

Postsurgical Evaluation of Secondary Nephrogenic Hyperparathyroidism*

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Summary: Parathyroidectomy is useful for the treatment of secondary hyperparathyroidism (SHPT) caused by chronic renal failure. The following three types of parathyroidectomy can be performed: subtotal parathyroidectomy, total parathyroidectomy and total parathyroidectomy plus autologous transplantation (tPTX+AT). Each of the three types of surgery has advantages and disadvantages. The present study retrospectively analyzed the efficacy of tPTX+AT for the treatment of SHPT over 1 year. Thirty-seven patients who were diagnosed with secondary nephrogenic hyperparathyroidism and treated with tPTX+AT were selected between September 2014 and October 2016 and followed up for 1 year. Their average age was 66.5±46.0 years, and the average time of dialysis was 48.1±8.2 months. The patients' conditions, including the levels of intact parathyroid hormone (iPTH) and bone metabolism, were compared preoperatively and 1 and 7 days and 1, 3, 6 and 12 months after surgery. In addition, the postoperative complications, pathological data, SHPT recurrence and prognosis were examined. The results showed that the postoperative level of ostealgia and cutaneous pruritus significantly decreased in the patients. An inspection of the parathyroid tissues during the operation confirmed the presence of parathyroid gland hyperplasia with no carcinoma detected. Three patients with hoarseness recovered within 1 month, and 1 patient with unilateral recurrent laryngeal nerve injury improved after 6 months of voice training. Compared to the preoperative condition, the postoperative serum iPTH, serum calcium and serum phosphate levels were significantly decreased ($P<0.001$), and these differences remained significant 12 months after surgery. Compared to the preoperative condition, the alkaline phosphatase (ALP) concentration was decreased on postoperative day 1 ($P<0.05$), but no differences were observed on day 7 or at 1 month ($P>0.05$). The ALP levels continuously decreased at 3, 6 and 12 months ($P<0.01$). In conclusion, tPTX+AT significantly improves the quality of life and serum biomarker levels of these patients. The convenient surgical removal of the hyperplastic parathyroid gland for postoperative recurrence supports tPTX+AT as the recommended treatment for relevant patients.

Key words: nephrogenic hyperparathyroidism; parathyroidectomy; transplantation, autologous

Secondary hyperparathyroidism (SHPT) is a common complication of chronic renal failure and results in renal osteopathy, calcification of the heart, and increased calcification of soft tissue due to calcium and phosphorus metabolic disorders.

The conservative treatment is ineffective, and parathyroidectomy may effectively control the further development of the disease and improve the patients'

quality of life^[1-3]. Three types of parathyroidectomy can be performed, including subtotal parathyroidectomy (sPTX), total parathyroidectomy (tPTX) and total parathyroidectomy plus autologous transplantation (tPTX+AT). However, no large-scale controlled clinical trials have compared the long-term effects of these 3 surgeries. Historical studies investigating tPTX+AT lack large samples, and some studies have only monitored the calcium, phosphorus and parathyroid hormone (PTH) changes over 30 days postoperatively^[2]. The present study retrospectively analyzed tPTX+AT in a 1-year follow-up study.

1 SUBJECTS AND METHODS

1.1 General Data

Thirty-seven patients who were diagnosed with

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secondary renal hyperparathyroidism at the Fifth Affiliated Hospital of Sun Yat-sen University were selected between September 2014 and October 2016 and followed up for 1 year. tPTX+AT was considered for patients who exhibited a history of chronic renal insufficiency with long-term blood or peritoneal dialysis and the following conditions: SHPT combined with severe clinical symptoms, such as osteoarthralgia, myasthenia, skin itch, uremia, and arteriolopathy; persistent hypercalcemia (>10.0 mg/dL); hyperphosphatemia (>6.0 mg/dL); PTH >53.00 pmol/L; ineffective treatment with active vitamin D drugs; parathyroid color Doppler ultrasound, CT or MRI scans revealing at least 1 parathyroid hyperplasia larger than 1.0 cm; and the presence of erythropoietin-resistant anemia and dilated cardiomyopathy.

The following exclusion criteria were used: cardiopulmonary disorders, intolerance to general anesthesia, low turnover osteopathy, long-term oral intake of an aluminum agent preoperatively, severe infection, malignant tumor, bone-related diseases and reluctance to undergo surgery. This study was approved by the Institutional Review Board of the Fifth Affiliated Hospital of Sun Yat-sen University.

