

Comparison of Long-term Clinical Outcomes of the Preferred Surgical Techniques in Secondary Hyperparathyroidism Cases

Sekonder Hiperparatiroidi Olgularında Tercih Edilen Cerrahi Tekniklerinin Uzun Dönem Klinik Sonuçlarının Karşılaştırılması

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Abstract

Objective: Secondary hyperparathyroidism (SHPT), that progresses with the deterioration of calcium-phosphorus metabolism detected in chronic kidney disease patients. Recurrence of SHPT may result in the recurrence of symptoms. Our aim was to compare the 5-year clinical results of autotransplantation after total parathyroidectomy (PTX-AT) with subtotal parathyroidectomy (SPTX).

Materials and Methods: We analyzed 140 patients retrospectively from January 2000 and October 2020 who were operated due to SHPT. Clinical and demographic characteristics of the patients, preoperative and postoperative (1st day, 1st month, 6th month, 1st year, 5th years) serum PTH, calcium (Ca), phosphorous (P) values and length of hospital stay (LOS) were compared in terms of operations performed. The Shapiro-Wilks test was used for analyzing normally distributed datas. Mann-Whitney U test used to evaluate of comparison of numerical data. Fisher's Exact or chi-square test was used for ratio comparisons or correlation. P<0.05 was considered statistical significance level.

Results: Of these 140 patients, 106 (75.7%) had SPTX. On the other hand, 34 patients (24.3%) underwent PTX-AT surgery. When the groups were compared in terms of the gender, age and comorbidities, the differences were statistically significant. Additionally, no statistically significant difference was found between the groups in terms of postoperative complications (p=0.206). The difference between the weights and sizes of the parathyroid glands removed between the operation groups was not statistically significant (p=0.751, p=0.176). The difference was not statistically significant between the groups in terms of PTH, Ca and P levels measured. LOS was statistically significantly longer in PTX-AT patients (p=0).

Conclusion: The surgical methods in the treatment of SHPT have no difference each other. Depending on the surgeon's preference, both surgical methods can be safely applied with high success rates.

Öz

Amaç: Sekonder hiperparatiroidi (SHPT) kronik böbrek yetmezliği hastalarında (CKD) görülen bozulmuş kalsiyum-fosfor metabolizması ile karakterizedir. SHPT'nin rekürrensi, semptomların tekrarlamasına neden olabilir. Bu çalışmanın amacı subtotal paratiroidektomi (SPTX) ile total paratiroidektomi ile birlikte ototransplantasyon (PTX-AT) yöntemlerinin 5 yıllık klinik sonuçlarını karşılaştırmaktır.

Gereç ve Yöntemler: SHPT nedeni ile Ocak 2000 ile Ekim 2020 tarihleri arasında ameliyat edilen 140 hastayı geriye dönük olarak taradık. Hastaların klinik ve

demografik özellikleri, ameliyat öncesi ve ameliyat sonrası (1. gün, 1. ay, 6. ay, 1. yıl, 5. yıl) serum PTH, kalsiyum (Ca), fosfor (P) değerleri ve hastane yatış süreleri yapılan ameliyatlardan karşılaştırıldı. Veri normal dağılımları Shapiro-Wilks testi ile değerlendirildi. Araştırma gruplarına göre sayısal ölçümlerin karşılaştırılması veri dağılımına uygun olarak Mann-Whitney U test ile değerlendirildi. Araştırma gruplarına göre oran karşılaştırmaları veya ilişki araştırmaları ki-kare veya Fisher Exact test ile araştırıldı. $P < 0,05$ değeri istatistiksel olarak anlamlı kabul edildi.

