# Sekonder hiperparatiroidizmde cerrahinin kısa ve uzun dönem sonuçları

## The effect of surgical procedures on short-term and long-term outcomes of the patients in secondary hyperparathyroidism

Ethem Sahan[1], Ahmet Dag[1], Mustafa Berkesoglu[1], Mehmet Ali Sungur[2], Ahmet Koray Ocal[1], Tamer Akca[1]

[1]*Mersin University Faculty of Medicine, Department of General Surgery, Mersin, Turkey*

[2]*Duzce University, Department of Biostatistics and Medical Informatics, Duzce, Turkey*

## Abstract

**Background:** Management of patients with secondary hyperparathyroidism (SHPT) is mainly medical. When medical treatment fails, subtotal parathyroidectomy (subtotal PTX) or total parathyroidectomy and authotransplantation (total PTX+AT) are standard procedures. But there is no globally accepted unique surgical procedure. We aimed to evaluate the effect of operation types on short-term and long-term outcomes in patients with SHPT who had 3 or 4 parathyroid glands exploration in surgery.

**Material and methods:** This study was included patients with SHPT who undergone PTX. Patients were divided into 3 groups: 3 PTX in Group A, subtotal PTX in Group B and total PTX+AT in Group C. Parathormone (PTH), calcium, phosphorous, 25-hydroxy-vitamin-D (25-OH Vit-D) levels, bone densitometry scores, persistence/recurrence rate and complaints were evaluated and compared before/after operation between the groups.

**Findings:** Six, eight and nine patients were situated in Group A, B and C, respectively. PTH levels decreased at 6th months in all groups, but elevated again in Group A. Patients had lower PTH, phosphorous and serum 25-OH Vit-D levels; better T-score and improvement in pruritis, prominently in Group B and C postoperatively during the follow-up.

## Özet

**Giriş:** Sekonder hiperparatiroidizmin (SHPT) tedavisi medikaldir. Medikal tedavi başarısız olduğunda cerrahi seçenekleri subtotal paratiroidektomi (subtotal PTX) veya total paratiroidektomi ve ototransplantasyondur (total PTX + AT). Ancak genel olarak kabul gören tek bir cerrahi yöntem bulunmamaktadır. Bu çalışmamızda cerrahi sırasında 3 veya 4 paratiroid bezi saptanan SHPT'li hastalarda, uygulanan cerrahi yöntemlerin kısa dönem ve uzun dönem sonuçlara etkisini değerlendirmeyi amaçladık.

**Yöntem-gereç:** Bu çalışma PTX yapılan SHPT'li hastalardan oluşmaktadır. Hastalar 3 grupta değerlendirildi; Grup A'da 3 PTX, Grup B'de subtotal PTX ve Grup C'de total PTX + AT. Preoperatif ve postoperatif dönemlerde ve gruplar arasında parathormon (PTH), kalsiyum, fosfor, 25-hidroksi-vitamin-D (25-OH Vit-D) düzeyleri, kemik mineral dansitometri skoru, peristans/rekürrens durumu ve şikayetler bakımından değerlendirildi ve karşılaştırıldı.

**Bulgular:** 6, 8 ve 9 hasta sırasıyla Grup A, B ve C'de yer almaktaydı. PTH düzeyleri 6.ayda tüm gruplarda azalmasına rağmen, Grup A'da tekrar yükseldi. Çalışma sonucunda özellikle Grup B ve C'de belirgin olmak üzere postoperatif dönemde hastalarda PTH, fosfor ve 25-OH Vit-D düzeylerinde düşme, T-skorunda iyileşme ve kaşıntıda azalma saptanmıştır.

**Yazışma Adresi | Correspondence:** Mustafa Berkesoglu,
Mersin University Hospital 33343 Yenişehir-Mersin/TURKEY
berkesoglu@yahoo.com

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**Conclusion:** In conclusion, removing of fewer than 3,5 glands were accepted as inappropriate surgery in SHPT. Surgeons should attribute to find out at least 4 parathyroid glands. Total PTX+AT and subtotal PTX in SHPT is significantly associated with stable lowered PTH levels and persistence/recurrence rates.