1.2 Preoperative Preparation

The preoperative treatment included a routine examination, surgical risk evaluation, anemia and blood pressure control, and management of hemodialysis-related complications. Oral calcitriol (0.5 μ g/day) was administered for 3 days preoperatively. Calcium carbonate and vitamin D3 tablets (0.6 g/day) were administered. Hemodialysis without heparin was administered 1 day prior to surgery.

1.3 Surgical Procedure

All patients underwent tPTX+AT. After successful general anesthesia induction, the surgeon performed an anterior cervical incision to expose the lateral lobe of the thyroid gland. The recurrent laryngeal nerve was identified, and the hyperparathyroid tissue was cut along the lateral lobe of the thyroid gland. The thymus tongue lobe was resected, and the peripheral fibrous adipose tissue was resected if necessary. The surgically removed hyperparathyroid tissue was preserved in ice-cold physiological saline buffer during the surgery. Four portions of the hyperparathyroid tissue were removed and confirmed via pathological examination. Hyperparathyroid tissues 0.2 cm^3 in size were selected and cut into 1 mm \times 1 mm \times 1 mm pieces and transplanted into the lateral forearm brachial and radial muscle fascia through a longitudinal incision. The autologous transplantation was not performed if only 3 pieces of hyperparathyroid tissue were removed.

1.4 Postoperative Management

Transient hypocalcemia may occur following parathyroid gland removal, and each patient received a calcium supplement postoperatively via vein infusion

and/or orally. The calcium infusion rate was 2 μ g/h. The calcitriol oral intake was 0.5 μ g/day, and adjustments were made based on the serum calcium concentrations. Hemodialysis was resumed 24 h postoperatively in each patient.

1.5 Follow-up

The postoperative examinations of the intact PTH (iPTH), serum calcium, serum phosphorus and alkaline phosphatase (ALP) levels were performed on day 1, week 1, and 1, 3, 6, and 12 months postoperatively. Surgical success was defined as a postoperative decrease in PTH greater than 50%. Recurrence was defined as a PTH level greater than 31.80 pmol/L.

1.6 Statistical Analysis

The data were analyzed using the Statistical Package for Social Sciences (SPSS version 13.0) for Windows (SPSS Inc., USA). The normally distributed data are represented as the means and standard deviations. Paired *t*-tests were used to compare the data before and after surgery. The nonnormally distributed data were analyzed with the rank-sum test. A *P*-value <0.05 represented statistical significance.

2 RESULTS

2.1 Demographic Characteristics of the Study Population

Thirty-seven patients, including 20 males and 17 females, were enrolled in this study. The average age was 48.1 ± 8.2 years (range: 22 to 69 years), and the average length of hemodialysis was 66.5 ± 46.0 months (range: 36–150 months). The subjects included 2 patients with brown tumors on the hip and shoulder, 4 patients with supramaxillary ectopic calcification, and 1 patient with skin ectopic calcification. Thirty patients presented with combined calcification in the cardiac valves and carotid artery. Thirty-two patients presented with osteodynia, 8 patients experienced whole-body skin itch, 34 patients exhibited renal hypertension, and 35 patients exhibited renal anemia.

2.2 Postoperative Outcomes

Only 3 parathyroid tissues were found in 1 patient. Four parathyroid tissues were found in the remaining patients, and autologous transplantation was performed in the forearm. The patients had hyperparathyroidism, and the pathological examination revealed no parathyroid tumors.

2.3 Postoperative Complications

The complications included 1 case of hemorrhage in the surgical area on the 2nd day postoperatively and 2 cases of hemorrhage in the surgical area on the 3rd day postoperatively. All patients with hemorrhage were treated in the operating room, and 2 patients required tracheotomy. Three patients had hoarseness, and 1 patient had unilateral recurrent nerve injury. All of these patients received voice training and the

symptoms improved after 6 months.

All patients with osteodynia and skin itch exhibited obvious alleviation 1 day postoperatively. Osteodynia persisted in 9 patients for 3 months postoperatively, but high serum calcium levels were not observed. One patient with an epidermal ulcer was improved, and antihypertensive drugs were withdrawn in 2 patients (2/34). Renal anemia was improved in 3 cases.

2.4 Changes in Serum Biochemical Indicators

The iPTH levels noticeably decreased on the 1st

postoperative day from a preoperative level of 211.10 (129.105, 254.95) pmol/L to 4.31 (1.93, 8.23) pmol/L. The postoperative examinations on day 7, 1st and 3rd month revealed iPTH levels of 2.06 (0.98, 4.20) pmol/L, 2.60 (1.22, 7.27) pmol/L, and 5.35 (1.64, 12.87) pmol/L, respectively (table 1), which were significantly lower than the preoperative level ($Z=-4.372$, $P=0.000$). The iPTH values at 6th and 12th month after surgery were significantly lower than the preoperative value ($Z=-4.345$, $P=0.000$; fig. 1A).

