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Original Investigation

Is three-gland-or-less parathyroidectomy a clinical failure for secondary hyperparathyroidism?

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ABSTRACT

Objective: To compare the clinical and biochemical outcomes between adequate and inadequate parathyroidectomies in patients with chronic renal failure.

Material and Methods: All secondary hyperparathyroidism patients who were previously operated in the Marmara University Hospital Breast and Endocrine Surgery Unit were planned to be included in the study. Patients were divided into two groups according to their extent of surgery: "adequate" and "inadequate" surgery groups. "Adequate surgery" was regarded as either subtotal (3½) or total parathyroidectomy. Removing fewer than 3½ parathyroids was defined as "inadequate surgery." Demographic, preoperative clinical symptoms, and their severity, as well as biochemical (e.g., tCa, PTH) findings, were recorded. Patients were followed monthly. The course of biochemical findings (tCa, PTH, P, ALP) and symptoms (by a scoring system of 1-4) was determined by comparing preoperative findings to those at the patient's last follow-up. Primary outcome of the study was treatment failure (biochemical persistence/recurrence) rates in both study cohorts. Secondary outcomes of the study were the levels of biochemical findings and improvement rates of clinical symptoms after parathyroidectomy, as well as complication rates related to the initial surgery in each surgery cohort.

Results: Forty-two patients with secondary hyperparathyroidism who underwent parathyroidectomy were included into the study. Twenty-six were male and 16 were female. Median age was 46. Forty (95%) patients had at least one symptom as the indication for surgery, whereas only 2 (5%) patients were asymptomatic, but biochemical findings were the indication. Twenty-two (52%) patients underwent adequate operation, whereas 20 (48%) patients had inadequate operation. Mean follow-up duration after initial parathyroidectomy was 60 [3-244] months. Significantly more patients (n=15; 75%) in the inadequate surgery group had biochemical persistence/recurrence when compared with those (n=8; 36%) who underwent adequate surgery (OR [odds ratio] 5.25; 95% CI 1.38-19.93; p=0.012). However, symptom improvement rates were similar in both adequate and inadequate surgery groups.

Conclusion: Although there is high biochemical treatment failure after inadequate parathyroidectomy in patients with renal hyperparathyroidism, clinical symptom improvement rates are also surprisingly high in this patient group. On the other hand, the adequate surgery group also had an increased biochemical failure rate well above expected in longer follow-ups.

Key Words: Secondary hyperparathyroidism, parathyroidectomy, recurrence, persistence

INTRODUCTION

Secondary hyperparathyroidism (sHPT) is a disease commonly seen in patients with chronic renal failure (CRF). Common symptoms of the disease are bone/joint pain, fatigue, and pruritus. Chronic renal failure can be controlled in most patients by dialysis and calcium and vitamin D supplementation (1). Cinacalcet, a calcimimetic that sensitizes parathyroid hormone receptors on parathyroid glands, helps lower parathyroid levels to the target rate in 40% of patients in comparison to the placebo group, which could achieve a rate of 4% (2). Today, despite hemodialysis, the rate of patients who become refractory to medical treatment and require parathyroidectomy is 15% in 10 years and 38% in 20 years (3).

Surgical treatment is indicated in patients who do not respond to medical treatment and in whom serious sequelae become prominent. Hypercalcemia with or without hyperphosphatemia along with significantly elevated parathormone (PTH) levels (>800 pg/mL), elevated PTH levels (>500 pg/mL) with calciphylaxis, anemia not responding to therapy, dilated cardiomyopathy, osteitis fibrosa cystica, and bone fractures are the indications for surgery (4).

The main goal of surgical treatment in sHPT is to ameliorate parathyroid hyperfunction. Subtotal parathyroidectomy (S/PTectomy) and total parathyroidectomy (T/PTectomy) with or without autotransplantation (AuTx) are the surgical options (5). In comparison to T/PTectomy without AuTx, which makes the patient dependent on medication, S/Ptectomy and T/Ptectomy with AuTx are the most commonly chosen surgical modalities, with similar recurrence and persistence rates (0%-10%) (6).

Response to successful surgical treatment is mostly convincing. Complaints, such as musculoskeletal pain, pruritus, and fatigue, disappear shortly after surgery, while calcification of the skin and ulceration usually take a longer time to disappear (7). Also, patients with cardiomyopathy show significant improvement after surgery; however, vascular and valvular calcifications persist (8).

