Short-term efficacy of surgical treatment of secondary hyperparathyroidism

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Abstract. – OBJECTIVE: We wished to explore short-term efficacy of surgical treatment of secondary hyperparathyroidism in patients with the end-stage renal disease. The treatment methods were subtotal or total parathyroidectomy, or total parathyroidectomy and autotransplantation.

PATIENTS AND METHODS: 63 patients with secondary hyperparathyroidism were randomly divided into three groups which were respectively treated with subtotal parathyroidectomy (SPTX group), total parathyroidectomy (TPTX group), or total parathyroidectomy and autotransplantation (TPTX+AT group). The surgical outcomes included operating time, transoperative bleeding volume, length of stay, and cost of hospitalization. In addition, complication (e.g., postoperative wound infection, hematoma, hypocalcemia in perioperative period) rates were compared among groups. Blood levels of calcium and parathyroid hormone were assessed before the surgery, and 1 day, 1 months, 3 months and 6 months after the surgery. The follow-up period comprised 6 months.

RESULTS: Surgical outcomes were the lowest in SPTX group and the highest in in TPTX+AT group. There were no significant differences among groups in treatment efficacy. Complication rates were also comparable among the three groups. The occurrence of hypocalcemia was the lowest in SPTX group ($p < 0.05$ vs. other groups). However, postoperative relapse rate was the highest in this group ($p < 0.05$ vs. other groups). There were no correlations between the levels of blood calcium and PTH preoperatively and postoperatively.

CONCLUSIONS: Appropriate surgical treatment is selected in accordance with the patient's condition and willingness, with the attention paid to the prevention of hypocalcemia.

Key Words:
 Total parathyroidectomy, Autotransplantation, Subtotal parathyroidectomy, Total parathyroidectomy, Secondary hyperparathyroidism, Blood calcium, Parathyroid hormone.

Introduction

Patients with the end-stage renal disease survive longer after hemodialysis. However, a full removal of toxins by hemodialysis is presently not achievable[1,2]. For example, parathyroid hormone, the hormone regulating calcium and phosphorus metabolism, excessively accumulates in these patients, causing multiple complications, such as osteodynia, pruritus, multiple fractures, metastatic calcification, or secondary hyperparathyroidism. This diminishes the quality of life[3-5].

At present, the main approach for treating secondary hyperparathyroidism is administration of active vitamin D_3. This approach, however, has poor efficacy in some of patients with moderate to severe secondary hyperparathyroidism. Subsequently, about 10% patients with secondary hyperparathyroidism require surgical treatment[4-7]. The surgical treatment options are subtotal parathyroidectomy, total parathyroidectomy, and total parathyroidectomy and autotransplantation[8]. There have been no previous studies to compare these three surgical options. To address this, we conducted a randomized study to compare surgery, efficacy, and safety indices of these three surgical approaches.

Patients and Methods

Patients

Sixty-three patients with secondary hyperparathyroidism who needed surgical treatment were enrolled from February 2010 throughout February 2014. All patients met the following inclusion criteria: (1) positive diagnosis of chronic renal failure (uremia stage)[1], (2) preoperative secondary hyperparathyroidism, (3) no symptom

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improvement after 3-6 months of standard medical therapy and blood parathyroid hormone (PTH) levels of > 1000 ng/L, (4) severe hypercalcemia or hyperphosphatemia; more than one parathyroid hyperplasion lesion on ultrasonography, with a diameter of > 1 cm, (5) normal hepatic function and parameter of blood coagulation. Exclusion criteria were: primary hyperparathyroidism, severe diseases of other organs, inability to cooperate during the study and subsequent follow-up.

The study design was approved by the Review Board of our Hospital, and all patients signed informed consent. There were 38 patients of male and 25 patients of female gender, with the age ranging from 28 to 72 years ([mean ± SD] 53.2 ± 12.7 years). The duration of the disease ranged between 3 and 18 years, with the average of 7.9 ± 3.2 years. All patients experienced bone pain and pruritus.