Bulgular: Toplam 140 hastanın 106 (75,7%)'sına SPTX, 34 (24,3%)'üne ise PTX-AT ameliyatı yapılmıştır. Hastaların yaşları, cinsiyetleri ve komorbiditeleri açısından gruplar arası istatistiksel olarak anlamlılık saptanmamıştır. Gruplar ameliyat sonrası komplikasyonlar açısından karşılaştırıldığında fark istatistiksel olarak anlamlı değildi ($p=0,206$). Ameliyat grupları arasında çıkarılan paratiroid bezlerinin ağırlıkları ve boyutları arasındaki fark istatistiksel olarak anlamlı değildi ($p=0,751$, $p=0,176$). Gruplardaki PTH, Ca ve P değerleri arasındaki fark istatistiksel olarak anlamlı değildi. PTX-AT grubunda hastane yatış süresi istatistiksel olarak anlamlı şekilde daha uzun saptandı ($p=0$).

Sonuç: CKD hastalarında SHPT'nin cerrahi tedavisinde SPTX ile PTX-AT yöntemleri arasında herhangi bir fark yoktur. Cerrahin tercihine göre her iki cerrahi yöntem de yüksek başarı oranları ile güvenle uygulanabilir.

Introduction

Secondary hyperparathyroidism (SHPT) can be seen in approximately 85% of patients with chronic kidney disease (CKD). This disease needs attention during treatment period as it can have fatal complications (1). It is manifested by impaired calcium (Ca)-phosphorus (P) metabolism, calcifications in the vascular areas and disruption of bone turnover (2). Its pathophysiology involves an abnormal parathyroid hormone (PTH) response to hyperphosphatemia and hypercalcemia, coupled with 1,25-dihydroxyvitamin D deficiency, in end-stage renal disease (3). It may cause itching, bone pain, and cardiovascular complications that may negatively affect patient's social life. Treatment of SHPT composed of vitamin D preparations, calcimimetics and Ca-free phosphate binders (3). In cases resistant to medical treatment, parathyroidectomy (PTX) is an effective treatment to reduce the PTH level and equilibrate calcium levels and P levels. The most commonly used surgical methods in the treatment of SHPT are parathyroidectomy subtotaly (SPTX) or auto-transplantation after total parathyroidectomy (PTX-AX) of a part of the normally appearing gland into the brachioradial muscle or sternocleidomastoid muscle from the neck. Disease recurrence, surgical morbidity, and the risk of hypoparathyroidism should be considered when selecting a surgical method. While the risk of hypocalcemia and permanent hypoparathyroidism is lower after SPTX, the risk of recurrence and thus the risk of the repeatition of the surgical procedure is lower with PTX-AX (4). For these reasons, the debate on PTX techniques is still ongoing. Recurrence of SHPT may cause recurrence of symptoms and lead to increased morbidity and mortality secondary to cardiovascular

problems as a result of increased PTH levels. In this study, our purpose was analyze the 5-year outcomes of PTX and to compare SPTX and PTX-AT techniques in CKD patients with SHPT.

Materials and Methods

In this study, we evaluated 348 patients who was performed surgical procedure for hyperparathyroidism between January 2000 and October 2020. We retrospectively reviewed the patients medical records. Among such patients, those with primary hyperparathyroidism or tertiary hyperparathyroidism, and those whose follow-up had not been performed at our center were excluded (Figure 1). So, the study included 140 patients. The demographic characteristics of the patients were analyzed. In addition, preoperative serum PTH, Ca, P levels were recorded. The corrected Ca levels were

