

Surgical treatment of secondary hyperparathyroidism

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Abstract

Aim: Initial treatment of secondary hyperparathyroidism (sHPT), often seen as a result of end-stage renal failure, is medical treatment. Treatment-resistant patients require surgery. The aim of this study is to evaluate the diagnosis and treatment of patients who underwent sHPT.

Material and Methods: Twenty-one patients who were operated for sHPT were included in the study. The demographic data of the patients and correlation of imaging results with correct localization and pathological diagnosis were evaluated.

Results: The mean age of the patients was 45.80 ± 1.10 . While the number of patients with growth in a parathyroid gland was 7 (32%), the number of patients with multiple glands was 8 (39%). According to scintigraphy evaluation, the same values were 4 (19%) and 12 (57%) patients. 7 (34%) patients were underwent adenoma excision, 11 (52%) patients were underwent subtotal parathyroidectomy and 3 (14%) patients were underwent total parathyroidectomy + parathyroid auto-implantation. Persistent hyperparathyroidism was seen in 2 patients who underwent subtotal parathyroidectomy and 1 patient who underwent adenoma excision.

Conclusion: Today, the treatment of sHPT is still the best treatment option, and as a treatment, subtotal parathyroidectomy and total parathyroidectomy + parathyroid autoimplantation surgery should be preferred.

Keywords: Chronic kidney failure; parathyroid hormone; secondary hyperparathyroidism; total parathyroidectomy

INTRODUCTION

Secondary hyperparathyroidism (sHPT) is defined as excessive parathormone (PTH) secretion caused by external factors stimulating the parathyroid glands. Although there are many causes of sHPT, it usually develops due to end-stage renal failure. sHPT is an important cause of morbidity and mortality potentially leading to metabolic bone diseases, vascular and soft tissue calcifications and severe cardiovascular events (1,2).

Pathophysiological factors that play a role in the development of hyperparathyroidism are hyperphosphatemia and low levels of 1,25-OH vitamin D₃. Hyperphosphatemia due to decrease in renal excretion of phosphate due to renal failure causes hypocalcemia by forming complexes with calcium (Ca), and directly affects PTH synthesis and parathyroid cell proliferation and causes hyperparathyroidism. On the other hand, 25-cholecalciferol conversion to 1,25-dihydroxycholecalciferol (active vitamin D₃) in the kidney reduces absorption of calcium from the intestine and indirectly causes hyperparathyroidism (2,3). While

some of the patients with sHPT may be asymptomatic patients presented only by laboratory and radiological examinations, another part of patients may present to the hospital with serious symptoms (4).

There are two treatment options for sHPT patients: medical and surgical. Initially, the majority of patients undergo medical treatment. Agents such as phosphate binders, vitamin D analogues, vitamin D receptor activators and calcimimetics are used in medical treatment, and surgical treatment is needed in approximately 10% of patients where medical treatment fails or is ineffective. Surgical treatment options include subtotal parathyroidectomy, total parathyroidectomy and total parathyroidectomy with autotransplantation (3,5). The aim of this study was to analyze the diagnosis and clinical follow-up of patients who underwent surgery for sHPT in our clinic

MATERIAL and METHODS

Study Plan

In this study, 21 sHPT patients operated from two different centers in June 2013-May 2016 according to

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the surgical indications recommended by the National Kidney Foundation of USA (6) (Table 1) was included after surgical local ethics committee approval. Preoperative and postoperative clinical findings, laboratory and imaging results and pathological diagnoses of the patients were examined. In addition to demographic data, the relationship between preoperative imaging results and correct localization and pathologic diagnosis was evaluated. The relationship between surgery and laboratory values in the early postoperative period was investigated.

Surgical Technique

The thyroid lobes are reached by standard thyroidectomy incision for bilateral neck exploration under general anesthesia. The thyroid lobes are released so that the posterior capsules of the thyroid lobe are visible. For easy detection of parathyroids, dissection is started near the carotid sheath. All parathyroid glands are seen without damaging the blood circulation. If the patient is decided to undergo a subtotal parathyroidectomy, first half of the normal or close to normal-looking parathyroid is removed. After the remaining half of the parathyroid tissue is seen to have good blood circulation, the other glands are removed. If a total parathyroidectomy is decided, all glands are removed and half of the normal-looking gland is autotransplanted into the sternocleidomastoid muscle or into the forearm.