The patients were randomly divided to receive subtotal parathyroidectomy, total parathyroidectomy, or total parathyroidectomy and autotransplantation. The three patient groups were comparable with regard to patient gender, age, and duration of the disease.

Surgery

Subtotal parathyroidectomy was done after general anesthesia. Patients were in supine position for anterior cervical transverse incision. Anterior cervical skin flap was dissociated by a blunt dissection method. Anterior cervical muscle was incised to expose thyroid gland. The middle thyroid vein was disconnected to expose dorsal thyroid gland. Caution was undertaken to protect the recurrent laryngeal nerve. The intumescent parathyroid gland was defined, and the smallest part of the gland was retained at the size of 5 mm × 5 mm × 3 mm. Frozen sections were prepared from the excised tissue and verified to be the parathyroid gland.

Patients in total parathyroidectomy group underwent the following procedure. All of the parathyroid gland tissue was exposed and excised. Frozen sections were prepared as above to confirm the removal of the parathyroid gland.

Finally, total parathyroidectomy and autotransplantation was done as follows. Small amount of normal tissue was selected from the excised parathyroid tissue and trimmed to a size of 1 mm × 1 mm × 1 mm. After that, the tissue was implanted into forearm muscle at the side of the non-dialysis fistula.

Blood calcium levels were monitored in all three groups after the surgery. Patients with hypocalcemia received calcium carbonate. In case of severe hypocalcemia, 10% calcium gluconate was injected intravenously[9].

Outcomes

Surgical outcomes were operating time, transoperative bleeding volume, length of stay, and cost of hospitalization. The treatment was considered significantly effective if there were complete improvement of bone pain, pruritus, and abnormal bone metabolism, and PTH levels were < 65 ng/L for 7 days after the surgery. If patients exhibited partial improvement of bone pain, pruritus, and abnormal bone metabolism, and PTH of < 65 ng/L for 7 days after the surgery, this was ranked as an effective treatment. Finally, an ineffective treatment was assigned if patients did not exhibit any improvement in bone pain, pruritus, or abnormal bone metabolism, and if their PTH was > 65 ng/L for 7 days after the surgery[10].

We also registered complications after the surgery, such as wound infections, wound hematomas, hypocalcemias, or recurrent laryngeal nerve injuries. Blood calcium and PTH were detected postoperatively.

The patients were followed up for 6 months. Relapse conditions were monitored during the follow-up. Blood calcium and PTH were detected at 1, 3, and 6 months after the surgery.

Statistical Analysis

SPSS 14.0 (IBM, New York, NY, USA) was utilized for statistical analysis. Quantitative data are presented as mean ± SD. The chi-square test was used for comparison of qualitative data, and partition of chi-square was used for pairwise comparisons. The ANOVA test was used for analysis of quantitative data (e.g., operation time, transoperative bleeding volume, length of stay, cost of hospitalization) among groups. The LST-t test was used for pairwise comparisons of quantitative data. For comparison of blood calcium and PTH at different time points, repeated measures ANOVA test was used. $p < 0.05$ was considered statistically significant.

Results

Study Outcomes

The surgical outcomes (operation time, transoperative bleeding volume, length of stay, and

cost of hospitalization) were the lowest in patients who underwent subtotal parathyroidectomy ($p < 0.05$ *vs.* two other groups; Table I), and the highest in the patients after total parathyroidectomy and autotransplantation.

Short-Term Efficacy in Study Groups

There was no significant difference in short-term efficacy among three groups (Table II).

Complications and Disease Relapse

There was no significant difference among groups with regard to occurrence of postoperative wound infections, hematomas, or recurrent laryngeal nerve injuries (Table III). The occurrence of hypocalcemia was the lowest in patients who underwent subtotal parathyroidectomy ($p < 0.05$ *vs.* two other groups; Table III). However, postoperative relapse rates were significantly higher in this group compared with two other groups ($p < 0.05$; Table III).