Table 1 Characteristics for patients with different histological types

	iPTH (pmol/L)	ALP (U/L)	Phosphorus (mmol/L)	Calcium (mmol/L)
Day 0	211.10 (129.105, 254.95)	193.00 (130.00, 629.50)	2.07 (1.82, 2.58)	2.53±0.25
Day 1	4.31 (1.93, 8.23)	182.00 (122.50, 511.50)	1.77 (1.05, 2.32)	2.16±0.24
Day 7	2.06 (0.98, 4.20)	258.00 (138.00, 679.50)	1.12 (0.84, 1.74)	2.15±0.28
1 M	2.60 (1.22, 7.27)	193.00 (123.00, 634.50)	1.12 (0.77, 1.67)	2.12±0.37
3 M	5.35 (1.64, 12.87)	105.00 (79.50, 254.00)	1.53 (0.86, 2.00)	2.14±0.42
6 M	6.04 (2.45, 17.33)	84.00 (60.50, 204.00)	1.59 (1.20, 2.35)	2.20±0.32
12 M	18.45 (4.40, 34.21)	73.00 (53.00, 123.00)	1.53 (1.10, 2.20)	2.31±0.23
Z/F	Z=81.817	Z=83.288	Z=53.535	F=6.873
P	0.000	0.000	0.000	0.001

The data of the iPTH, ALP and phosphorus levels are reported as the median (25%, 75%). The calcium level is presented as $\bar{x}\pm s$. Day 0 indicates the day prior to surgery. Day 1 indicates the 1st day after surgery. M indicates month(s) after surgery. The Friedman test was used to determine the iPTH, ALP and phosphorus levels. A multivariate test was used to assess the calcium levels.

The ALP levels were decreased postoperatively compared to the preoperative levels ($Z=-2.099$, $P=0.036$), but these measurements did not obviously differ on day 7 and 1 month after surgery ($Z=-1.063$, $P=0.288$; $Z=-0.471$, $P=0.638$). The ALP levels continuously decreased at 3, 6 and 12 months ($Z=-3.417$, $P=0.001$; $Z=-4.157$, $P=0.000$; $Z=-4.2924$, $P=0.000$; fig. 1B).

The serum calcium significantly changed in the 37 patients. The measurements were 2.53±0.25 mmol/L preoperatively and 2.16±0.24 mmol/L on postoperative day 1 ($P=0.0000$). The serum calcium levels of the 37 patients significantly differed on postoperative day 7 and 1 year after surgery ($F=6.873$, $P=0.001$) compared to the preoperative levels. Thirty-four patients (91.9%) required intravenous, oral or high calcium dialysis during the 1st postoperative week, and 30 patients needed intravenous calcium supplement (81.1%) during the 1st postoperative month. Nineteen patients needed intravenous calcium supplement (51.4%) during the 3rd month postoperatively, and 3 patients required intravenous calcium delivery (8.1%) during the 12th postoperative month (fig. 1C).

The serum phosphorus levels were decreased at 1 day postoperatively, and the phosphorus measurement reduced from 7 days to 3 months postoperatively. The phosphorus measurements obviously differed 1 year after surgery as compared with those before surgery (fig. 1D).

3 DISCUSSION

Secondary renal hyperparathyroidism is a common complication of chronic renal failure that injures multiple systems in the body^[3] and poses a severe threat to the patients' lives and quality of life^[4, 5]. Parathyroidectomy is one option when conservative treatment fails. The following three types of parathyroidectomy can be performed: tPTX, sPTX and tPTX+AT.

sPTX exhibits several advantages, including a short operation time, reduced injury and easy management of low calcium levels postoperatively^[6]. One disadvantage is that the postoperative recurrence rate is higher than that of tPTX^[7].

tPTX (without autologous transplantation) exhibits a low recurrence rate^[8], few postoperative complications and a short hospitalization time. tPTX is the optimal treatment for chronic renal failure with hyperparathyroidism^[9], but one disadvantage is a low refractory serum calcium level, which may be treated with calcium and calcitriol. Whether a long-term low postoperative PTH level is beneficial to patients is unclear.