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Nevertheless, despite extensive neck dissection, surgeons are not always able to achieve a successful outcome after surgery due to anatomical and numerical variability. All glands are hyperplastic in secondary hyperparathyroidism, and the supernumerary gland is important for the success of the treatment. In the literature, the frequency of supernumerary glands is 18.4%, and the most common location is the thymus (46.2%). For this reason, removal of thymic tissue is commonly recommended to diminish persistence and recurrence (5). By definition, persistence and recurrence are commonly determined by biochemical findings but not physical (9-11). In the literature, data in regard to the course of complaints and physical findings are scarce in this group of patients.

In this retrospective cohort study, we compared two cohorts of patients who underwent parathyroidectomy with bilateral neck exploration for sHPT in regard to their biochemical and physical findings as well as persistence and recurrence rates. One cohort consisted of patients who received adequate surgery, such as S/PTectomy or T/PTectomy, with or without AuTx, whereas the other consisted of those who underwent fewer than 3½-gland parathyroidectomy. Each cohort's postoperative findings were compared with those recorded preoperatively in order to assess the impact of extension of surgery on clinical findings.

MATERIAL AND METHODS

Study Type, Setting and Sampling

All sHPT patients who were previously operated on in the Marmara University Hospital Breast and Endocrine Surgery Unit and accepted to participate in the study were planned to be included in the study. It was designed as a retrospective observational study comparing two surgically treated cohorts.

Inclusion Criteria

Accepted to participate in the study, being operated on due to sHPT, and followed for at least 3 months after surgery were determined as the inclusion criteria. Patients who lived at least 3 months after the operation but died before the study were also included.

Exclusion Criteria

Patients who had parathyroidectomy while having a well-functioning transplanted kidney were excluded.

Definitions

Patients were divided into two groups according to their extent of surgery: "adequate" and "inadequate" surgery groups. "Adequate surgery" was regarded as either S/PTectomy (3½) or T/PTectomy±AuTx. Removing fewer than 3½ parathyroids during bilateral neck exploration was defined as "inadequate surgery."

"Intractability" was defined as having a PTH level of 800 ngr/L or above despite all medical therapies. Having a persistent elevation of PTH (>80 ngr/L) and/or total Ca (tCa; above 10.5 mg/dL) levels within 6 months after parathyroidectomy was defined as "persistence," whereas those patients whose PTH as well as tCa levels returned to normal after surgery but happened to increase after 6 months during the follow-up were regarded as "recurrence."

Study Parameters

Patients' age; gender; history; type and duration of dialysis before initial surgery; presence and, if any, severity of symptoms, such as bone/joint pain, itchiness, abdominal pain, and chronic fatigue; preoperative levels of serum tCa, phosphorus (P), PTH, and alkaline phosphatase (ALP); extent of initial parathyroidectomy; complications due to initial surgery; follow-up duration; additional explorations for hyperparathyroidism; renal transplantation history; and its function were all retrieved from their records.

The course of biochemical findings (tCa, PTH, P, ALP) and symptoms was determined by comparing preoperative findings to those at the patient's last follow-up. Presence of any symptoms and their severity were questioned both before surgery and at every visit during regular follow-up. For postoperative symptom assessment, a score between 1 and 4 was given for each symptom: "1" for complete amelioration, "2" for partial improvement, "3" for persistence (no change), and "4" for worsening or recent appearance of the symptom. Assessment results at their last follow-up were taken under consideration for comparison.

Scores of 1 and 2 were regarded as "improvement" for each symptom. Results for each symptom assessment were given as "percentage of patients who had improvement." Symptom improvement rates were compared between study groups.

Follow-up

Serum samples were taken weekly for tCa and monthly for PTH, P, and ALP measurements in patients on hemodialysis and monthly for all measurements in those on peritoneal dialysis. Physical exam and symptom questionnaire were done monthly for all patients.

Outcomes

Primary outcome of the study was treatment failure (biochemical persistence/recurrence) rates in both study cohorts. Secondary outcomes of the study were the levels of biochemical findings and improvement rates of clinical symptoms after parathyroidectomy, as well as complication rates related to initial surgery in each surgery cohort.

Data Record and Statistics

The Statistical Package for the Social Sciences (SPSS Inc, Chicago, IL, USA) Statistics 18 software package was used for collecting and analyzing the data. Patients who experienced persistence or recurrence by definition were recorded as "treatment failure" as a single endpoint in each study group. Independent comparisons were done between "adequate" and "inadequate" surgery cohorts. Also, dependent comparisons between preoperative and postoperative findings were done in each study cohort. Student's t-test was used for comparing independent continuous variables (age, number of symptoms, duration of dialysis, follow-up time, serum tCa, PTH, P, ALP levels), whereas for comparison of nominal and ordinal variables (gender, type of symptom), chi-square and Fisher`s exact tests were used. McNemar test was used for comparison of dependent continuous variables. A p value less than 0.05 was regarded as significant.