Preoperative and Postoperative Levels of Blood Calcium and PTH

The kinetics of blood calcium and PTH levels before and after the operation were different in patient groups (Table IV). PTH levels on day 1 after the operation were decreased in all three groups (Table IV).

Discussion

Secondary hyperparathyroidism is a common and severe complication of the end-stage renal disease[11,12]. Studies indicate that PTH levels in patients with glomerular filtration rate are higher than 50-60 ml/min[12]. Glomerular filtration rate negatively correlates with PTH. In patients with the end-stage renal disease, prevalence of secondary hyperparathyroidism is as high as 86.55%[13]. This condition mainly manifests as osteolysis, heterotopic ossification, and cardiovascular events[13]. The main approach to treat secondary hyperparathyroidism is to administer vitamin D_3[14]. However, in patients with ineffective treatment results, hypercalcemia / hyperphosphatemia, severe condition, or patients with continuous PTH of > 1000 ng/L, and patients with parathyroid adenoma nodules, surgical treatment is recommended[15]. At present, there are three principal operational approaches for treating secondary hyperparathyroidism: subtotal parathyroidectomy, total parathyroidectomy, or total parathyroidectomy and autotransplantation[16]. Most reports pertaining to efficacy of each of these three surgical approaches are either observational or retrospective, and there is a clear lack of randomized studies. Here we present a result of a prospective randomized trial comparing these three approaches.

Malmaeus et al[17] retrospectively compared the outcomes of subtotal parathyroidectomy and total parathyroidectomy/autotransplantation. They reported that operating time, transoperative bleeding volume, length of stay, and cost of hospitalization were significantly higher in patients after the latter method. We also observed a similar trend in our study. This is because the parathyroid gland tissue is small, and its position needs to be determined by imaging methods preoperatively to reduce operating time. Total parathyroidectomy with autotransplantation requires additional operating time. Still, there was no significant difference in the efficacy of surgical treatment among the three main operation methods. For example, PTH levels on day 1 post-operation were decreased in all three groups, indicating equal efficiency of these surgical approaching in reducing PTH levels. Chou et al[18] reported no occurrence of postoperative infection and hematoma, but there were inadequate excision

Table I. Outcomes in study groups.

Groups	Operating time, min	Transoperative bleeding volume, ml	Length of stay, days	Cost of hospitalization, yuan
Subtotal parathyroidectomy	42.5 ± 18.8	16.5 ± 2.8	7.5 ± 2.0	4524.3 ± 280.4
Total parathyroidectomy	68.6 ± 24.3*	25.5 ± 5.4*	10.1 ± 3.1*	5824.1 ± 386.0*
Total parathyroidectomy and autotransplantation	85.5 ± 30.2*,&	26.4 ± 6.2*	12.2 ± 3.8*,&	6541.1 ± 420.1*,&

Footnote: Data are presented as mean ± SD. *$p < 0.05$ vs. subtotal parathyroidectomy group; &$p < 0.05$ vs. total parathyroidectomy group.

Table II. Treatment efficacy in study groups.

Groups	Significantly effective	Effective	Ineffective	Efficiency
Subtotal parathyroidectomy	4	12	5	76.2%
Total parathyroidectomy	5	12	4	81.0%
Total parathyroidectomy and autotransplantation	5	13	3	85.7%
p				0.734

Table III. Complications and disease relapse.