Usually in the postoperative period, patients are followed closely at the hospital for at least 48 hours. Serum Ca, phosphor (P), albumin and PTH values are obtained as standard in the 24th and 48th hours in patients without clinically obvious hypocalcemia. In the postoperative period, oral Ca replacement is initiated to prevent hypocalcemia due to hungry bone syndrome. Despite oral replacement, patients with clinically severe hypocalcemia and patients with Ca levels below 7 mg / 100 ml are received parenteral Ca supplementation.

Statistical Analysis

Data were analyzed by SPSS (Windows 15.0). Categorical variables were expressed as number (n) and percentage (%). Numerical variables were expressed as mean \pm standard deviation and Student t test was used to compare the means of two independent groups. A p value of <0.05 was considered statistically significant for all results

RESULTS

The demographic data of the patients are summarized in Table 2. The mean age of the patients was 45.80 \pm 1.10 and the mean age was 8/13. The mean follow-up was 20 months. The most common symptom was joint pain and usually associated with other symptoms. The number of patients with severe bone pain was 4 (19%). Most of the patients were followed up with hemodialysis and only one patient was followed with peritoneal dialysis. The duration of medical treatment for sHPT was at least 2 years.

Table 1. sHPT Surgical indications recommended by the American Kidney Foundation

- 1.High PTH level (PTH> 500 pg / mL)
 - 2.Detection of large parathyroid glands by imaging methods
 - 3.Radiological "osteitis fibrosa cystica" finding or high bone turnover rate based on metabolic markers
- (1) + (2) + (3) and at least one of the following factors:**
- a. Hypercalcemia
 - b. Uncontrolled hyperphosphatemia
 - c. Progressive ectopic calcification
 - d. The presence of serious symptoms
 - e. Severe skeletal deformity
 - f. Progressive bone loss
 - g. Kalsifilaksis
 - h. Erythropoietin resistant anemia
 - i. Serious itching

(Note: PTH; parathyroid hormone)

Table 2. Demographic characteristics of patients

Gender (Male/Female)	13 (%61.9) / 8 (%38.1)
Mean age (years)	45.80 \pm 1.10
Complaints	
Arthralgia	3 (%14)
Weakness	1 (%5)
Bone pain	4 (%19)
Itching	2 (%9)
Multiple	11 (%67)
Dialysis duration (years)	7.85 \pm 3.39
Previous operations	
Parathyroidectomy	2 (%9)
Kidney transplantation	2 (%9)
Operation Type	
Adenoma excision	7 (%34)
Subtotal parathyroidectomy	11 (%52)
Total parathyroidectomy + implantation	3 (%14)
Length of stay (days)	5.76 \pm 2.91
Reoperation rate	3 (%14)
Pathology	
Adenoma	8 (%39)
Hyperplasia	13 (%61)

Table 3. Laboratory and imaging results of patients	
Preoperative laboratory data	1979.39 ± 879.38
PTH (pg/mL)	10.37 ± 1.12
Ca (mg/dL)	5.63 ± 0.92
P (mg/dL)	
Postoperative laboratory data	
PTH (pg/mL)	225.15 ± 231.80
Ca (mg/dL)	7.17 ± 1.20
P (mg/dL)	4.15 ± 0.62
Ultrasonographic pathological gland localization	
Right upper	2 (%9)
Right lower	3 (%14)
Left upper	0 (%0)
Left lower	2 (%9)
Multiple	8 (%39)
Normal	6 (%29)
Others (intrathyroidal, mediastinum etc.)	0 (%0)
Ultrasonographic histopathological appearance	
Adenoma	8 (%39)
Hyperplasia	7 (%33)
Normal	6 (%28)
Scintigrafic pathological gland localization	
Right upper	1 (%5)
Right lower	2 (%9)
Left upper	0 (%0)
Left lower	1 (%5)
Multiple	12 (%39)
Normal	5 (%24)
Others (intrathyroidal, mediastinum etc.)	0 (%0)
Scintigrafic histopathological appearance	
Adenom	10 (%48)
Hiperplazi	6 (%28)
Normal	5 (%24)

(Note: PTH; parathyroid hormone, Ca; calcium, P; phosphor)

Laboratory and imaging data of the patients are given in Table 3 and 4. Preoperative mean PTH, Ca and P levels were 1979.39±879.38 pg / mL, 10.37±1.12 mg / dL and 5.63±0.92 mg / dL, respectively. The same parameters during the postoperative discharge were 225.15±231.80 pg / mL, 7.17±1.20 mg / dL and 4.15±0.62 mg / dL,

respectively. Ultrasonographic evaluation showed that 7 (32%) patients had growth in one parathyroid gland while 8 (39%) patients had growth in more than one gland. According to scintigraphic evaluation, the same values were 4 (19%) versus 12 (57%) patients. Six patients (29%) had normal ultrasonographic evaluation despite hyperparathyroidism, and 5 (24%) according to scintigraphic evaluation.

