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Efficacy analysis of medical and surgical treatments in chronic kidney disease patients with secondary hyperparathyroidism

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ABSTRACT

Purpose: To investigate the effects of surgical and medical treatments on chronic kidney disease (CKD) patients with secondary hyperparathyroidism (SHPT).

Materials and methods: A total of 198 CKD patients with SHPT were identified at Tongji Hospital from January 2013 to June 2017.

Results: Surgical group (53 patients) received maintenance dialysis for 78.0 ± 4.9 months, while medical group (84 patients) for 62.0 ± 6.4 months. The serum intact parathyroid hormone (iPTH) in surgical group reduced apparently compared with medical group ($P = 0.015$) and maintained satisfied result during three years of follow-up (67.4 ± 7.4 pg/ml). The recurrence rate in surgical group was 7.5% and in medical group was 15.5% ($P = 0.024$). Beyond that, 5 (5.9%) patients suffered persistent hyperparathyroidism in medical group.

Conclusion: Although the progress of medical treatment is changing rapidly, surgical treatment is still an effective way to control serum iPTH and calcium chronically for SHPT patients. Complex SHPT patients can also receive satisfied effect by surgical treatment, without apparently increasing the risk of complications.

1. Introduction

Secondary hyperparathyroidism (SHPT) is a frequent metabolic complication of chronic kidney disease (CKD) [1,2], accompanied by progressively deregulating of calcium and phosphate homeostasis, which results in CKD-related mineral and bone disorders (CKD-MBD), especially for haemodialysis patients [3,4]. Furthermore, SHPT has been associated with adverse effects such as severe bone disorders and calciphylaxis that increases cardiovascular morbidity and mortality [3,5–8]. According to dialysis transplant registration system data in China, there are many haemodialysis patients every year (200 thousand inhabitants in 2016) and the morbidity of end-stage renal disease (ESRD) is continuously increasing year after year. About 90% of patients with ESRD develop SHPT by the time haemodialysis is initiated [9]. Successful kidney transplantation can reverse partial SHPT. But we have very limited opportunity to perform kidney transplantation because of lack of donors, so SHPT patients have to continue haemodialysis for long term. Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines from U.S. have proposed that medical treatment should be recommended for patients with persistent intact parathyroid hormone (iPTH) > 300 pg/ml [10] and surgical treatment for patients with persistent iPTH > 800 pg/ml [11]. However, with the rapid advances in medical treatment, calcimimetic agents have been approved one after another, such as cinacalcet and etelcalcetide [12], and the intervention time has been prolonged as long as possible. Whether delaying surgery with long-term medical therapy is truly beneficial for SHPT patients is unknown. To address this, we performed a retrospective, single-center observational study to compare the clinical efficacy of surgical and medical treatments and discuss the important status of surgical treatment in SHPT.

2. Materials and methods

2.1. Study population

The study population of this retrospective, single-center study was consisted of 198 CKD patients with SHPT in Tongji Hospital from January 2013 to June 2017. Patients who had history of renal transplantation, precious surgery in the neck area and/or (para-)thyroid malignancy in their medical history were excluded. Data of the included patients was extracted from the hospital's electronic patient record system.

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2.2. Study design, primary and secondary endpoints

The primary objective of this study was to provide robust data on the improvement of laboratory values after different treatments. Secondary objectives were the positive rate of preoperative localization, rate of recurrence and complications (e.g. permanent hypocalcemia and permanent hypoparathyroidism) after different treatments until the end of follow-up.

Depending on the treatment, patients were categorized into 2 groups: surgical group and medical group. The inclusion criteria were as follows: surgical group: severe SHPT (persistent iPTH > 800 pg/ml), ≥1 parathyroid gland could be found with ultrasonography or ^{99m}Tc-sestimibi scintigraphy, symptoms such as bone pain, pathologic bone fracture, pruritus, urinary calculus, calciphylaxis and so on; medical group: earlier HPT (persistent iPTH > 300 pg/ml). Routine examinations should be completed before treatments. Ultrasound and ^{99m}Tc-sestimibi scintigraphy were used for preoperative localization. If only one enlarged parathyroid gland was found or ^{99m}Tc-sestimibi scintigraphy was negative, then CT or MRI examination was performed. Laboratory tests included serum calcium, phosphorus, iPTH levels, vitamin D levels and other conventional biochemical markers.

