Outcomes of Total Parathyroidectomy with Autotransplantation *versus* Subtotal Parathyroidectomy Techniques for Secondary Hyperparathyroidism in Chronic Renal Failure

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Abstract

Objective: To compare the safety and the effectiveness of total parathyroidectomy with autotransplantation *versus* subtotal parathyroidectomy for refractory secondary hyperparathyroidism in patients with chronic kidney disease.

Study Design: A comparative study.

Place and Duration of Study: Baskent University, Adana Medical and Research Center, Adana, Turkey, from January 2012 to November 2018.

Methodology: Patients operated upon for refractory secondary hyperparathyroidism by the general surgery team were inducted. Overall, 25 (40%) patients underwent total parathyroidectomy with autotransplantation (Group 1), whereas 37 (60%) patients underwent subtotal parathyroidectomy (Group 2). Patient files were retrospectively analysed for recurrence or persistence of hyperparathyroidism.

Results: A total of 62 patients, 32 (52%) of whom were females, with a mean age of 41.4 ±15.8 years for group 1; and 30 patients were males with a mean age of 43.1 ±16.7 years for group 2 were assessed in this study. The presenting complaints were bone pains and malaise supported by laboratory values that showed consistently elevated parathyroid hormone levels (>200 pg/ml). In the postoperative follow-up, 29 patients (46.8%) had transient hypocalcemia, while 3 (5%) had persistent hypoparathyroidism. In Group 1, one (4%) patient had a recurrence, while 4 (16%) patients had persistent hyperparathyroidism. In contrast, two (5.6%) patients in Group 2 had recurrence, whereas 8 (22%) patients had persistent hyperparathyroidism.

Conclusion: Both surgical options can be safely utilised in the management of refarctory secondary hyperparathyroidism. Moreover, regardless of the procedure used, all the parathyroid glands must be explored. However, due to high morbidity and failure rates of subsequent surgeries, the surgeon should be keen and thorough in the initial procedure.

Key Words: *Chronic renal failure, Secondary hyperparathyroidism, Parathyroidectomy.*

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INTRODUCTION

Secondary hyperparathyroidism (sHPT) is common in chronic kidney disease (CKD). It is characterised by markedly elevated parathyroid hormone levels due to persistent stimulation of parathyroid tissue and resultant parathyroid hyperplasia in response to hypocalcemia.[1] The chronically elevated parathyroid hormone causes bone pain, general weakness, malaise, neuropsychiatric symptoms, and renal osteodystrophy. Secondary hyperparathyroidism has also been linked to cardiovascular mortality in patients with heart failure.[2]

To manage this condition, agents like phosphate binders, activated vitamin D (calcitriol), and calcimimetics are generally used.[3] Though medical management is adequate in mild to moderate cases, studies have shown that only 22% of severe cases respond to medical management.[4] Approximately 20% of sHPT patients with 3-10 year history of CKD require surgery; these rates are as high as 40% in patients with 20 years history of CKD.[5] After parathyroidectomy, parathyroid hormone levels drop rapidly to normal range resulting in reduced mortality and morbidity rates.[6]

Surgically, the most commonly used procedures are subtotal parathyroidectomy (stPT), which is the removal of all parathyroid glands, save half of the most normal-looking gland; and parathyroidectomy with auto-transplantation (tPTO), which is the removal of all the four glands and implantation of a section of one of the glands into a muscle. While stPT carries a lower risk of hypocalcemia and permanent hypoparathyroidism, tPTO reportedly has a lower risk of recurrence and needs subsequent re-exploration.[7]

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There are studies that compare the two procedures in the set up of sHPT. This study differs to answer the question of the better procedure when a surgeon is faced with both options at a centre with a team that is dedicated to the management of these conditions.

The objective of this study was to compare the safety and the effectiveness of total parathyroidectomy with autotransplantation *versus* subtotal parathyroidectomy in terms of recurrence and persistence of refractory secondary hyperparathyroidism in patients with chronic kidney disease.