**Key words:** Parathyroid, parathyroidectomy, secondary hyperparathyroidism, T-score, vitamin D

**Sonuç:** Sonuç olarak SHPT'li hastalarda 3,5 paratiroid bezinden daha az bez çıkarılması uygun olmayan bir cerrahidir. Cerrah en az 4 paratiroid bezini de bulmak için tüm çabayı göstermelidir. Bu hastalarda total PTX + AT ve subtotal PTX; anlamlı düzeyde düşük ve stabil PTH değerleri ve daha az persistans/rekürrens oranları sağlamaktadır.

**Anahtar kelimeler:** paratiroid, paratiroidektomi, sekonder hiperparatiroidizm, T-skoru, vitamin D.

## Introduction

Secondary hyperparathyroidism (SHPT) is a minority of the patients with hyperparathyroidism and usually results from parathyroid gland hyperplasia that releases excess parathyroid hormone (PTH)[1]. SHPT occurs most commonly secondary to chronic renal failure (CRF). For this reason, SHPT is frequently referred to as renal hyperparathyroidism[2]. It may result in potentially serious complications including metabolic bone diseases, severe atherosclerosis, undesirable cardiovascular events and also high parathormone (PTH) levels were associated with mortality[3,4]

Management of patients with SHPT is predominantly medical. When medical treatment fails, subtotal parathyroidectomy (subtotal PTX) or total parathyroidectomy and authotransplantation (total PTX+AT) are standard surgery procedures[1,5]. Any of surgical procedure is not globally accepted, the surgical technique is mostly the surgeon's choice. No large randomized controlled trials comparing one surgical approach to another exist[6].

In this study; we aimed to evaluate the effect of different operation types on short-term and long-term outcomes in patients with SHPT who had 3 and 4 parathyroid glands exploration in surgery.

## Material and methods

Study was approved by Local Ethical Committee of our tertiary center University Hospital Faculty of Medicine. All patients enrolled in the study were informed about the study and provided written informed consent.

### *Study Population*

This study was included patients who were consulted to General Surgery Department for surgery due to SHPT between January 2006 and January 2010 and undergone parathyroidectomy. SHPT was diagnosed in all of the patients on the basis of clinical, biochemical, radiological and finally histological evaluation. Inclusion criterias were determined that all patients as long-term dialysis treatment (>12 months) in CRF patients, age (≥18 years), with symptoms and/or high levels of parathyroid hormone (PTH) (>500 pg/mL, normally 15-65 pg/mL) that could not be normalized with the medical treatment. Patients with concomitant thyroid surgery and history of neck surgery for thyroid, parathyroid or any other disorders were excluded from the study.

### *Patients*

The study was begun with 30 SHPT patients. Two patients were excluded due to concomitant thyroidectomy surgeries; one patient was excluded since he refused the follow-up. Six patients had higher PTH levels (>500) during the study period; five patients were in Group A; one patient was in Group B. Four of them were reexplorated due to high PTH levels, and excluded from the study, other two patients refused the reoperation in Group A and included in the study. The study was enrolled with remaining 23 patients ***(Figure 1)***. Patients with the CRF underwent routine dialysis the day before surgery to correct electrolyte abnormalities without heparin. Neck ultrasonography (USG) and Tc-99 m sestamibi parathyroid scans were performed for all patients included in the study to assess the preoperative localization. 23 patients were divided into 3 surgical groups; Group A (3 PTX), Group B (subtotal PTX) and Group C (total PTX+AT). When lesser than 4 glands were found, 3 glands were removed and named as Group A. When 4 glands were found, subtotal PTX or total PTX+AT were performed and named as Group B and Group C, respectively (detailed below). Patients were discharged with/without drains, when were relieved.

