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ABSTRACT

Background. Patients with end-stage renal disease (ESRD) have a decreased quality of life (QoL), which is attributable in part to secondary hyperparathyroidism (2HPT). Surgery is the definitive treatment of 2HPT. The aim of this study is to assess the effect of total parathyroidectomy with deltoid autotransplantation on the QoL.

Methods: A total of 201 ESRD with 2HPT were enrolled. The operation efficacy was evaluated by analyzing preoperative and postoperative values, including levels of intact parathyroid hormone (iPTH), serum phosphorus, serum calcium, alkaline phosphatase (ALP) and calcium-phosphorus product. The QoL was evaluated by MOS 36-item short-form health survey (SF-36) scores preoperatively and at 6 months postoperation.

Results: Compared with the preoperative values, levels of PTH(2033pg/ml vs 62.5 pg/ml), serum phosphorus(2.30mg/dl vs 1.60mg/dl), serum calcium(3.62mg/dl vs 1.84mg/dl), and calcium-phosphorus product were all decreased postoperative. Number variation and anatomic location variation of thyroid glands were found in the patients. Quality of life improved significantly in all 8 individual and 2 component summary scales, with a more significant decrease in the physical health scales.

Conclusion: Parathyroidectomy significantly improves quality of life in patients with secondary hyperparathyroidism.

Key Words Quality of Life Total Parathyroidectomy Secondary Hyperparathyroidism

Introduction

In the past 10 years, chronic kidney disease has received increased attention as a leading public health problem. The overall prevalence of chronic kidney disease was 10.8% in China. The number was 13.0% in the USA.[1]

Chronic renal failure is the cause of serious derangements in parameters related to mineral metabolism. Underlying renal disease leads to calcium excretion and loss, inability to activate vitamin D, and hyperphosphatemia. This ultimately results in hypocalcemia, and ongoing parathyroid gland stimulation.[2] Furthermore, HPT contributes to progressively disturbed calcium-phosphate homeostasis and eventually to hypercalcaemia. [3]

Secondary hyperparathyroidism (SHPT) is an adaptative process, which ultimately becomes maladaptative, in response to an impairment of renal function. Elevated PTH levels are associated with many complications, such as psychological and neurological disorders, mineral bone disorder, ectopic calcifications in the cardiovascular system, malnutrition, and inflammation.[4] These complications can severely compromise the quality of life (QoL) of the already impaired SHPT patients, due to both the symptoms of ESRD itself and the burden of dialysis treatment[5] SHPT occurs commonly in patients with end stage renal disease (ESRD) (30 – 50%)[6] In one study, the prevalence is as much as 90% by the time they reach the ESRD. [7]

Parathyroidectomy can significantly provide reductions in serum parathyroid hormone (PTH) and to a lesser degree phosphate, but can exacerbate issues with hypocalcemia [7]. KDIGO guidelines recommend parathyroidectomy (PTx) in patients with severe HPT (>800 pg/mL) who

are refractory to medical therapy. [8]The beneficial effects of Parathyroidectomy (PTX) for 2HPT have been reported by quite a few of studies.[9-12]After PTX, serum Ca and P have generally easily achieved recommended target values (9). Bone metabolism (10), and diastolic cardiomyopathy (11) are markedly improved and also reduced incidence of major cardiovascular events. Bone pain, malaise, pruritus or calciphylaxis is likely to improve after PTX(12).

The aim of this study is to assess the evolution of QoL inpatients with SHPT and ESRD that received surgical treatment and to identify the different clinical, biological or pathological variables that influence this evolution.

Results

From July 2013 to December 2018, 201 patients with SHPT and ESRD were prospectively enrolled in the study. All patients were enrolled in a dialysis protocol at admission.

Patient history and demographic data are listed in Table 1. The male/female ratio was almost 2:1. The median of patients' dialysis age was 78 months. Except ESRD were significant, the most common being hypertension, coronary heart disease, anemia, diabetes and chronic viral hepatitis. Three patients received kidney transplant, but were all back on dialysis years later.

The most common indication for parathyroidectomy was failure to control PTH levels, 197 patients (98.0%) having preoperative PTH >800 pg/ml. The median value of preoperative PTH was 2033 pg/ml. Preoperative blood calcium 3.62 mmol/L (Table 2). All patients were planned to undergo total parathyroidectomy with autotransplantation.

However, only 186 (92.5%) patients' PTH levels dropped to normal at 7 days postoperative. There are 13 patients still had PTH levels >200 pg/ml. 5 of them accepted reoperation months later, and finally PTH levels dropped to normal. The rest of the patients are currently under observation.