METHODOLOGY

Baskent University Medical and Health Sciences Research Board Ethics Committee approved this study (Project No. KA 19/175). Sixty-two CKD patients operated upon for secondary hyperparathyroidism refractory to medical management between January 2012 and November 2018 in Baskent University's Adana Hospital, were included in the study. Exclusion criteria comprised a history of a previous thyroid or parathyroid operation, re-operation because of technical inadequacy, and incomplete patient files. The files and data of the patients were retrospectively analysed. The patients were put into two groups: Group 1 for tPTO (n=25) and Group 2 for stPT (n= 37). Demographic and clinical characteristics, preoperative laboratory results, preoperative ultrasound, parathyroid scintigraphy and surgical notes were recorded.

In both groups, all four glands were explored and the frozen section used to confirm the tissue as parathyroid. In Group 1, the most normal-appearing gland was immersed in physiologic serum at +4°C and then subdivided into 1mm^3 pieces before being transplanted into the brachioradialis muscle in the forearm. In Group 2, approximately 50 mg (½ - ⅓) of the most normal-appearing gland was left *in situ* and marked with surgical clips. The patients were discharged on oral calcium and vitamin D. Patients with symptomatic hypocalcemia received IV calcium treatment. The hospitalisation duration and postoperative complications were noted. Laboratory values were analysed at one week, one month, and six months. Persistent hypoparathyroidism was defined as PTH levels above 200 pg/ml before six months, whereas recurrence was defined as PTH levels rising above 200 pg/ml after the six months.

Statistical analysis was performed using the statistical package SPSS (Version 23.0, SPSS Inc., Chicago, IL, USA). If continuous variables were normal, they were described as the mean ±standard deviation (p >0.05 in Kolmogorov-Smirnov test or Shapiro-Wilk (n <30)), but if the continuous variables were not normal, they were described as the median with IQR (interquartile range). Comparisons between groups were applied using the Student t-test for normally distributed data, and the Mann-Whitney U-test was used for the data not normally distributed. The categorical variables between the groups were analysed using the Chi-square test or the Fisher exact test. Values of p <0.05 were considered statistically significant.

RESULTS

A total of 62 patients including 32 females [52%] were inducted in this study. Their mean age was 41.4 ±15.8 years for group 1 and 43.1 ±16.7 years for group 2. The presenting complaints were bone pain, malaise and laboratory studies that showed consistently elevated parathyroid hormone levels (>200 pg/ml). Demographic and clinical characteristics were similar in both groups. The mean preoperative laboratory results, preoperative parathyroid ultrasonography, and scintigraphic findings were recorded as given in Table I.

Four patients in group 1 and six in group 2 had simultaneous thyroidectomy. Four parathyroid glands were identified in 51 (82%) patients. In 3 (5%) patients, only 2 glands were identified during exploration. These patients subsequently developed persistent hyperparathyroidism. In 2 (3%) patients, 5 parathyroid glands were identified. Ectopic glands identified in 5 (8%) patients were mostly intrathymic.

Twenty-nine (46.8%) patients developed hypocalcemia and 3 (5%) patients developed permanent hypoparathyroidism, whereas 29 (46.8%) patients had no compli-

Table I: The demographic details and perioperative values of the patients.

	Group-1 (n:25)	Group-2 (n:37)	P
Age (Mean ±SD)	41.4 ±15.8	43.1 ±16.7	0.572
Gender			
Male	14 (56%)	16 (43.2%)	0.438
Female	11 (44%)	21 (56.8%)	
Comorbidity			
Yes	8 (32%)	9 (24.3%)	0.569
No	17 (68%)	28 (75.7%)	
CKD years (Mean ±SD)	11.1 ±5.1	8.7 ±3.9	0.054
Presenting complaint			
Bone pain	13 (52%)	15 (41%)	0.669
Malaise	12 (48%)	22 (59%)	
Ca (mg/dl)	9.39 ±1.49	9.646 ±1.20	0.463
Pth (pg/ml)	1612 (691)	1539 (971)	0.428
P (mg/dl)	6.25 ±1.59	5.25 ±1.44	0.015
Alp (u/l)	297 (363)	330 (440)	0.859
USG finding			
Positive	24 (96%)	30 (81%)	0.128
Negative	1 (4%)	7 (19%)	
Scintigraphy finding			
Positive	24 (96%)	33 (89%)	0.640
Negative	1 (4%)	4 (11%)	

**CKD: Chronic kidney disease.*
Data are presented as mean ± standard deviation or number (%).
p<0.05 value is statistically significant.

cations. The mean hospitalisation period was 5.1±4.1 days, while follow-up was 38.7 ±22.9 months. The post-operative follow-up data of the patients is shown in Table II.