### *Surgery and Study Groups*

In all surgical procedures intraoperative nerve monitoring systems were used (NIM 3.0 Nerve Monitors, Medtronic, US). Surgery was performed under general anesthesia; frontal cervical transverse incision was made, similar to that for thyroidectomy[6]. When 3 or 4 parathyroid glands were revealed; the same surgeon in all patients decided surgical types intraoperatively ac-

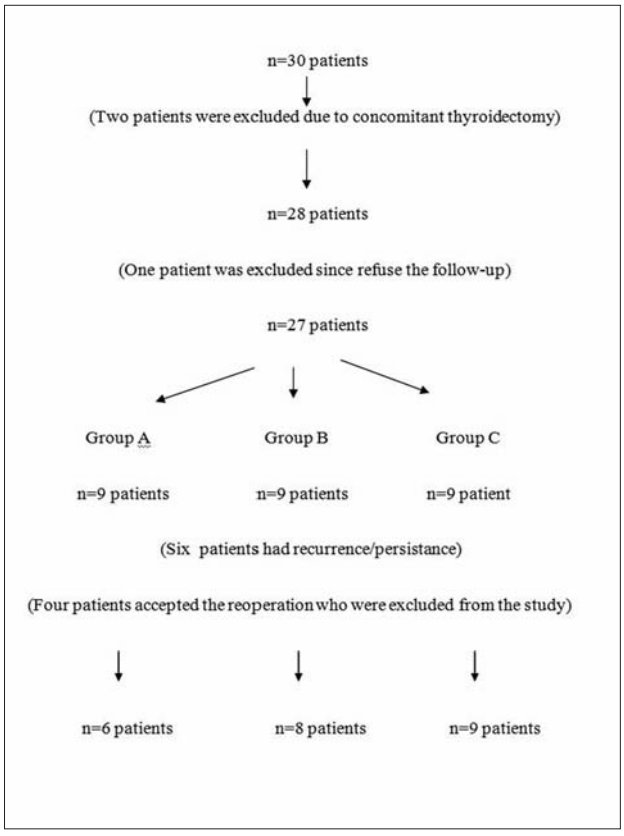


**Figure 1.** Study design

cording to number of gland which were found, gland perfusion state and candidate for renal transplantation in the future. In the Group A, although neck exploration was made for all 4 glands, but less than 4 glands were found and also removed with thymectomy. In the Group B, all 4 glands were explored and one of the healthy appearing inferior glands was remained in situ position and signed with a small titanium clip. The other ones were removed and added thymectomy to procedure. All of the revealed parathyroid tissues that were removed and remained in situ were confirmed with histological. In the Group C, all 4 glands were also explored, removed totally and added thymectomy to procedure, the most normal-appearing sites of the parathyroid gland were divided into pieces 1 $mm^3$ in size, and 15-20 of these pieces were placed into brachioradialis muscle and signed with a titanium clip. All surgical procedures were performed at the same center by the same surgical team.

***Data Collection and Follow-up***

All patients were evaluated at preoperative time and postoperative 6, 12, 18 and 24-months. Serum calcium (Ca) and phosphorus (P) were measured preoperatively and at postoperative 24$^{th}$ hours. Serum PTH levels were measured preoperatively and at postoperative 1$^{st}$ hour. All patients were evaluated for surgical drain usage, complication (bleeding, hoarseness, hypocalcemia, hypoparathyroidism and persistence/recurrence) and length of hospital-stay (LOS). During the first 48-hours postoperatively, hypocalcemia was managed with intravenous injections of 10% calcium gluconate according to serum calcium level or symptoms or signs of hypocalcemia. Patients were discharged from the hospital after serum calcium levels were achieved normally with oral calcium replacement drugs.

Serum Ca, P and PTH levels were also measured at each six months after the surgery. 'Persistence' after surgery was defined as a high level of PTH persisting throughout postoperative 6 months[7]. 'Recurrence' was defined as PTH levels returned normal after surgery but increase after 6 months during the follow-up[7]. Oral calcium replacement and calcitriol drugs were prescribed in different doses for all patients postoperatively with consulted to Nephrology. All patients' serum 25-hydroxy vitamin D (25-OH Vit-D) level and bone mineral density test with using dual energy X-ray absorptiometry were measured preoperatively and at postoperative 6$^{th}$ months.