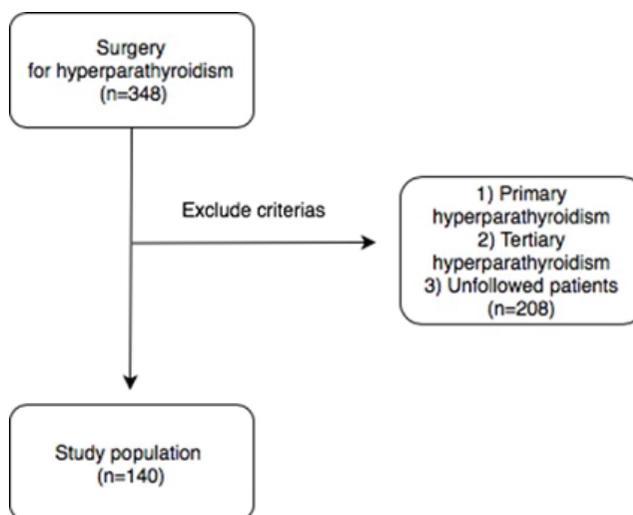


Figure 1. Flowchart of study design

determined on the basis of the serum albumin levels [corrected Ca level (mg/dL) = Total Ca level (mg/dL) + $[0.8 \times (4.0 - \text{albumin (g/L)})]$. Serum PTH, Ca, P levels at first postoperative day, first month, the sixth month, first year, and fifth-year were recorded. The normal laboratory ranges were determined as Ca: 8,8-10 mg/dL, PTH: 12-88 pg/mL, P: 2.3-4.7 mg/dL. The largest gland was evaluated by preoperative imaging studies, and weight the excised parathyroid glands weights were measured and recorded. After surgery, the recurrent cases within the first six months were considered as persistence, and the recurrent cases after that period were considered as recurrence. The study groups were assessed in terms of clinical, demographic, biochemical, and pathological parameters. Also, comparison was performed between the groups with respect to length of hospital stay (LOS). Additionally, the groups were compared in terms of postoperative complications, recurrence, and persistence rates.

Surgical Indications

Surgical indications were determined as failed medical therapy and/or dialysis; persistence of symptoms like bone pain and itching; a CxP product greater than 70; a high PTH level coupled with a Ca level above 11 mg/dL; parathyroid gland size greater than 1 cm or 500 mm³ in imaging studies; and increased vascularity of the parathyroid gland in preoperative Doppler ultrasonography.

Surgical Technique

The patients were taken on dialysis the day before the surgery to eliminate electrolyte imbalances. The surgeon performed subtotal or total PTX operations according to his own decision. All surgical procedures were performed with the patient's head in extension, using the Kocher's incision under general anesthesia. Unilateral or bilateral thyroidectomy operation was carried out if a thyroid pathology was detected at the preoperative period or the parathyroid gland could not be visualized. Bilateral neck exploration was used in all surgical operations. In order to verify that the excised specimens were the true parathyroid glands, a frozen examination was performed. In addition, serum PTH level was intraoperatively measured 20 minutes after parathyroid gland excision to demonstrate an 80% drop in the PTH level compared to the preoperative level as an indication of procedural success. In patients who underwent SPTX, half of the

parathyroid gland with the most normal appearance was spared if it was smaller than 1 cm³, or 1/3 to 1/4 of it if it was larger than 1 cm³. In patients who underwent PTX-AT, after removing all parathyroid glands, the normal-appearing parathyroid tissue was cut into 1 mm pieces and auto-transplanted into the musculus sternocleidomastoideus or the musculus brachioradialis. We preferred the non-dominant forearm for auto-transplantation. After placing a minivac into the surgical site depending on the hemostatic status, the operation was ended. We removed the drains on the first day after surgery.

Statistical Analysis

The study was intended to have a retrospective design. For numbers and percentages we used categorical variables. Mean \pm standard deviation or median (minimum-maximum) were used for numerical variables. The Mann-Whitney U test was used in the comparison of two groups that did not show normal distribution. Chi-square test and Fisher's Exact test were used to compare the proportions between the study groups. Statistical significance was set at $p < 0.05$.

Results

Among 140 patients, 106 (75.7%) underwent SPTX, and 34 (24.3%) PTX-AT procedure. Seventy-eight (55.7%) patients gender were male, and 62 (44.3%) patients gender were female. The mean age of the study population was 44.9 (21-77) years. At the time of operation, 18 (12.9%) patients had Type 2 diabetes mellitus (DM); 45 (32.1%) had hypertension (HT); and 34 (24.3%) had coronary artery disease (CAD) as a comorbidity. The difference was not statistically between the groups with respect to age, gender distribution, and comorbidities (Table 1). A comparison of the study groups by postoperative complications showed no significant difference ($p = 0.206$). Hoarseness was not observed in the SPTX group, while 2 (1.9%) patients in the same group developed no hematoma, and 16 (15.1%) patients developed no hypocalcemia. None of the patients who developed hematoma required re-operation. In the PTX-AT group, 1 (3%) patient suffered hoarseness and 3 (9.1%) patients suffered hypocalcemia while none of them developed a hematoma. When the groups were compared in terms of LOS, it was 2.09 (1-10) days in the SPTX group and 6 (1-12) days in the PTX-AT

group (p=0). Postoperative pathology examinations revealed no malignancy in any specimen. The mean parathyroid gland weight was 1895,08 (26-8900) mgr, and the mean parathyroid gland size was 14.06 (5-33) mm. There was a difference, but not significant, in terms of mean weight or mean size of the excised parathyroid glands (p=0.751, p=0.176, respectively) (Table 2).