Most publications recommend tPTX+AT, which effectively alleviates the symptoms and avoids refractory low calcium levels postoperatively by maintaining normal parathyroid function^[10]. Parathyroid tissue is easily removed after transplantation with little injury. The autologous

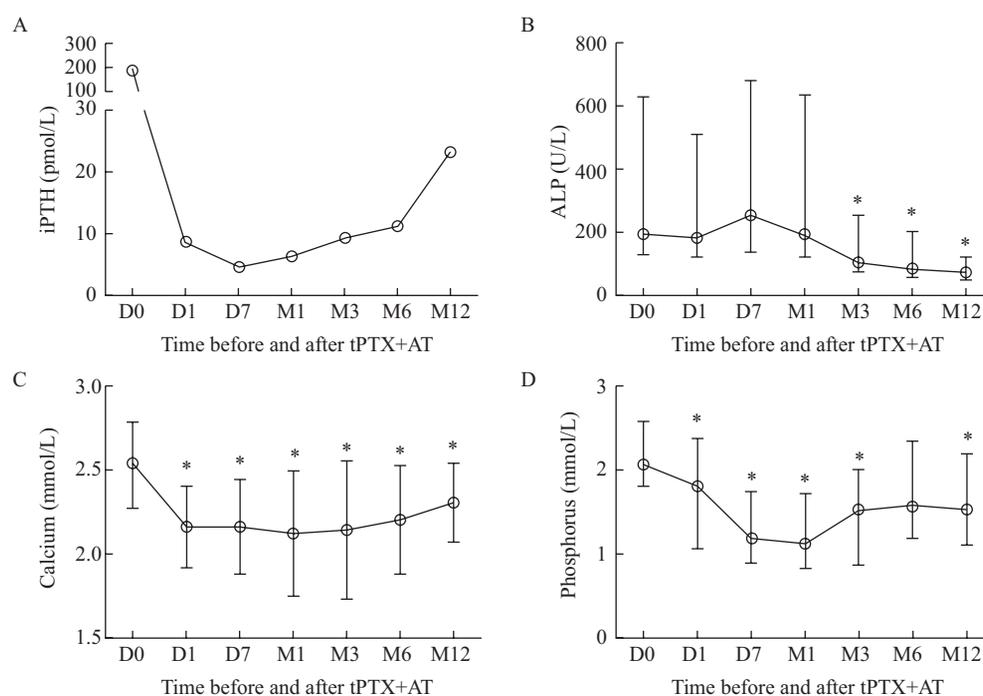


Fig. 1 Serum levels of the intact parathyroid hormone (iPTH) (A), alkaline phosphatase (ALP) (B), calcium (C) and phosphorus (D) before and after total parathyroidectomy plus autologous transplantation (tPTX+AT)

Before tPTX+AT: baseline (D0). After tPTX+AT: 1 day (D1), 7 days (D7), 1 month (M1), 3 months (M3), 6 months (M6) and 12 months (M12) after tPTX+AT. * $P < 0.05$ compared to the baseline data (D0)

transplantation site may be inside the brachial radial muscle or sternocleidomastoid muscle^[11]. Our study used the lateral humeral radial muscle fasciae due to the convenience of removal under local anesthesia. Based on the retrospective study, few patients underwent the other two types of surgery, and follow-up was insufficient. Therefore, we only analyzed tPTX+AT.

Parathyroidectomy under endoscopy maintains a smaller incision, but it is not recommended due to the high cost, difficulty in locating the gland and difficulty in stopping bleeding in cases of intraoperative hemorrhage. Robotic parathyroidectomy provides superior early cosmesis^[12] and has higher success rates^[13]; however, robotic parathyroidectomy differs from parathyroidectomy under endoscopy, and clinical experience with this procedure is limited^[14].

Some studies have demonstrated that nanoparticle-negative imaging can clearly locate the parathyroid gland during surgery^[15], but this technique is expensive. Intraoperative MRI is a new technique that might be useful for the identification of parathyroid adenomas^[16]. One study demonstrated that four-dimensional computed tomography (4DCT) can aid surgical planning in cases without concordant sestamibi-SPECT (SeS) and ultrasound (US) findings^[17]. Our study demonstrated that energy spectrum CT or diffusion-weighted MRI may be a better technique (manuscripts in preparation).

No randomized controlled trial has examined the

3 types of surgeries to determine which is the best technique. A study by Rajeev showed that tPTX is superior to sPTX in the short to intermediate term^[18]. Recently, one study showed that sPTX and tPTX-AT have similar outcomes^[19]. SHPT recurs due to the presence of residual parathyroid gland. Therefore, we prefer tPTX+AT and performed a retrospective study of this specific technique with a 1-year follow-up period.