***Statistical Analysis***

Each result of continuous variables were presented as mean±SD (standard deviation) and (minimum-maximum), results of categorical variables were presented as frequency and percentage. In the preoperative and postoperative period obtained measurements at different time were tested with Repeated Measurement ANOVA. Variables between time periods were evaluated with Repeated Contrast. At the preoperative and postoperative time measurements were compared with Paired Sample T-Test. Symptoms were evaluated with McNemar's Test. The level of significance was set at 0.05 ($p<0.05$). Statistical analyses were performed using the statistical package SPSS v 18.0.

## Findings

In this study, when the inclusion criteria was ensured; six, eight and nine patients were situated in Group A, B and C, respectively. Mean age of 23 patients was 47.87±14.769 (24-73) at operation time. 12 male patients were situated in the study. There were no statistically significant differences in mean age and gender between the groups. Demographics and clinical data of the patients were summarized in ***table 1***.

22 patients (95.7%) were hemodialysis-dependent with CRF, one patient had symptoms and high PTH levels with malabsorbtion without CRF. 12 patients (52.2%) had nephrolithiasis history, 10 patients (43.5%) with HT. Eight patients (34.8%) had severely pruritis in all groups (one, four and three in Group A, B and C, respectively).

**Table 1.** Demographics and clinical data of patients

| | Group A n=6 | Group B n=8 | Group C n=9 | p value |
|---|---|---|---|---|
| **Mean age (years)** | 53.83±14.47 (33-67) | 44.88±14.27 (24-57) | 46.56±15.90 (27-73) | NSa |
| **Gender (male/female)** | 4/2 | 4/4 | 4/5 | NSa |
| **Mean operation time (minutes)** | 152.67±20.5 (125-175) | 134.75±12.1 (110-150) | 155.33±14.0 (131-186) | p=0.033 |
| **Mean LOSb (days)** | 3.17±1.32(2-5) | 2±0.53(2-4) | 2.44±0.52(2-4) | p=0.047 |
| **Hypocalcemia (first 48-hours)** | 3/6 (50%) | 0 (0%) | 1/9 (11.1%) | p=0.036 |

**a** (NS): not significance (p>0.05), **b** (LOS): length of hospital stay

Postoperatively no new-onset pruritis symptoms had seen, but two patients in Group B had also pruritis. Improvement in pruritis postoperatively was seen in all patients (p=0.031), but there was no statistically significant difference in pruritis between the groups (p>0.05).

Preoperative localization studies with combined USG and Tc-99m sestamibi parathyroid scans revealed parathyroid pathology at least one gland in 14 patients (60.9%).

Mean operation time was 147.48±17.812 (110–186) minutes in all groups (For Group A: 152.67±20.559 (125-175), Group B: 134.75±12.199 (110-150), Group C: 155.33±14.050 (131-186) minutes). Mean operation time was significantly different in Group C compared to the others (p=0.033).

Drains were used in six patients (26.1%). Mean LOS time was 2.45 ± 0.898 (2-5) days in all groups (For Group A: 3.17±1.32 (2-5), Group B: 2±0.53 (2-4), Group C: 2.44±0.52 (2-4) days). Mean LOS time was significantly different in Group A compared to the others (p=0.047).

No patients had vocal cord paralysis temporarily or permanently other than severe hypocalcemia. Low level of serum calcium with symptoms was seen in four patients (17.4%) within postoperative first 48-hours and they were treated medically. Postoperative intravenous and oral calcium replacement was required in three patients for Group A (one of them had hypocalcemia induced convulsion) and in one patient for Group C. Early period hypocalcemia was significantly different in Group A compared to the other groups (p=0.036).

Serum calcium and phosphorou levels were significantly different in all groups postoperatively compared to preoperative levels (p=0.002 for each one). However decreases in serum calcium and phosphorous levels were similar between the groups (p>0.05 for each one). Calcium levels of the patients were summarized in ***figure 2***.