The surgical strategy is not only focused on the target range of iPTH between 150 and 300 pg/ml for patients on permanent dialysis according the KDOQI guidelines [11], but also on the realistic prospect of kidney transplantation and the prospective time on dialysis. Total parathyroidectomy (TPTX) with autotransplantation (AT) of parathyroid tissue and bilateral cervical thymectomy (BCT) was the main approach for surgical group.

In addition, we performed intraoperative parathormone assay (IOPTH) monitoring and recorded the serum iPTH levels 2 h before operation, 15 min and 30 min after total resection. If more than four parathyroid glands were detected and the iPTH levels 15 min after resection decreased by 80%, then we could consider that parathyroid glands were completely removed. If less than four parathyroid glands were detected and the iPTH levels 15 min after resection ≥400 pg/ml, we considered that whether omissive or ectopic parathyroid gland was present, supplemented by intraoperative ultrasound. Serum calcium and iPTH were re-examined 1 day after surgery to determine whether severe hypocalcemia occurred. All patients received calcium supplement after operation for 1 month to 6 months.

Medication intervention therapy included phosphate binders, bisphosphonates, active vitamin D analogues, calcimimetics and calcium supplements. Because each patient took different kinds, quantities or compatibilities medicines, we collected them into medical group without specific division.

The follow-up began from the first day of hospitalization, and had median time when SHPT recurred or persistent hyperparathyroidism occurred, and finished at the end of follow-up period. Persistent hyperparathyroidism was defined as a serum calcium level > 2.62 mmol/l and/or a PTH level more than four times the upper normal value (above 240 pg/ml) during the first 6 months after treatment, and recurrent disease as these levels 6 months after treatment [13,14].

2.3. Statistical analysis

Data recording were performed using Excel version 2016. We used descriptive tests to express continuous variables as mean ± √standard deviation (SD). We described categorical variables as count (n) and percentage (%). Statistical analyses were performed using SPSS statistical version 22.0. Clinical characteristics before and after each treatment and the changes of laboratory values were compared using independent sample *t*-test or Mann-Whitney *U* test for continuous variables, and Pearson χ^2 test for differences between variables. In univariate analysis, *P* value < 0.05 was considered statistically significant.

Table 1
Patients characteristics before treatment.

	Surgical group (n = 53)	Medical group (n = 84)
Age (years)	55.7 ± 3.6	44.6 ± 3.6
Sex (M/F)	21/32	40/44
BMI (kg/m^2)	23.6 ± 0.9	24.8 ± 1.0
History of diabetes	8(15.1)	14(16.7)
History of urinary tract lithotripsy	12(22.6)	13(15.5)
Receiving dialysis	45(84.9)	55(65.5)
Duration of dialysis (months)	78.0 ± 4.9	62.0 ± 6.4

Data are shown as mean ± √SD or n (%).
BMI, body mass index.

3. Results

3.1. Study population

A total of 198 SHPT patients were identified at Tongji Hospital from January 2013 to June 2017. 137 patients were included in the study after applying the inclusion and exclusion criteria.

3.2. Patient characteristics

There were 53 patients in surgical group, with an average follow-up time of 15.0 ± 3.1 months, and 84 patients in medical group, with the median follow-up time of 25.0 ± 2.5 months. The average duration of dialysis was 78.0 ± 4.9 months in surgical group (45 cases, 84.9%) and 62.0 ± 6.4 months in medical group (55 cases, 65.5%). 22.6% (12 cases) of patients had history of urinary tract lithotripsy in surgical group, 15.5% (13 cases) in medical group. The average frequency of urinary tract lithotripsy per patient in surgical group was 2–3 times higher than that in medical group. Patients characteristics of two groups are listed in Table 1.

3.3. Preoperative localization imaging

In surgical group, all patients were examined by ultrasound. 0–4 (mainly 3) enlarged parathyroid glands were detected. The detection rate of superior gland was significantly higher than that of inferior gland ($P = 0.027$, upper: 87%, inferior: 54%). In the total 207 lesions, the positive rate of ultrasound was 86.5% (179/207). 45 patients (84.9%) received ^{99m}Tc-sestimibi scintigraphy. In the total 176 lesions, the positive rate was 90.3% (159/176). The positive rate of ultrasound combined with ^{99m}Tc-sestimibi scintigraphy could be as high as 93.8% (165/176).