Table 1. Indications for parathyroidectomy

Indication for surgery	n (%)
Symptoms*	40 (95)
Bone and joint pain	36
Fatigue	35
Locomotor disability	30
Pruritus	28
Abdominal pain	9
Intractability (no symptoms)	2 (5)

*Most patients had more than 1 symptom

Table 2. Number of symptoms preoperatively

Number of symptoms	n (%)
No symptom	2 (5)
1 symptom	4 (10)
2 symptoms	3 (7)
3 symptoms	11 (26)
4 symptoms	15 (35)
5 symptoms	7 (17)

Table 3. Type of parathyroidectomy

Type of surgery	n (%)
Adequate surgery	22 (52)
Subtotal (3½) parathyroidectomy	18
Total parathyroidectomy	4
Inadequate surgery	20 (48)
3 gland parathyroidectomy	14
2 gland parathyroidectomy	4
1 gland parathyroidectomy	2

RESULTS

Descriptive Data of Patients

Forty-seven patients with sHPT who underwent parathyroidectomy between 1989 and 2009 were included in the study. Overall, 5 patients were excluded from the analysis. Three patients had a follow-up period of less than 3 months at the time of study, and 2 patients had missing records for preoperative biochemical measurements. Therefore, 42 patients were included in the analysis. Twenty-six were male and 16 were female. Median age of the patients was 46 [21-75], and median preoperative dialysis duration was 9 [4-17] years. Six (13%) patients underwent renal transplantation after parathyroidectomy. Graft rejection occurred in all 6 patients. Mean rejection time was 60 [36-216] months. Median follow-up time was 60 [3-244] months.

Forty (95%) patients had at least one symptom as the indication for surgery, whereas only 2 (5%) patients were asymptomatic but biochemical findings were the indication (Table 1). Thirty-three (79%) patients had 3 or more symptoms (Table 2). Twenty-two (52%) patients underwent adequate operation, while 20 (48%) patients had inadequate operation. In the adequate surgery group, most patients (n=18; 82%) had S/PTectomy (3½), while in the inadequate surgery group, most patients (n=14; 70%) had 3-gland parathyroidectomy (Table 3). Median follow-up duration after initial parathyroidectomy was 60 [3-244] months.

Patients in both the adequate and inadequate surgery groups had similar demographic and clinical characteristics as well as preoperative biochemical findings (Table 4).

Treatment Failure (Biochemical Persistence/Recurrence)

The risk of biochemical persistence/recurrence (n=15; 75%) in the inadequate surgery group was significantly higher compared with those (n=8; 36%) in the adequate surgery group (OR 5.25 95% CI 1.38-19.93; p=0.012) (Table 5).

Biochemical Findings

In the adequate surgery group, postoperative serum tCa, PTH, P, and ALP levels of patients were significantly lower than the preoperative values (Table 6). Also, in the inadequate surgery group, patients had significantly lower postoperative serum tCa, PTH, and ALP levels when compared with their preoperative measurements (Table 7).

Clinical Symptom Assessment

No asymptomatic patient developed a new symptom during his follow-up. Therefore, the course of clinical symptoms was assessed in 40 patients with at least one symptom before surgery. Though not significant, symptom improvement rates were higher in the adequate surgery group than in the inadequate surgery group (Table 8).

Complications and Mortality

Although the complication rate in the inadequate surgery group (n=4; 20%) was less than the adequate surgery group (n=8; 36%), the difference did not reach statistical significance (OR 0.55; 95% CI 0.20-1.55; p=0.32). Two (10%) patients died in the inadequate surgery group, whereas 6 (27%) patients died in the adequate surgery group. All of these patients died because of cardiac reasons. Also, the difference between mortality rates did not reach statistical significance (OR 0.30; 95% CI 0.52-1.68; p=0.24; Table 9).

DISCUSSION

In this study, we found that inadequate parathyroidectomy resulted in a 2-fold increase in rate of failure either as persistent or recurrent hyperparathyroidism. Despite numerically adequate removal of parathyroid glands, treatment failure rate was as high as 40% after a long period of follow-up. On the other hand, complication and mortality rates were similar in both surgery groups. Though not statistically significant, biochemical and clinical improvements were higher in the adequate surgery group compared with the inadequate surgery group after surgery.