Adenoma excision was performed in 7 (34%) patients, subtotal parathyroidectomy in 11 (52%) patients and total parathyroidectomy + parathyroid auto-implantation in 3 (14%) patients. Persistent hyperparathyroidism was seen in 2 patients who underwent subtotal parathyroidectomy and 1 patient who underwent adenoma excision and underwent total parathyroidectomy plus parathyroid auto-implantation.

Parathyroid glands showed parathyroid adenoma in 8 patients (39%) and parathyroid hyperplasia in 13 patients (61%). In patients operated for persistent hyperparathyroidism, one of them had adenoma, the other two had hyperplasia and the second pathology results of them were similar. Severe hypocalcemia symptoms were seen and treated in 3 patients postoperatively. Thyroid papillary carcinoma was detected in 1 of 2 patients whom we determined during thyroidectomy preoperatively during parathyroidectomy.

When the ultrasonographic evaluation results were analyzed histopathologically, the number of patients with hyperparathyroidism was considered as adenoma was 8 (39%) and 7 (33%) patients with hyperplasia. The number of patients without ultrasonographic pathology was 6 (28%). When ultrasonographic evaluations were compared with actual pathology results; while adenoma was detected in 5 of 8 patients with suspected adenoma on ultrasonography, hyperplasia was detected in 3 patients. On the other hand, while hyperplasia was detected in 5 of 7 patients with suspected hyperplasia on ultrasonography, adenoma was detected in 2 patients. Adenoma was detected in 1 and hyperplasia was detected in 5 of 6 patients who were evaluated as normal. According to these results, the accuracy rate of ultrasonography in adenomas was 62.5%, while 71.4% in hyperplasia.

When the scintigrafic evaluation results were analyzed histopathologically, the number of patients with hyperparathyroidism was considered as adenoma was 10 (48%) and 6 (28%) patients with hyperplasia. The number of patients without scintigrafic pathology was 5 (24%). When scintigrafic evaluations were compared with actual pathology results; while adenoma was detected in 6 of 10 patients with suspected adenoma on scintigraphy, hyperplasia was detected in 4 patients. On the other hand, hyperplasia was detected in 5 of 6 patients with suspected hyperplasia on scintigraphy; adenoma was detected in a patient. Adenoma was detected in 1 and hyperplasia was detected in 4 of 5 patients who were evaluated as normal. According to these results, the accuracy rate of scintigraphy in adenomas was 60%, while 83.3% in

Table 4. Data of all patients

Patient No.	Age (Year)	Gender	Preoper. PTH (pg/mL)	Postoper. PTH (pg/mL)	Ultrasonographic Imaging	Scintigraphic Imaging	Operation	Pathology	Reoperation	Reoperation Pathology
1	38	Male	1276	247	Adenoma, solitary	Adenoma, solitary	Adenoma exc.	Adenoma	SPT	Adenoma
2	38	Male	2158	101	Adenoma, solitary	Adenoma, solitary	Adenoma exc.	Adenoma	None	N/A
3	33	Male	1800	923	Adenoma, multiple	Adenoma, multiple	Adenoma exc.	Adenoma	TPT	Adenoma
4	43	Male	2350	15	Adenoma, multiple	Adenoma, multiple	Adenoma exc.	Hyperplasia	None	N/A
5	45	Male	1577	215	Adenoma, multiple	Normal	TPT	Adenoma	None	N/A
6	40	Female	1044	57	Adenoma, multiple	Adenoma, multiple	SPT	Hyperplasia	TPT	Hyperplasia
7	55	Female	940	48	Hyperplasia, multiple	Hyperplasia, multiple	SPT	Adenoma	None	N/A
8	61	Male	1776	694	Hyperplasia, solitary	Adenoma, solitary	Adenoma exc.	Adenoma	None	N/A
9	47	Male	1007	142	Normal	Normal	SPT	Hyperplasia	None	N/A
10	41	Female	1816	37	Normal	Normal	SPT	Hyperplasia	None	N/A
11	48	Male	3498	141	Hyperplasia, solitary	Normal	SPT	Hyperplasia	None	N/A
12	39	Male	2091	156	Hyperplasia, multiple	Normal	SPT	Hyperplasia	None	N/A
13	44	Female	1348	6	Normal	Adenoma, solitary	Adenoma exc.	Adenoma	None	N/A
14	47	Male	3384	438	Hyperplasia, multiple	Hyperplasia, multiple	SPT	Hyperplasia	None	N/A
15	35	Male	2448	76	Normal	Hyperplasia, multiple	SPT	Hyperplasia	None	N/A
16	39	Female	2693	184	Normal	Normal	TPT	Hyperplasia	None	N/A
17	71	Male	700	371	Adenoma, multiple	Normal	Adenoma exc.	Adenoma	None	N/A
18	37	Female	1724	365	Normal	Adenoma, multiple	SPT	Hyperplasia	None	N/A
19	33	Female	3939	38	Hyperplasia, solitary	Hyperplasia, multiple	SPT	Hyperplasia	None	N/A
20	62	Female	2580	221	Hyperplasia, solitary	Normal	SPT	Hyperplasia	None	N/A
21	66	Male	1416	252	Adenoma, solitary	Normal	SPT	Hyperplasia	None	N/A