3.4. Biochemistry

1. Before and after surgical treatment

The levels of serum iPTH decreased significantly after one month of operation ($P < 0.001$) and was still maintained at a relatively low level during 3 years of follow-up (67.4 ± 7.4 pg/ml), while the change of serum calcium was not obvious ($P = 0.351$). Preoperative and postoperative clinical characteristics are shown in Table 2.

2. Before and after medical treatment

The serum iPTH one month later was significantly lower than that before treatment ($P = 0.037$), while the change of serum calcium was not obvious ($P = 0.443$). In the meantime, we found two more cases of vascular calcification after one month. The improvement rate of clinical symptoms in surgical group was 87.0% (40/46) and in medical group

Table 2
Clinical characteristics before and after surgical treatment.

	Surgical treatment		P	Medical treatment		P
	Before (n = 53)	After[a] (n = 53)		Before (n = 84)	After[b] (n = 84)	
Vascular calcification	8 (15.1)	7 (13.2)	0.082	7 (8.3)	9 (10.7)	0.058
Corrected calcium (mmol/l)	2.5 ± 0.7	2.3 ± 0.9	0.351	2.2 ± 0.5	2.0 ± 0.4	0.443
Phosphorus (mmol/l)	1.4 ± 0.8	1.2 ± 0.9	0.053	1.8 ± 0.8	1.7 ± 0.8	0.064
iPTH (pg/ml)	1846.3 ± 35.3	258.1 ± 23.6	< 0.001	799.4 ± 28.0	399.7 ± 23.2	0.037
Calcium-phosphorus product ($mmol^2/l^2$)	4.01 (3.35–5.72)	3.34 (3.01–4.24)	< 0.001	3.78 (2.55–4.76)	3.71 (2.45–4.63)	0.051
Clinical symptoms	46 (86.8)	40 (75.5)	0.054	51 (60.7)	37 (44.0)	0.043
Pruritus	9	6		13	7	
Bone pain	16	14		16	10	
Pathologic bone fracture	6	6		5	5	

Data are expressed as mean ± √SD or mean (range) or n (%).
[a] After surgery means one month after operation.
[b] After treatment means one month after medical treatment.

was 72.5% (37/51), which might attribute to relatively complex conditions in surgical group (Table 2).

3. Changes of laboratory values between two treatments

The decrease range of iPTH was more significant in surgical group ($P = 0.015$). During follow-up period, the iPTH level in medical group was not as stable as that in surgical group [484.3 pg/ml (323.6–967.5) in medical group vs. 67.4 pg/ml (55.2–80.1) in surgical group]. The trends of iPTH in two groups are shown in Fig. 1.

Although serum calcium of both groups didn't decrease obviously, it remained in normal range during the follow-up period. Unlike the surgical group, there was a slightly upward trend in medical group (Fig. 2). The changes of laboratory values between two groups are shown in Table 3.

3.5. Recurrence rate

15.5% (13 cases) of patients recurred in medical group and 7.5% (4 cases) in surgical group. The difference in recurrence rate was statistically significant ($P = 0.024$). One of four patients in surgical group underwent sPTX + BCT, and three patients underwent TPTX + AT. One of the patients who underwent TPTX + AT + BCT was resected 2 enlarged parathyroid glands in the first operation (right inferior, left superior), which recurred half a year later. The remained 2 cases were resected 4 enlarged parathyroid glands in the first operation. In the meantime, 5 cases had persistent hyperparathyroidism (HPT) in medical group and the condition could not be improved after increasing drug dosage, while no similar cases were found in surgical group.

3.6. Complications

In surgical group, one case presented with hoarseness. 44 cases (83.0%) developed temporary hypocalcemia (serum calcium < 2.0 mmol/l) 1 day after operation. 28 of 44 patients felt perioral or upper limb numbness. The other 16 cases had no clinical symptoms. No one presented with permanent hypocalcemia and hypoparathyroidism after parathyroidectomy (PTX). In medical group, all patients had no obvious complications.