The following three types of PTH are detected in circulating blood: iPTH, N-terminal PTH, and C-terminal PTH^[20]. iPTH is an indicator used in the clinic for monitoring of renal osteopathy and exhibits a short half-life of approximately 1.68 ± 0.94 min^[21]. Therefore, the PTH concentrations dramatically decrease after surgery. However, the high frequency of blood collection, the need for rapid diagnostic equipment and prolonged operative time make this method unpopular. Our study ensured successful surgery by using a complete preoperative examination and locating the 4 parathyroid glands during surgery. We did not use intraoperative PTH monitoring. One patient exhibited increased PTH levels 2 weeks after surgery after an initial postoperative decline, which was likely due to the localization of only 3 glands in this patient. The 1-year follow-up evaluation revealed no apparent residual parathyroid gland on MRI or ultrasonic imaging of the neck. The remaining 36 patients exhibited a decline in PTH to the lowest level on postoperative day 1 to day 7, and the PTH levels increased over the

subsequent days, indicating the proper functioning of the transplanted parathyroid glands. Our study found that 39% of the patients had functioning parathyroid glands on day 7 using a PTH assay of blood samples taken from the proximal transplantation site and the parallel side without transplantation. In total, 76% of the patients exhibited functioning parathyroid glands on day 14 using the same assay. In total, 13% of the patients exhibited lower blood PTH measurements at the transplanted site. This finding indicates that the survival rate of transplanted glands is low, which may be a reason for another surgical operation because the local blood supply is insufficient due to the excessive bandage pressure after surgery, and the activity of the selected transplanted glands is poor. These patients required long-term calcium compensation treatment. Two patients were diagnosed with transplanted parathyroid gland hyperfunction during the 1-year follow-up period. This finding may be due to local transplanted gland hyperplasia due to hyperfunction or excessive number of transplanted glands. These patients underwent a removal surgery under local anesthesia.

Our study demonstrated that the ALP levels declined 1 day postoperatively and were higher on day 7 than the preoperative levels. The slow decline 90 days after surgery indicates the cessation of the high turnover of bone and the long recovery time of normal bone metabolism, which is consistent with previous reports^[22, 23]. The absence of continuous PTH stimulation and postoperative calcium compensation may produce a decline in the ALP levels.

Bone calcium loss and the loss of PTH control, i.e., serum calcium starvation resulting from parathyroidectomy, may lead to twitching, hand numbness, fatigue, or arrhythmia during hemodialysis. We compensated calcium using a dose calculated from the preoperative PTH measurements as recommended in the literature^[24]. A study showed that low postoperative calcium levels are positively correlated with the preoperative PTH and ALP levels, validating the need for calcium compensation in the high PTH patients to avoid low calcium symptoms^[25]. The low serum calcium levels resulted from low PTH following parathyroidectomy, consequent blood calcium flux into the bones and less intestinal calcium absorption. The combination of serum calcium uptake by bones and lower intestinal absorption after the reduction in PTH reduced the serum calcium level to 60% postoperatively in some cases, which is similar to a previous report^[26]. However, some patients did not exhibit low serum calcium levels, which cannot currently be explained. The postoperative serum phosphorus levels were significantly decreased, which is consistent with other reports. The progressively lower levels of serum ALP and phosphorus supported the increase in bone density,

which improved the symptoms and maintained a better prognosis in the long term.

The blood phosphorus levels were significantly reduced postoperatively, which is consistent with a previous report^[27]. A progressive reduction in the blood ALP and phosphorus levels indicates improved bone density, which supports long-term clinical improvement and a good prognosis.

The recurrent laryngeal nerve injury rate varies in different reports^[28]. Four cases of hoarseness were observed in our study, including 3 cases resulting from a side effect of the ultrasound blade and electric heat blade, and the symptom recovered in 1 month, and 1 case of unilateral recurrent laryngeal nerve injury, and that improved after 6 months of voice training.

Overall, our study demonstrated that patients undergoing tPTX+AT exhibited apparent improvements in the serum biochemical indicators and reduced osteodynia, skin itch, sleeplessness and epidermal ulcers during the 1-year follow-up period. Our patients also reported improved nutrition and quality of life during the 1-year follow-up period. Therefore, tPTX+AT is the recommended surgery for patients who experience failure of internal medicine treatment and are suitable candidates for parathyroidectomy.

In conclusion, tPTX+AT significantly improves the quality of life and serum biomarker levels of patients with SHPT caused by chronic renal failure. The convenient surgical removal of the hyperplastic parathyroid gland and postoperative benign conditions support tPTX+AT as the recommended treatment for relevant patients.

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Conflict of Interest Statement

The authors declare that they have no conflicts of interest.

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