During the study period, all parathyroidectomies were performed by 4 different staff surgeons who had the necessary experience in parathyroid surgery. This excluded a potential

Table 4. Comparison of demographic, preoperative clinical, and preoperative biochemical findings

	Adequate surgery (n=22)	Inadequate surgery (n=20)	p
Demographics			
Age; (SD)	47.1 (±15.1)	45.3 (±12)	0.67
Sex; n (%)			
Female	10 (45)	6 (30)	0.35
Male	12 (55)	14 (70)	
Duration of dialysis; mean years (SD)	9.4 (±3.9)	9.7 (±3.9)	0.81
Follow up; mean months (SD)	53.5 (±73.2)	70.3 (±30.6)	0.49
Serum biochemistry			
tCa; mean (SD) mgr/dL	10.3 (±1.3)	10.2 (±1.7)	0.78
PTH; mean (SD) ngr/L	1742 (±874)	1353 (±989)	0.18
P; mean (SD) ngr/dL	5.9 (±1.9)	6.4 (±2.1)	0.38
ALP; mean (SD) IU/L	1072 (±976)	1118 (±720)	0.87
Symptoms, n (%)			
Bone and joint pain	18 (82)	18 (90)	0.67
Pruritus	15 (68)	13 (65)	1.0
Fatigue	17 (77)	18 (90)	0.41
Abdominal pain	3 (14)	6 (30)	0.26
Locomotor disability	14 (64)	16 (80)	0.32
Number of symptoms (SD)	3.1 (±1.5)	3.6 (±1.2)	0.24

SD: standard deviation

Table 5. Comparison of biochemical persistence/recurrence between groups

	Adequate surgery n (%)	Inadequate surgery n (%)	p
Biochemical persistence/recurrence	8 (36%)	15 (75%)	0.0012 OR 5.25 [1.38-19.93]

bias that could have occurred due to different experience levels of surgeons. We followed our patients for a longer period in comparison to similar studies, which we believe made our results be interpreted as more evident.

In our cohort, 20 of 42 patients received inadequate parathyroidectomy surgery. We were using preoperative imaging diagnostic techniques only for primary hyperparathyroidism patients and not in sHPT patients in a standard fashion, and we think that this was the main reason of our high inadequate surgery rate. After this study, we added standard preoperative scintigraphy to our protocol as a preoperative imaging diagnostic technique in sHPT patients. However, we do not stress the reasons for inadequate surgery, since this facilitated us to compare the outcome of two predefined study groups consisting of similar case numbers. Thus, we believe this was the main interesting point of our study, along with its long follow-up period.

Table 6. Comparison of biochemical findings pre- and postoperatively in the adequate surgery group

	Preoperatively mean (SD*)	Postoperatively mean (SD*)	p
tCa mgr/dL	10.3 (±1.3)	8.5 (±0.9)	0.0001
PTH ngr/L	1768 (±887)	110 (±202)	0.0001
P mgr/dL	5.9 (±1.9)	4.6 (±1.4)	0.029
ALP IU/L	1072 (±976)	261 (±143)	0.001

SD: standard deviation

Table 7. Comparison of biochemical findings pre- and postoperatively in the inadequate surgery group

	Preoperatively mean (SD*)	Postoperatively mean (SD*)	p
tCa mgr/dL	10.2 (±1.7)	8.9 (±1.2)	0.013
PTH ngr/L	1302 (±989)	361 (±389)	0.0001
P mgr/dL	6.4 (±2.1)	5.4 (±1.6)	0.13
ALP IU/L	1041 (±652)	407 (±371)	0.003

*SD: standard deviation

Table 8. Comparison of improvement rates for each clinical symptom after surgery

		Improvement rate		
	Number of patients	Adequate surgery (%)	Inadequate surgery (%)	p
Bone and joint pain	36	94	67	0.09
Pruritus	28	93	69	0.15
Fatigue	35	94	72	0.18
Abdominal pain	9	100	50	0.46
Locomotor disability	30	93	69	0.18

Table 9. Complication and mortality rates in study groups

	Adequate surgery n=22 (%)	Inadequate surgery n=20 (%)	OR (95% CI)	p
Complications	8 (36)*	4 (20)#	0.55 (0.20-1.55)	0.32
Mortality	6 (27)	2 (10)	0.30 (09.52-1.68)	0.24

*Of these 8 patients, 1 patient had a bleeding complication and 7 patients had hypocalcemia after surgery.
#Of these 4 patients, 1 patient had a bleeding complication and 3 patients had hypocalcemia after surgery.