Abb: PTH: parathyroid hormone, SPT: subtotal parathyroidectomy, TPT: total parathyroidectomy

DISCUSSION

In this study, we present the results of surgical treatment in patients with sHPT, which is a major problem especially in patients with end-stage renal disease and shows differences in treatment time and pattern.

sHPT is a physiopathological response showing compensatory over activity of the parathyroid glands to maintain Ca balance in any condition associated with a chronic decrease in serum Ca levels. Chronic renal failure is the most common cause of sHPT. In addition, sHPT may develop in diseases leading to inappropriate Ca intake, steatorrhea and vitamin D deficiency in the diet (7). sHPT is found in the majority of patients with chronic renal failure. In the natural history of renal failure, progression of sHPT findings (such as increased bone and muscle pain, weakness, bone fractures, pruritus and calcyphylaxis) is seen and this directly affects morbidity and mortality. While 2-fold higher than normal upper limit of PTH levels causes cardiac toxicity, 2-fold higher causes adynamic bone disease. Observational studies in this area have shown that increases in serum Ca, P and PTH levels lead to an increase in mortality related to cardiovascular causes (8,9). In our study, especially adynamic bone diseases and related complaints were prominent and serum PTH levels were at least 4 times higher than normal in almost all patients.

Clinical, imaging and laboratory results should be evaluated together in the diagnosis of patients with sHPT. While some of the patients with sHPT may be only asymptomatic patients who have been demonstrated radiologically and radiologically, some of the patients may be characterized by progressive bone disease, osteitis fibrosis cystica, nephrolithiasis, soft tissue calcifications (pancreatic, vascular and skin), pruritis, mental changes, anemia, insulin resistance and hypertension, which may cause bone pain and pathological fractures (2). In terms of laboratory findings, patients are hypocalcemic or normocalcemic, and also hyperphosphatemic. Although PTH levels are generally high, they increase regularly with the progression of the disease. PTH increases up to 3 times normal are considered physiological to compensate for low 1.25 OH vitamin D3 levels. As sHPT progresses, PTH rises and dose of medical therapy should be increased. When resistance to medical treatment develops, surgery becomes the only valid treatment option (10). In our patients, PTH values were quite high, mean Ca levels were 10.37 and mean P levels were 5.63, which were slightly above normal.

Currently, although preoperative parathyroid USG and scintigraphy are routine in determining the localization of the pathological gland in the diagnosis of primary hyperparathyroidism, preoperative imaging is not routine in the primary surgery of sHPT. As with primary hyperparathyroidism, the idea that preoperative imaging may help to locate the pathological gland is valid for single gland disease. However, sHPT is usually characterized by multiglandular hyperplasia and the sensitivity of

preoperative imaging methods such as scintigraphy and ultrasonography is very low. In contrast to primary surgery, imaging methods are indicated for determining the localization of the enlarged gland in patients with persistent and recurrent sHPT (11-13). It may also be used to assist in the localization of the ectopic gland and the selection of the gland to be remnant or autotransplanted. In our study, we examined the general accuracy rates of ultrasonography and scintigraphy as well as the accuracy rates in the diagnosis of adenoma and hyperplasia. In patients undergoing total or total parathyroidectomy, the accuracy of preoperative ultrasonography in adenomas was 62.5% to determine the gland to be autotransplanted or left in place, whereas the accuracy rate in hyperplasia was 71.4%. Likewise, similar accuracy rates in scintigraphy were 60% and 83.3%, respectively.