Preoperative and postoperative serum PTH levels were significantly different between groups (p=0.001). At follow-up period PTH levels were decreased at 6-months, and again increased in Group A. However distinctly lowered and stable levels within 24-months were

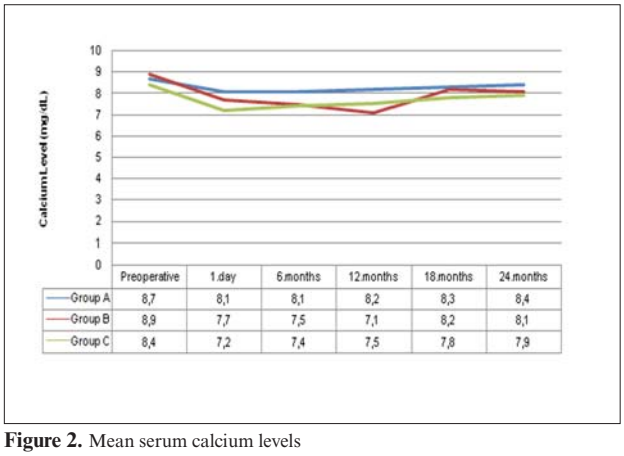


**Figure 2.** Mean serum calcium levels

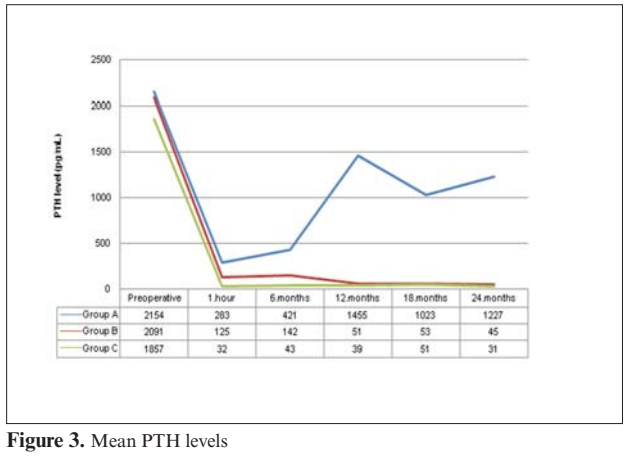


**Figure 3.** Mean PTH levels

maintained in Group B and Group C compared to Group A. Five patients in Group A and one patient in Group B had high PTH levels during the study period. We proposed reoperation (total PTX) to six patients, but only four patients (three patients in Group A and one patient in Group B) accepted, the other two patients in Group A refused the operation due to improvement symptoms and risk of reoperation. PTH levels of the patients were summarized in ***figure 3***.

Serum 25-OH Vit-D levels increased postoperatively in all groups ($p<0.001$) ***(figure 4)***, however there was no significant difference between the groups ($p>0.05$). Bone mineral densitometry values improved in all groups postoperatively ($p=0.041$) ***(figure 5)***. However there was no significant difference between the groups ($p>0.05$).

## Discussion

CRF is the most common cause of SHPT [8]. Other etiological reasons of SHPT are malabsorption, osteomalacia and rickets[1]. PTX is required in about 20% of CRF patients after 3-10 years of dialysis and in up to 40% after 20 years[5]. Most of patients (%95.7) in our study were also dialysis-dependent. Improvement of pruritis was seen in all groups postoperatively.

The National Kidney Foundation of the USA proposed for renal HPT patients on dialysis in the Kidney Disease Outcomes Quality Initiative (K/DOQI) a serum calcium level between 8.4 and 9.5 mg/dl, serum phosphorous level of 3.5–5.5 mg/dl, calcium/phosphorus product of < 55 $mg^2/dl^2$, and PTH of 150–300 pg/ml[6]. Patients with a severe renal HPT, including PTH levels of >800 pg/mL and hypercalcemia or hyperphosphatemia despite medical treatment, will benefit from surgical treatment[6]. In the present study lowest preoperative PTH level was higher ten times than upper limit (>500 pg/mL), and mean PTH level was 1924 pg/mL.

Imaging of the neck is normally unnecessary, because SHPT primarily results from 4-gland hyperplasia. However, preoperative imaging may be useful in facilitating surgery, especially in the reoperative setting and if one of the glands is in an ectopic position[1]. USG and MIBI offer little benefit in localizing ectopic glands and rarely change the conduct of a standard four-gland exploration[9]. Vulpio et al reported that the combined use of USG and MIBI were with higher sensitivity[10]. Sukam et al reported that preoperative evaluation with USG and scintigraphy in SHPT, the sensitivity was been 60% for both imaging procedures, and also the overall sensitivity of combined US and MIBI in SHPT was been 71%[11]. We also used combined USG and Tc-99 m sestamibi parathyroid scans in the study patients and partial benefit was obtained in 60.9% of patients in the present study.