Parathyroid hormone drop on postoperative day 1 was meaningful in group 1 compared to group 2, with a statistically significant difference (p=0.03). But during follow-up serum Ca, PTH levels on week 1, 1st month and 6th month showed no statistically significant difference (p>0.05). The mean values of these data are given in Figures 1a and 1b.

Table II: Postoperative follow-up data.

	Group-1 (n:25)	Group-2 (n:37)	p
Complication			
Transient hypocalcemia	13 (52%)	16 (43.2%)	0.789
Permanent hypocalcemia	1 (4%)	2 (5.4%)	
Myocardial Infarction	-	1(2.7%)	
Hospitalisation	5(6) day	3(5) day	0.304
Follow-up time	41(28) month	37,5(36) month	0.417
Recurrent HPT			
Yes	1 (4%)	2 (5.6%)	1
No	24 (96%)	35 (94.6%)	
Persistent HPT			
Yes	4 (16%)	8 (21.6%)	0.745
No	21 (84%)	29 (28.4%)	

Data are presented as median (interquartile range) or number (%).
p<0.05 value is statistically significant.

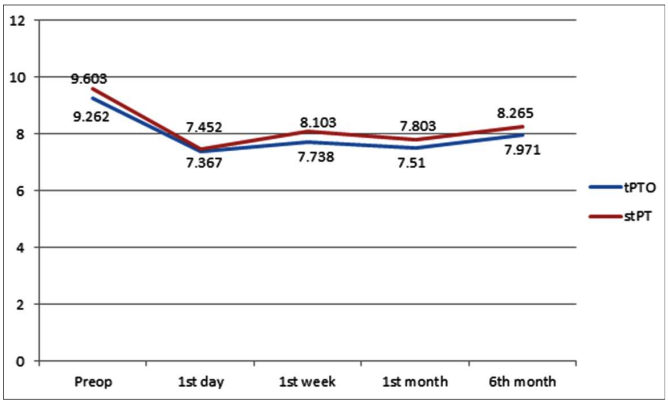

Figure 1 (a): Calcium level changes.

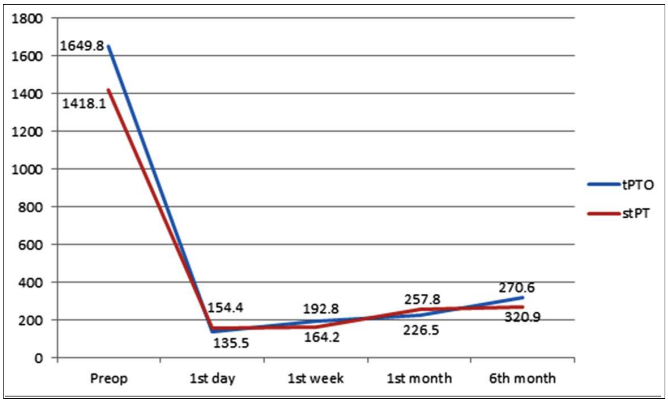

Figure 1 (b): Parathyroid hormone level changes

DISCUSSION

Secondary hyperparathyroidism is a CKD-related condition that compounds its morbidity and mortality. sHPT prevalence is almost 86% in end-stage renal disease.[8] Although vitamin D and calcimimetics are useful in medical management, these medications are not always effective and are expensive.[9] Therefore, 1-2% of sHPT patients require surgery every year.[10] There is a need for surgery when parathyroid hormone levels rise rapidly, and if there is extensive osteitis fibrosa cystica on imaging or rapid bone turnover that is refractory to medical treatment.[11] The quality of life and symptoms have been shown to improve after parathyroidectomy.