In 162 (80.60%) cases, 4 glands were found. 3 glands were found in 21 (10.45%) cases. 4 of the patients accepted reoperation, and the left gland was found. In 11 (5.47%) cases, 5 glands were found. There was only 1 patient who had 6 glands. However, 2 glands were found in 2 (0.9%) cases and 1 gland was found in 5 (2.49%) cases, whose PTH levels dropped to normal after operation. (Figure 1)

The anatomic location of parathyroids was also variant. Glands were found in the thoracic cavity in 4 (2.3%) cases, within thyroid in 4 (2.3%) cases, posterior esophagus in 3 (1.72%) cases and 1 (0.57%) in carotid sheath. (Figure 2)

As expected, PTH levels dropped significantly after surgery to a median of 62.5 pg/ml, 186 patients having PTH levels within normal limits at 7 days postoperatively and 191 patients at 6 months. (Table 2). All patients required calcium supplementation after surgery, normalization occurring in 2 to 7 days. 3 patients received emergency dialysis because of hyperkalemia. There were no other postoperative complications reported, including bleeding, recurrent laryngeal nerve injury.

The responses to the Sf-36 Health Survey are shown in Table 3. The surveys completed prior to surgery showed that SHPT patients had lower scores than the general population in all 8 individual and 2 component summary scales, with a more significant decrease in the physical health scales. 6 months after surgery, patients improved significantly in 8 scales: Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Physical component summary, Emotional well being, Mental Component Summary ($p < 0.001$), Social function ($p = 0.002$). Role-emotional was also improved, but not significant ($p = 0.087$).

Significant progress at 6 months follow-up was obtained in the following Sf-36 scales: Body Pain, Role-physical, and Physical functioning. The most commonly reported symptoms preoperatively were: joint pain, bone pain, pruritus, feeling weak, difficulty standing up, which were all significantly decreased at 7 days postoperatively, and the decrease continued at 6 months postoperatively.

Discussion

Most patients on dialysis with secondary hyperparathyroidism have multiple enlarged parathyroid glands, for which the definitive treatment is surgery. Parathyroidectomy is required in about 15% of patients after 10 years and 38% of patients after 20 years of ongoing dialysis therapy [12]. The surgical options are subtotal and total parathyroidectomy. Subtotal parathyroidectomy is preferred if there is a single or double adenoma causing tertiary hyperparathyroidism after kidney transplantation, for which the incidence of recurrent secondary hyperparathyroidism is low. Conversely, total parathyroidectomy with autotransplantation is preferred for patients with compelling reasons to avoid reoperative neck surgery.[13]

In our center, we perform total parathyroidectomy with autotransplantation in all ESRD patients with 2HPT. No deaths occurred among patients suffering from SHPT during the perioperative period. He also demonstrated that total total parathyroidectomy with autotransplantation procedure was a safe, feasible, and effective surgical option for SHPT patients owing to the results that reveal no deaths occurred among the 47 study subjects[14]. When total parathyroidectomy with autotransplantation is done, a fragment of parathyroid tissue is placed into the sternocleidomastoid or forearm muscle or the subcutaneous abdominal adipose tissue. [13] In our center, a fragment of parathyroid tissue was placed into the deltoid or forearm muscle. There are no significant differences in the level of PTH postoperative between the two groups. However, placing into the deltoid can shorten the operation time and More convenient. The number of parathyroid glands found in our center was variant from 2 to 6. 4 glands were found in most of the cases(80.6%). In 11(5.47%)cases, 5 glands were found. There was only 1 patient who had 6 glands. However, 2 glands were found In 2(0.9%) cases, whose PTH levels dropped to normal after operation. Only 186(92.5%)patients' PTH levels dropped to normal at 7 days postoperative. The anatomic location of parathyroids was also variant. Glands were found in the thoracic cavity in 4(2.3%) cases, within thyroid in 4(2.3%) cases, posterior esophagus in 3(1.72%) cases and 1 (0.57%)in carotid sheath. 99mTc-MIBI is the most important imaging technique for these cases, especially for those in the thoracic cavity.

Besides, the present study provides evidence of the significant improvement of the QoL in patients undergoing total parathyroidectomy with autotransplantation. Patients with ESRD have important physical, mental, emotional, and psychosocial limitations that can have a major impact on QoL. In the present study, we prospectively evaluated 201 patients undergoing total parathyroidectomy, which analyzed preoperatively and postoperatively. We chose SF-36 survey to evaluate QoL. The SF-36 is a measure of health status and an abbreviated variant of it, and is commonly used in health economics as a variable in the quality-adjusted life year calculation to determine the cost-effectiveness of a health treatment. There are two limitations of the survey. One is not taking into consideration a sleep variable, the other is having a low response rate in the >65 population[15]

In our series, we observed significant improvements in PCS and MCS when comparing the preoperative and postoperative periods. Like previous research, there were also significant

improvements in almost all eight SF-36 dimensions before and after surgery. The only exception is Role-emotional (RE). However, a possible explanation for the less pronounced increase in our study may be a tendency for better REQoL at baseline. In our study the median RE score at time of diagnosis was higher (51.23 ± 4.80) compared with the previous study and did not improve to the same magnitude following parathyroidectomy.[16] Another explanation may be more than half patients were asymptomatic. In four RCTs only including asymptomatic PHPT patients using the SF-36 survey, three of the studies observed a modest improvement in two to four of the domains (emotional-, social function, general health, and vitality) in the parathyroidectomy compared to the medical observation group.[17-19]Whereas, the fourth RCT showed ambiguous results with a slight but significant difference in score in favour for surgery in emotional role and physical domain while the mental health subdomain scored higher (better) at 2 years follow-up in favour for medical observation.[20]

Materials and Methods

Subjects

During a 5 year period, from July 2013 to July 2018, a series of 201 consecutive unselected patients with SPTH underwent total parathyroidectomy by a single surgical team.