Kuo et al reported longer operation time in total PTX+AT patients similarly the present study probably due to simultaneous performance of additional procedures [12]. In the recent study, LOS varied between 2 and 10 days relating to early time complication[12,13]. In the present study postoperatively, no vocal cord paralysis or substantial bleeding, hematoma or seroma requiring reoperation was recorded. The mean LOS was between 2 and 5 days and was higher in Group A ($p=0.047$); dealed with in early period after postoperative hypocalcemia also is seen mostly in Group A ($p=0.036$).

Previous studies were reported that hypocalcemia occurred frequently and phosphate levels were lowered after PTX in SHPT[7,14,15]. Wetmore et al reported that calcium levels remained very low in about one-quarter of patients through postoperative 3 months, approximately 17% of patients were hospitalized for hypocalcemia within 90 days and persistent hypocalcemia was not uncommon; levels were 7.1 mg/dL or less for 10% of patients even 1 year after the procedure[15]. Puccini et al also reported %23 patients developed hypocalcemia that required treatment for more than three days after

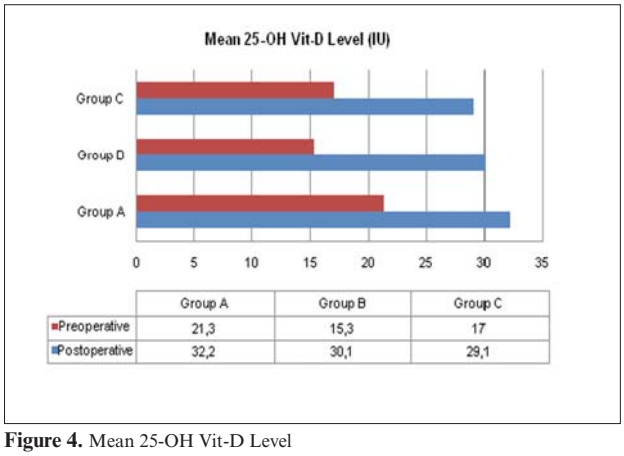


**Figure 4.** Mean 25-OH Vit-D Level

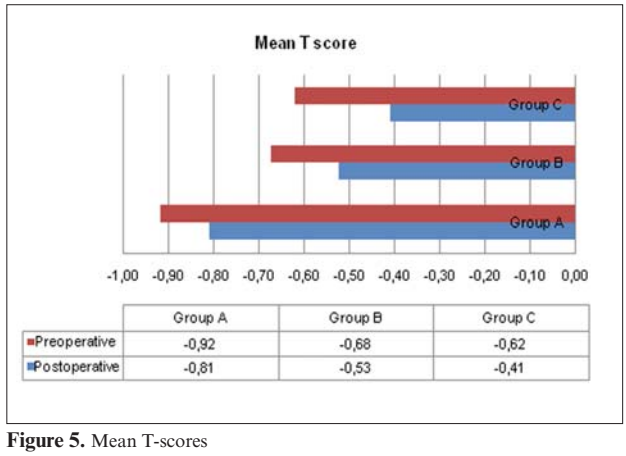


**Figure 5.** Mean T-scores

total PTX without AT[16]. In the present study 17.4% patients had symptomatic hypocalcemia during the postoperative 48 hours and were treated medically in hospital. Although they received in-adequate parathyroidectomy in Group A, 50% of those also experienced hypocalcemia to an extent. This showed that "adynamic bone disease" could be observed. Phosphate levels were also decreased obviously in all groups after operation such as would have been expected[13].