Imaging techniques are not so highly sensitive and specific in diagnosing parathyroid hyperplasia,[12] rendering localisation of these hyperplastic glands quite difficult and expensive. Thus, these localisation techniques should be preserved for persistent and recurrent cases. In this study, imaging was positive for hyperplasia, if at least one hyperplastic gland was identified on USG or if scintigraphy showed increased activity in at least one gland. This explains the positive findings in 87% of USG imaging and 92% of scintigraphic findings. The main strategy in surgery is to balance adequate parathyroid tissue resection and avoidance of permanent postoperative hypoparathyroidism.[13] According to kidney disease outcomes and quality initiative (KDOQI) principles, the management should be based on patient's chances of renal transplantation such that patients on long-term dialysis should have their PTH levels maintained at 150-300 pg/ml.[14]

The two main surgical management options are stPT and tPTO. Thymectomy should be added to routine bilateral cervical exploration so as no ectopic glands are overlooked. In tPTO, normal-looking gland is minced into 1*1*1 mm pieces and transplanted into sternocleidomastoid, brachioradialis or pectoralis muscles.[15] In this study, brachioradialis muscle was preferred to avoid repeat neck exploration in case of persistence or recurrence and attain low morbidity in case of re-operation. stPT is associated with complications such as high recurrence rates, need for general anesthesia in case of re-operation and increased risk of recurrent laryngeal nerve injury during re-operation.[16] In contrast, tPTO carries a high risk of autograft failure resulting in permanent hypoparathyroidism. A systemic meta-analysis showed that both methods are effective in lowering serum PTH and calcium levels. One year follow-up revealed no recurrence as there was no detectable rise in PTH and calcium levels or an increase in the size of parathyroid tissue even in the subtotal parathyroidectomy group.[17]

In this study, first day PTH levels were significantly lower in the tPTO group (p<0.05); but 6th month PTH, Ca, and

P levels showed no significant difference between the groups. Although there are studies that have shown a difference between the two methods, a meta-analysis of 13 studies looking at parameters such as clinical resolution, radiological improvement, recurrence, and persistent disease, found no statistically significant difference between the groups.[18] In this study, there was 1 (4%) case of recurrence and 4 (16%) cases of persistent disease in the tPTO group. In contrast, recurrence was seen in 2 (5.6%) patients and persistent disease in 8 (22%) patients in the stPT group. These figures seem to favour the tPTO group, but the study showed no statistically significant difference between the groups. Relatively, high persistent rates in this study can be attributed to inadequate exploration for ectopic glands as substantiated by recurrence or persistent disease in 8 (89%) of 9 cases in which less than 4 glands were explored.

Total parathyroidectomy without autotransplantation (tPT) is another surgical technique used in sHPT management. A study comparing the three techniques found that there was no recurrence for the tPT group in a 3-year follow-up period.[19] However, tPT is associated with debilitating clinical outcomes of permanent hypoparathyroidism.

The groups were also compared on complication rates and hospitalisation period. The calcium levels of the patients were checked daily, and if low, supplemented. Transient hypocalcemia was relatively high in both groups (52% vs 43%), but with no statistically significant difference ($p>0.05$). This difference in transient hypocalcemia may explain the longer hospitalisation period in the tPTO group (5.76 days *vs.* 4.65 days), but with no related statistical significance. Permanent hypoparathyroidism was 4% in tPTO and 5% in stPT with no statistically significant difference.

Because of increased morbidity and high failure rates associated with re-operation, the first operation should be done with the utmost dedication.

This study has limitations, such as its retrospective nature and lack of randomisation of surgical techniques. There are also variable recurrences and complication rates caused by the inexperience of a subgroup of surgeons at the Center of study. Determining the appropriate surgical technique for this subset of patients, will require a standardised randomised prospective study with a larger cohort.

CONCLUSION

Both surgical techniques are comparably effective in the treatment of hyperparathyroidism associated with CKD. Thymectomy should be added to the bilateral cervical exploration technique of choice to reduce the risk of recurrent or persistent disease due to ectopic hyperparathyroid gland.

ETHICAL APPROVAL:
This study was approved by Baskent University Institutional Review Board (Project No. KA 19/175) prior to initiation of the research work.

PATIENTS' CONSENT:
Informed consents were obtained from all patients to publish the data concerning this case.

CONFLICT OF INTEREST:
Authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
RS: Design of the work, authored the manuscript.
HY: Conception of idea and final approval.
ASH: Helped to draft the manuscript and interpretation.
MK: Data collection and analysis.
IMA: Data analysis and critical review of article.

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