independent risk factor of postoperative calcium regulation time, that is, preoperative calcium value is negatively related to postoperative hypocalcemia, that is, the preoperative blood calcium value indirectly reflects the preoperative basic calcium level of patients, especially those whose blood calcium value is lower than (2.55±0.33) mol / L, which reminds us that the patients are potential low basal calcium values, The more calcium needed after operation, the greater the probability of hypocalcemia. Therefore, the blood calcium adjustment should run through the whole treatment process, even before the operation. Routine application of oral calcium before surgery can reduce the incidence of postoperative hypocalcemia and shorten the postoperative calcium regulation time. At the same time, the results of this study confirm that the appropriate use of oral calcium before operation can alleviate bone hunger in varying degrees, so as to shorten the postoperative calcium regulation time, which can be used as a routine treatment in the perioperative period.

The preoperative PTH value reflects parathyroid function. In patients with chronic renal failure in the uremic stage undergoing dialysis treatment for a long time, the release of PTH in blood is stimulated by the whole body's osteolysis reflex to promote bone absorption. After surgical removal of the pathological parathyroid gland, the PTH value drops sharply, bone resorption is impaired, and serious hypocalcaemia occurs. Some scholars^[18-19] have confirmed that when the preoperative PTH value is more than 1750 ng/L, the probability of hypocalcaemia increases 6.8-fold. This study shows that when PTH value is greater than 1449.30 ng/L, it is necessary to strictly implement calcium regulation program to avoid hypocalcemia caused by premature suspension or reduction of calcium pumping. This study also confirms that preoperative PTH value was positively correlated with the postoperative calcium regulation time, that is, the higher preoperative PTH value, the more postoperative calcium demand, and the longer calcium regulation time.

Serum ALP is a key enzyme to promote bone calcification, which will increase in varying degrees for liver disease and bone marrow disease. Serum ALP value in the patients with chronic renal failure in uremic stage can reflect the severity of renal osteodystrophy, that is, the severity of bone hunger syndrome after operation. Kidney Disease: Improving Global Outcomes (KDIGO) suggests that Serum ALP value in blood can be used to evaluate the severity of CKD-MBD^[1]. Ho LY and other scholars^[16] have confirmed that the higher the preoperative ALP value is, the greater the probability of hypocalcaemia is after surgery, and the more the calcium dose needs to be supplemented. This study combines with preoperative ALP value to determine the degree of bone hunger in the whole body and indirectly guide the time of postoperative calcium regulation, especially the preoperative ALP value is greater than 243.43U/L, that is, the higher the preoperative ALP value is, the greater the degree of bone hunger is, the longer the time of calcium supplementation is, that is necessary to strictly implement a calcium regulation programme to avoid hypocalcaemia caused by premature suspension or reduction of calcium pumping.

In the process of perioperative treatment for SHPT, the factors affecting calcium regulation are diverse and complex^[20]. Studies with a large sample size are still needed to support whether the sustained and sufficient calcium regulation scheme can reduce the incidence of hypocalcaemia. This is in accordance with the current treatment method, covering the whole perioperative period. For example, after sufficient continuous calcium supplementation, some patients maintain the stability of serum calcium levels in a short period without discomfort. After stopping the intravenous calcium pump, the serum calcium level will progressively decrease but without serious hypocalcaemia. Therefore, the adjustment time of the calcium pump needs to be explored.

Conclusions

Accurate and detailed postoperative calcium regulation scheme in perioperative period is very important for the postoperative recovery of patients with SHPT. The calcium regulation scheme recorded in this study has been proved to be simple, safe and easy in clinical application. Meanwhile, the relevant factors affecting the postoperative calcium regulation have been detailed analyzed and the timely intervention could be taken to reduce the occurrence of serious complications, especially hypocalcemia, which could lead to serious consequences.

Abbreviations

secondary hyperparathyroidism [SHPT]

Subtotal parathyroidectomy (SPTX)

Total parathyroidectomy (tPTX)

Total Parathyroidectomy with autotransplantation (TPTX-AT)

Parathyroid Hormone (PTH)

Alkaline phosphatase (ALP)

Hemoglobin (HB)

computed tomography (CT)

mineral bone metabolism in chronic kidney disease (CKD-MBD)

The Dialysis Outcomes and Practice Pattern Study (DOPPS)

Kidney Disease: Improving Global Outcomes (KDIGO)

Declarations

Ethics approval and consent to participate

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. The operation and the related treatment plans approved by the clinical practice guideline. The study has been granted an exemption from the Ethics Committee of the Second Affiliated Hospital of Dalian Medical University and Jinzhou Central Hospital Ethics Committee. Informed consent was obtained from all individual participants included in the study. The patients and their families signed the informed consent related to the study.

Consent for publication

All authors agreed with the content and all gave explicit consent for publication.

Availability of data and material

All authors have indeed provided all raw data on which our study is based. All data generated or analyzed during this study are provide in supplementary information files.

Competing interests

There is no conflict of interest in this research.

Funding Not applicable

Authors' contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by JIA D, YF W, BZ, JIN D, and YM. Dr. XSZ summarized the overall treatment plan, designed the experimental ideas, checked the experimental data,

calculated the statistical data. The first draft was written by WBZ and the previous versions of the manuscript were commented by all the other authors. The final manuscript was read and approved by all the authors.

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Tables

Table 1: Summary of general information

	Sex		age (years)	preoperative calcium intake (n)		preoperative dialysis time (years)	preoperative dialysis mode		operation mode			complications (n)	
	Male (n)	Female (n)		Yes	No		Hemodialysis (n)	peritoneal dialysis (n)	SPTX(n)	tPTX (n)	TPTX-AT (n)	Yes	No
Observation group	30	38	54.01±9.215	47	21	5.05±2.855	39	29	28	19	21	39	29
Control group	30	38	44.10±12.964	24	44	6.99±3.436	31	37	33	19	16	37	31
c ² /P	c ² =0.392, P=0.332		P=0.01	c ² =9.941, P=0.002		P=0.01	P=0.467		P=0.026			P=0.467	

SPTX: Subtotal parathyroidectomy

tPTX: Total parathyroidectomy

TPTX-AT Total Parathyroidectomy with autotransplantation

The two groups was statistically significant (P<0.05)

Table 2: Single factor analysis of the influence of preoperative indexes on postoperative calcium regulation

	calcium pumping time (days)	Preoperative HB value (g/L)	preoperative calcium (mmol/L)	preoperative PTH (ng/L)	preoperative ALP (U/L)
Observation group	5.25±1.164	119.324±22.59	2.55±0.33	1449.30±711.70	243.43±257.73
Control group	10.09±1.682	111.84±20.29	2.32±0.22	2422.84±1045.34	496.26±518.84
t/P value	t=53.529; P=0.001	t=1.972; P=0.053	t=4.795; P=0.001	t=6.327; P=0.001	t=3.527; P=0.001

The two groups was statistically significant (P<0.05)

Table 3: Multivariate analysis of the influence of preoperative indexes on postoperative calcium regulation

	c ²	P value
Operation method	9.042	0.618
Gender	7.989	0.714
Preoperative dialysis time	14.316	0.216
Preoperative dialysis	4.572	0.950
Complications	6.179	0.861
Preoperative PTH value	32.899	0.001
Preoperative calcium value	31.202	0.001
Preoperative HB value	15.507	0.160
Preoperative ALP value	11.408	0.010
Age	27.084	0.004
Preoperative calcium value	34.045	0.000

The two groups was statistically significant ($P < 0.05$)

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