The pathophysiology of SHPT commonly results from the relationship between CRF and parathyroid hyperplasia[1]. In combination, elevated serum phosphate levels and reduced vitamin D production result in decreases in serum calcium levels[1]. Hyperphosphatemia and low vitamin D also cause elevated PTH levels[1]. As a consequence of prolonged hypocalcemia, parathyroid chief cell hyperplasia occurs and PTH secretion increases[1]. Skeletal resistance to PTH results in persistent and frequently extremely elevated PTH levels and renal osteopathy[1,17]. In the present study, patients had lower mean PTH levels after PTX compared to preoperative levels, but only in Group B and Group C patients significantly maintained the normal PTH levels throughout 24-months. However, most of the recently studies reported persistence/recurrence SHPT rates between 10 and 20% after a mean follow-up of 36 months following PTX[18-25].

In the present study, after the removing the patients who had concomitant thyroidectomy and refusing of the follow-up, remaining 27 patients could be followed and 6 of them (22%) had need for reoperation: 5 in Group A and 1 in Group B, totally higher ratio than would have been expected. In the study persistence/recurrence rates after incomplete parathyroidectomy (Group A) were found very high 5/9 (55.6%). Gasparri et al reported also less satisfactory results were obtained after incomplete parathyroidectomy; when a gland was not found, the recurrence rate was 34.7%[26]. Ozmen et al reported higher rate biochemical persistence/recurrence rates after the median 60 months follow-up period for both adequate and inadequate surgery groups, 40% and 75%, respectively. High recurrence rates could be thought to deal with inadequate surgery, undetermined extranumerary glands, hypersecretion by remaining gland tissue and low renal transplantation rate in that study[7].

When we focused on Group B and C in which revealed 4 glands, only one patient (5.9%) in Group B had need for reoperation, lower rate compared to study of Schneider et al in which recurrence was been reported 9% for subtotal PTX and 5.4% for TPTX+AT [18].

Resection of less than 3.5 parathyroid glands in SHPT patients with asymmetric parathyroid hyperplasia may not be considered an adequate option due to the high risk of persistence/recurrence[6]. Cases showing fewer than four glands are described in different percentages (2%-31%) in the literature. Declaration of different percentages in different studies could be deal with varying total number, undetermined due to small size or ectopic location of glands, length of follow-up period or technical failure in autopsies or surgery[27,28]. In the present study, patients with revealed 3 parathyroid glands were also 33.3%, and most of them (55.5%) had also elevated PTH levels compared to normal upper limit postoperatively. Need for reoperation ratio was high in this group (Group A), we thought due to mainly undetermined gland and inefficient surgery other than possible mentioned reasons. We didn't use intraoperative parathormone (IOPTH) assay monitoring, but high reoperation need ratio couldn't be lowered with it, because effectivity of IOPTH assay monitoring in SHPT remains undefined and is certainly not as clear in its potential for use in surgery as it is for primary HPT[6].

PTX increases long-term survival in dialysis patients and also improves bone mineral density (BMD) and decreases the risk of fracture[29]. We didn't evaluate the survival, but found amelioration in T-score and serum 25-OH Vit-D level of all patients after the following surgery.

Jing et al reported symptomatic relief after total PTX+AT, Ozmen et al reported also symptomatic relief in both adequate and inadequate surgery group[7,13]. Cheng et al reported that PTX had attenuated most of symptoms during midterm follow-up (12 months)[29]. Puccini et al reported the results after total PTX without AT, patients had symptomatic relief (69-87%) similarly both at postoperative first week and at last follow-up (median 8 years)[16]. In the present study, we found improvement in pruritis postoperatively with different levels in all study groups.

## Conclusion

At the end of the study, patients had lower PTH, phosphorous and serum 25-OH Vit-D levels; better T-score and improvement in pruritis, prominently in Group B and C postoperatively.

PTX is important treatment modality especially in our country with low renal transplantation rate in SHPT patients. PTX is associated with improvement in pruritis complaints, bone mineral density and 25-OH Vit-D level. Even though partially amelioration, resection of less than 3.5 parathyroid glands in SHPT patients should not be considered an adequate option due to the high risk of persistence/recurrence. Surgical technique is certainly valueable in SHPT because of lowering need for reoperation rates and morbidities; surgeons should attribute to find out at least 4 glands. Total PTX+AT and subtotal PTX in patients with SHPT is associated with significant stable lowered PTH levels and persistence/recurrence rates.

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