4. Discussion

By comparing efficacy of medical and surgical treatment, the results of this single-center, retrospective study were as follows: although there were many clinical adverse factors in surgical group, including longer average dialysis time, higher serum iPTH and more sophisticated clinical symptoms such as pruritus, bone pain and pathological fracture, surgical treatment could achieve significant and sustained efficacy in a shorter period with lower risk of complications. While medical group also received some therapeutic effects, it showed relatively poor performance in terms of continuity. Firstly, the iPTH fluctuation was large and the serum calcium level had a slightly upward trend during follow-up period. Secondly, the recurrence rate of medical group was higher than that of surgical group. The above conclusions illustrated that surgical treatment is more effective than medical therapy even for more complicated SHPT patients. So, PTX still remains a cornerstone in the treatment of SHPT.

Several reasons may illustrate the significant advantages of surgical therapy. Firstly, opportunity to preclude manifest and retrievable renal

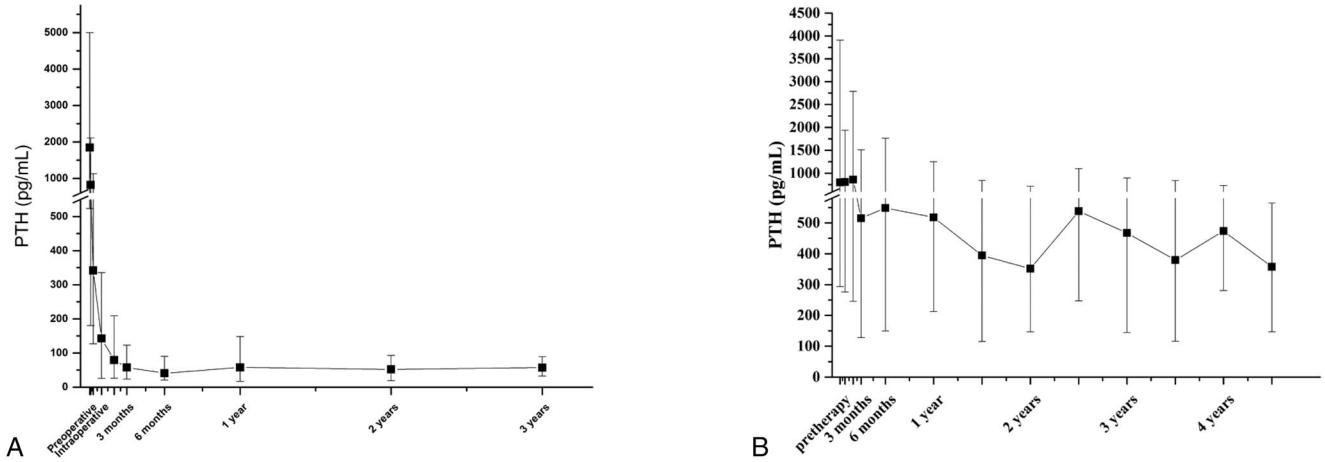

Fig. 1. The trend of iPTH in surgical group (A) and medical group (B).