Groups	Wound infection	Hematoma	Hypocalcemia	Recurrent laryngeal nerve injury	Relapse
Subtotal parathyroidectomy	0 (0)	1 (4.8)	2 (9.6)	0 (0)	8 (38.1)
Total parathyroidectomy	1 (4.8)	0 (0)	12 (57.1)	0 (0)	1 (4.8)
Total parathyroidectomy and autotransplantation	0 (0)	0 (0)	5 (23.8)	1 (4.8)	2 (9.6)
p	0.362	0.362	0.003	0.362	0.009

Footnote: Data are presented as absolute numbers (%).

and hypocalcemia after using total parathyroidectomy with autotransplantation. We did not observe any differences in the occurrence of wound infections, hematomas, or recurrent laryngeal nerve injuries among patients treated with one of these three approaches. Still, the rates of hypocalcemia in the total parathyroidectomy group were the highest. This could be because total excision of parathyroid glands drastically diminishes the PTH-induced rebounding reduction of blood calcium. Hypocalcemia also occurred in two other groups, indicating that blood calcium should be closely detected and timely replenished if needed.

Secondary hyperparathyroidism relapse is also the key factor that affects the success of the operation. Sakman et al[19] reported that relapse occurs in 50% of patients treated with subtotal parathyroidectomy. A ten-year follow-up study showed the relapse rate being at 21.4% after total parathyroidectomy and autotransplantation[20]. In our study, the relapse rates were comparable to the previous study: 38.1% in the subtotal parathyroidectomy group at 6 months, which was significantly higher than in two other groups.

We also analyzed an association between PTH and blood calcium levels. The calcium and phosphorus metabolism is abnormal in these patients.

Table IV. Preoperative and postoperative levels of blood calcium and PTH.

Outcomes	Groups	Preoperative	Postoperative 1 day	1 month	3 months	6 months
Blood calcium	Subtotal parathyroidectomy	2.21 ± 0.48	2.15 ± 0.78	2.10 ± 0.89	2.25 ± 0.48	2.40 ± 0.52
	Total parathyroidectomy	2.26 ± 0.49	2.20 ± 0.34	1.39 ± 0.40	1.55 ± 0.52	1.60 ± 0.45
	Total parathyroidectomy and autotransplantation	2.18 ± 0.55	2.12 ± 0.24	1.56 ± 0.91	1.90 ± 0.88	2.27 ± 0.78
PTH	Subtotal parathyroidectomy	1895.42 ± 542.27	185.43 ± 85.4	190.22 ± 90.89	205.46 ± 85.41	225.8 ± 90.21
	Total parathyroidectomy	1985.22 ± 684.15	54.43 ± 10.22	65.41 ± 19.41	60.41 ± 18.41	55.42 ± 17.56
	Total parathyroidectomy and autotransplantation	1798.32 ± 785.4	48.57 ± 14.43	72.68 ± 25.41	80.21 ± 20.41	85.12 ± 26.41

Footnote: Data are presented as mean ± SD.

Decreased glomerular filtration rate causes hyperphosphatemia; this, coupled with deficiency of active vitamin D_3, metabolic acidosis and other factors, leads to calcium deficiency[20]. Hyperphosphatemia and hypocalcemia causes increased secretion of PTH, inducing secondary hyperparathyroidism. Secondary hyperparathyroidism promotes osteoclast activity and increases the ratio of ionized calcium. Therefore, blood calcium levels in these patients can be normal, but calcium can still be deficient. This explains the lack of an association with blood calcium and PTH levels preoperatively. However, after the surgery, serum PTH levels diminish markedly, causing rebounding reduction of blood calcium. Due to the existing part of parathyroid tissue in patients undergoing subtotal parathyroidectomy, decrease in PTH levels is relatively less pronounced, similar to decrease in blood calcium. The occurrence of hypocalcemia is lower. This is in contrast to total parathyroidectomy with autotransplantation, which avoids the relapse and occurrence of sever hypocalcemia observed in patients after subtotal parathyroidectomy.

Conclusions

Subtotal parathyroidectomy, total parathyroidectomy and total parathyroidectomy with autotransplantation are the surgical methods used to treat patients with secondary hyperparathyroidism after failure of treatment with vitamin D_3. The selection of the appropriate surgical approach should be done in accordance with the patient's condition and consent, with especial attention addressed to prevention of hypocalcemia.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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