In our study, we found that in both study groups, regardless of the adequacy of parathyroidectomy, there were significant improvements in both biochemical measurements and level of disease-related symptoms after surgery. Although there were significant decreases in PTH levels in both groups, 75% of those in the inadequate surgery group still had a serum PTH level above normal. Hibi et al. (12) showed in their study that 70% of patients who received 3-gland parathyroidectomy had a PTH level of 60 pg/dL or lower after surgery. They explained

this biochemical improvement by circumstances in which either the fourth gland could have been removed or its blood supply was disturbed unintentionally. However, this explanation can not be applied to our cohort, since 75% of those who underwent 3-or-less parathyroidectomy maintained their high level of PTH after surgery. Therefore, our cohort mostly represents those with actual surgical failure according to the definition. On the other hand, although most of the patients in the inadequate group remained with persistently high PTH levels, their symptoms improved as those in the adequate surgery group. Although the treatment failures between study groups were different (75% vs. 40%), this was not significant. This was with a great probability, due to the type II error. All symptoms improved more than 90% in the adequate surgery group, whereas the most striking improvement was achieved in the level of fatigue with a rate of 72% after inadequate surgery. It is most probable that with a larger sample size with a stronger power of the statistical test, a statistical difference between study groups would be found. But, the fact is that even after an inadequate parathyroidectomy, patients' disease-related symptoms improved at least by 50%. Therefore, in our cohort, biochemically defined persistence was not reflecting the patients' actual clinical symptom-related conditions.

Another striking finding of our study was the high rate of persistence and/or recurrence rate after adequate parathyroidectomy. Forty percent of those who had more-than-3-gland parathyroidectomy recurred during the follow-up period. Previous studies reported that persistence and/or resistance rates were found to be as low as 10% after subtotal parathyroidectomy or total parathyroidectomy ± autotransplantation (13, 14). But, in countries with low kidney transplantation rates, rates of persistence and/or recurrence were reported as high as 30% (15). In our cohort, only 13% of patients received kidney transplantation, but all failed to function at the time of the current study. Therefore, this high rate of recurrence can be explained by the circumstances in which either the left remnant or extranumerary glands recovered to produce inappropriate PTH due to chronic stimulation as the interval was prolonged after adequate parathyroidectomy. Pattou et al. (16) previously showed that nearly one-third of patients with renal hyperparathyroidism had more than 4 parathyroid glands. They found these extranumerary glands in the thymus most of the time. Therefore, for those remaining with insufficient kidney function, as time elapses after surgery, even adequate surgery would not prevent recurrence due to this high probability of extranumerary glands, especially for those who underwent 4-gland parathyroidectomy at most. Also, hypersecretion by remaining gland tissue would also be the reason for recurrence in those without extranumerary glands due to chronic stimulation in renal function impairment.

Although more complications were observed in those who underwent adequate surgery, the difference between groups was not significant. Hypocalcemia was the most common complication in the whole cohort, and patients who underwent adequate surgery experienced it more commonly. Again, probably, the small sample size prevented us to show the real difference between two groups. Although they received inadequate parathyroidectomy, 20% of those also experienced hypocalcemia to an extent. This showed us that "hungry bone syndrome" could be observed, even after 3-or-less parathyroidectomy. This was parallel to our findings in which we found more than 50% improvement in disease-related symptoms after inadequate surgery.

The main limiting factor of our study was its retrospective design. Another stressing factor that made the study have limited quality was its inadequate sampling size. Although we included all patients who received parathyroidectomy for renal hyperparathyroidism during the study period, along with a low exclusion rate, the total number of patients for the analysis was small.

CONCLUSION

Although the gold standard surgical treatment of renal hyperparathyroidism is either subtotal parathyroidectomy or total parathyroidectomy ± autotransplantation, all 4 glands might not be found in every patient, despite bilateral cervical exploration. Nevertheless, in these patients, the disease mostly persists biochemically, and disease-related symptoms can improve to a larger extent, even after a long follow-up. This is also evident with hungry bone syndrome observed after inadequate surgery. Also, in circumstances where renal insufficiency remains (due to either lack of transplantation or graft failure), recurrence should be an expected event, even in those who had adequate parathyroidectomy, especially as time elapses after surgery.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Marmara University Faculty of Medicine.

Informed Consent: Datas were collected retrospectively and informed consent cannot be collected.
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