All patients had been on peritoneal dialysis or hemodialysis for more than three months, they were older than 18 years of age, had no mental disorders, were able to speak clearly, and had no evidence of malignancy. During hospital admission, we explained the research purposes to potential subjects and their families, and obtained informed consent. Demographic, biochemical, radiological, operative, and histological details were recorded in a prospective database. Demographic data included age, gender, education, occupation, primary disease that resulted in ESRD, dialysis modality (hemodialysis or peritoneal dialysis), dialysis frequency, total months of dialysis, presence of other chronic diseases. Routine blood biochemistry, blood cell counts, serum calcium, inorganic phosphate, and PTH were measured preoperatively, at the day after operation, 5-7 days postoperatively and at scheduled 6 months follow-up visit.

QoL and symptoms measurement tools

QoL was measured using the Medical Outcomes Study Short- Form Health Survey (SF-36) (21), adapted for the China population. (22) This instrument was selected because it is practical, well suited for clinical use, inexpensive and has been validated in a variety of disease conditions in adults, including ESRD. (23)SF-36 is a commonly applied questionnaire of 36 simple questions on eight health domains. Each dimension can be transformed into a 0 – 100 scale, where a higher score represents better selfperceived well-being and QoL. By means of 36 simple questions that are scored from 1 to 6, the SF-36 allows reproducible measures of patientperceived wellness on eight dimensions: physical functioning (PF), social functioning (SF), role-functioning emotional (RE), role-functioning physical (RP), vitality (VT), pain (BP), mental health (MH) and general health (GH) perceptions. These eight domains are divided into two summery scores: the physical component summary score (PCS) and the mental component summary score (MCS).

Patients completed the SF-36 questionnaire at 2 distinct times: after admission, prior to surgery and at 6 months follow-up.

Statistical analysis

Data analysis was performed by SPSS software, version 20 (SPSS, Chicago, IL). Nonskewed data are presented as means $\pm$ standard deviation (SD). Skewed data were analyzed by using the Anderson-Darling Normality Test, and presented as median values. As appropriate to the

presented data, Wilcoxon Matched-Pairs Signed-Ranks Test for paired observations, independent sample t-test, paired sample t-test, and Pearson chi2 were used were used to identify any correlations between clinical data, laboratory values, SF-36 scores and the response to surgery. A conservative alpha for any correlation was set at $p < 0.01$.

Statement

All experiments were approved by Medical Ethics Committee of the First Hospital Affiliated with Shandong First Medical University

Statement

All methods were performed in accordance with the relevant guidelines and regulations

Table 1. Patient preoperative characteristics

Variables	No. of pts.	Percentage %	Mean $\pm$ SD
Sex (male/female)	134/67		
Age (years)			46 ± 12
Duration of dialysis (months)			78 ± 34
Diabetes	13	6.5	
Hypertension	178	88.8	
Stroke history	50	25.2	
Drinking history	48	24.3	
Renal transplant history	4	2.0	

Table 2. Laboratory Data before and after surgery

Variables	Preoperative	Postoperative	6 months
Calcium (mg/dl)	3.62	1.84	1.99
Phosphorus (mg/dl)	2.30	1.60	1.43
PTH (pg/ml) (months)	2033.6	62.5	149.68

Table 3. SF-36 Health Survey Results

SF-36 Scale	Preoperative.	Postoperative 6 months	p
Physical functioning (PF)	48.57 ± 15.06	76.55 ± 17.43	<0.001
Role-physical (RP)	53.24 ± 30.44	84.74 ± 18.20	<0.001
Pain (BP)	41.31 ± 20.21	74.50 ± 17.95	<0.001
General Health (GH)	11.10 ± 5.70	17.46 ± 6.42	<0.001
Role-emotional (RE)	51.23 ± 4.80	52.40 ± 3.49	.087

Social function (SF)	48.86 ± 7.36	54.38 ± 13.71	.002
Vitality (VT)	29.43 ± 24.76	84.84 ± 18.37	<0.001
Emotional well-being (MH)	49.71 ± 4.17	64.00 ± 10.84	<0.001
Physical component summary (PCS)	38.56 ± 25.80	63.32 ± 31.06	<0.001
Mental component summary (MCS)	46.19 ± 17.47	62.53 ± 17.26	<0.001

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Author contributions statements

YuL Wang and RongZ Fu undertaken the project administration, Jia Xu wrote the main manuscript text , Jia Xu and Zil Zhang done the follow-up visit. All authors reviewed the manuscript.

Competing Interests

The authors declare no competing interests.

Data availability statement

Materials, data and associated protocols promptly are available to readers without undue qualifications in material transfer agreements.

Ethics approval and consent to participate

The ethics committee reviewed and discussed the research. The research is in accordance with the Helsinki Declaration of the World Medical Congress and approved by the Ethics Committee for its implementation.

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Figures

Figure 1

Number of glands

Figure 2

Anatomic location of glands