Renal transplantation is the best way to prevent progressive adynamic bone disorder, skeletal deformities and cardiovascular complications in end-stage renal failure. However, in practice, because this is unlikely to happen, surgical treatment of parathyroids is needed in most of these cases. The aim of surgery is not to eliminate the disease but to reduce the complications and mortality. Nowadays, the criteria determined by the American Kidney Foundation are based on the determination of surgical indications in sHPT and decision on surgery (Table 1) (6). The most important indications are enlarged parathyroid gland and high PTH levels. Generally, high PTH levels are directly proportional to the size of the gland and this also increases the sensitivity of the imaging methods (14,15). In a study, it was shown that parathyroid glands could be scintigraphically visualized in 78% of those with intact PTH levels at a level of 500 pg / ml, and 92% in those with a level of 1000 pg / ml and above (16). In our study, the mean PTH level was found to be 1979 and the overall accuracy rate of ultrasonography was 72% and the overall accuracy rate of scintigraphy was 76%

The majority of patients with sHPT can be treated with medical therapy. Despite advances in medical treatment, control of sHPT is not always achieved and surgical treatment of these patients is required. In this context, parathyroidectomy is required in approximately 15% of patients receiving dialysis for more than 10 years and in 38% of patients receiving dialysis for more than 20 years (17). Surgical treatments include subtotal parathyroidectomy, total parathyroidectomy with forearm parathyroid autotransplantation, and total parathyroidectomy only. In the outline of the American kidney foundation, one of the operations of subtotal parathyroidectomy and total parathyroidectomy with parathyroid autotransplantation of the forearm is recommended (18). Surgical strategy in sHPT should be planned according to the appropriate balance between prevention of persistent / recurrent disease and avoidance of postoperative permanent hypoparathyroidism. In subtotal parathyroidectomy, how and how much tissue left behind is not fully described. If the excess parathyroid gland is left behind, the rate of persistent or recurrent sHPT will be high. The main goal

is to leave half of one of the parathyroid glands that seem normal, while maintaining the blood flow intact. (19-21)

Approximately 90% of sHPT operations are subtotal parathyroidectomy and total parathyroidectomy+parathyroid autotransplantation. In a meta-analysis of subtotal parathyroidectomy, the recurrence rate was 8.2% and the hypoparathyroidism rate was 2% on average (22). The same rates were 4.8% and 2.2%, respectively, in patients undergoing total parathyroidectomy+parathyroid autotransplantation (23). In a prospective randomized trial comparing subtotal parathyroidectomy with total parathyroidectomy+parathyroid autotransplantation, total parathyroidectomy + parathyroid autoimplantation showed significantly lower recurrence rate, more frequent normalization of serum Ca and alkaline phosphatase, more pruritic and pruritic symptoms than subtotal parathyroidectomy. (19). In our study, surgery rates were; 34% (7 patients) had adenoma excision, 52% (11 patients) subtotal parathyroidectomy and 14%(3 patients) were total parathyroidectomy+parathyroid auto-transplantation. Early recurrence occurred in 2 patients who underwent subtotal parathyroidectomy and 1 patient who underwent adenoma excision, and these patients were re-operated and underwent total parathyroidectomy + parathyroid autotransplantation. None of the patients who underwent total parathyroidectomy + parathyroid auto-implantation had recurrence.

CONCLUSION

As a result, surgical treatment is still the best treatment option in patients followed up for sHPT and whose medical treatment has failed. In these patients, significant improvement in clinical complaints and rapid improvement in laboratory values are observed after surgical treatment. According to both the literature data and the data obtained from this study, subtotal parathyroidectomy or total parathyroidectomy+parathyroid autotransplantation surgery should be preferred in patients with sHPT. However, high-volume randomized controlled trials are needed to determine which method is superior.

Competing interests: The authors declare that they have no competing interest.

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Ethical approval: Ethics committee approval could not be obtained because the study was planned retrospectively. But, local ethics approval was obtained from the hospital management for the study

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