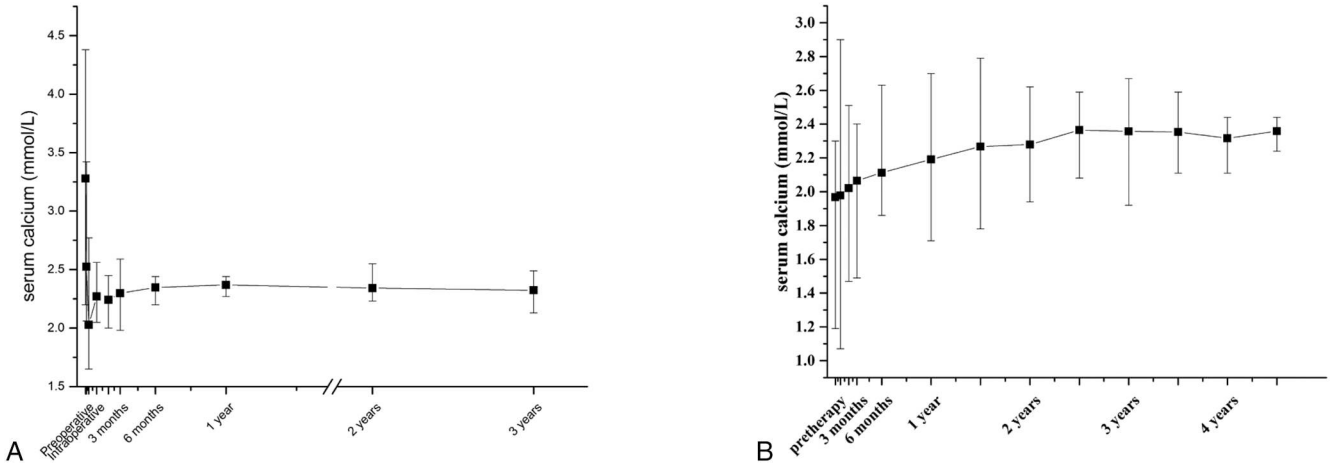

Fig. 2. The trend of serum calcium in surgical group (A) and medical group (B).

Table 3
The changes of laboratory values between two groups.

	Surgical group	Medical group	*P*
iPTH (%)	86.0 ± 11.3	50.0 ± 7.1	0.015
Corrected calcium (%)	8.8 ± 5.7	9.1 ± 2.9	0.274
Phosphorus (%)	7.7 ± 4.5	5.9 ± 2.6	0.091
Calcium-phosphorus product (%)	3.9 ± 4.3	3.4 ± 0.8	0.128

Data are expressed as mean ± √SD.
The changes of laboratory values = [(before treatment-after treatment) / before treatment] × 100%.
iPTH, intact parathyroid hormone.

HPT in CKD is probably narrow because any degree of renal insufficiency functions as parathyroid stimulus, and only full restoration of renal function, mainly renal transplantation, will provide cure [15]. Nevertheless, we have very limited opportunity to perform kidney transplantation and the majority of SHPT patients have to continue haemodialysis for long term. Surgical treatment eliminates the main source of iPTH through resecting almost all parathyroid glands, which achieves a dramatic drop of iPTH. Secondly, as CKD advances, diffuse lesions of parathyroid glands gradually turn into nodular lesions. Nodular hyperplastic glands have less vitamin D receptors (VDRs) and calcium-sensing receptors (CASRs) compared with diffusely hyperplastic glands [16]. While cinacalcet can reduce PTH secretion by increasing the sensitivity of CASRs [17]. As the disease progresses, the PTH level is not sufficiently suppressed by cinacalcet. Lastly, if patients receive medical therapy, a long-term and regular treatment is needed. It has higher cost than surgical treatment, especially cinacalcet. Greater financial burden may affect the compliance of patients, which aggravates their condition.

Due to small size, large number and uncertain position of parathyroid glands and the higher incidence of ectopic parathyroid glands, preoperative localization imaging is necessary for intraoperative exploration to avoid excessive neck exploration, which might increase risk of parathyromatosis [18]. Our study showed that ultrasound combined with ^{99m}Tc-sestimibi scintigraphy could improve positive rate. In addition to above approaches, CT, MRI and PET-CT could also be chosen as complements.

This study was not designed to conclude whether patients would benefit from earlier surgery. However, the longer SHPT patients are exposed to high iPTH level, the more likely it is to have serious complications, of which the calcification of heart valve is the most serious and fatal complication of SHPT [5,6]. Once vascular and valvular calcifications are formed, they are not usually affected even by a successful PTX [19]. Conversely, it was reported that successful PTX for early SHPT patients was associated with decrease in blood pressure [20], improvement of lipid profile [14] and increase of bone mineral density [21–23]. So it is important to perform PTX at an early stage, especially before the calcification has become progressive. However, the optimal time of surgery need to be further studied.

The current study also has some limitations. Firstly, we do not know whether calcium levels in dialysis fluids were changed in some patients after treatment. But in theory, it is unlikely that this could affect our outcome and apply long term after treatment. Secondly, our data may have some bias because it is a single-center retrospective study.

It can be concluded that despite of the advances in medical treatment, PTX is still a safe and effective treatment for SHPT, especially for refractory HPT.

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Declaration of Competing Interest

The authors declare no conflict of interest.

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