Biochemical analysis revealed that the mean preoperative PTH level was 1621 (6.3-3573); the mean Ca level was 9.8 (6-12.9), and the mean P level was 5.45 (0.6-9.3). There was a difference between surgical techniques in terms of the levels of these parameters, but it was not significant. Similarly, the study groups were comparable in terms of PTH, Ca, P levels measured on the first day, first month, the sixth month, first year, and fifth-year postoperatively (Table 3).

Four (3.8%) patients in the SPTX group were found to have persistence, and 8 (7.5%) of them were found to have a recurrence. In the PTX-AT group, 2 (5.9%) patients had persistence, and 7 (20.6%) patients had a recurrence. No statistically difference was found in

terms of persistence and recurrence rates (p=0.678, p=0.064 respectively). While 14 (10%) of those who developed recurrence or persistence were re-operated, 126 (90%) patients continued to receive medical treatment.

Discussion

According to our study results, SPTX and PTX-AT are the similar surgical treatment method in terms of postoperative complications, pathological diagnosis, biochemical tests, or persistence rates during a long-term follow-up period.

Previous studies in the literature have reported that alterations in Ca and P values in patients with SHPT lead to increased mortality rates over the long term (5-7). Therefore, SHPT should be brought under control, either medically or surgically. We take the values defined by Kidney Disease: Improving Global Outcomes as the reference for the treatment of SHPT at our center. However, PTH targets can be attained in only 22% of medically managed patients. Furthermore, it is well known that part of medically managed patients may show treatment incompliance (8,9). For

Table 1. Demographic and clinical parameters of the study population

	SPTX (n=106)	PTX + AT (n=34)	p-value
Age	70.58*	70.25*	0.967
Sex (female/male)	50/56	12/22	0.225
Comorbidity			
DM	12 (11.3%)	6 (17.6%)	0.338
HT	34 (32.1%)	11 (32.4%)	0.976
CAD	24 (22.6%)	10 (29.4%)	0.423

SPTX: Subtotal parathyroidectomy, PTX-AT: Total parathyroidectomy with auto-transplantation, DM: Diabetes Mellitus, HT: Hypertension, CAD: Coronary artery disease, *Mann-Whitney U test-mean rank level

Table 2. Comparison of specimens in terms of weight and size

	SPTX (n=106)	PTX + AT (n=34)	p-value
The weight of the parathyroid gland (mgr)	70.13*	71.66*	0.848
The size of the parathyroid gland (mm)	71*	68.94*	0.796

SPTX: Subtotal parathyroidectomy, PTX-AT: Total parathyroidectomy with auto-transplantation, *Mann-Whitney U test-mean rank level

Table 3. Comparison of the biochemical parameters between subtotal parathyroidectomy and auto-transplantation after total parathyroidectomy groups

		SPTX (n=106)	PTX-AT (n=34)	p-value
PTH level (pg/mL)	1 day	70.7*	69.87*	0.917
	1 months	70.3*	71.12*	0.919
	6 months	69.47*	73.71*	0.596
	1 year	70.44*	70.68*	0.977
	5 years	69.54*	73.49*	0.622
Calcium level (mg/dL)	1 day	72.37*	64.66*	0.334
	1 months	68.73*	76.03*	0.360
	6 months	74.02*	59.51*	0.069
	1 year	73.50*	61.15*	0.122
	5 years	73.69*	60.56*	0.100
Phosphorus level (mg/dL)	1 day	68.24*	77.54*	0.244
	1 months	71.24*	68.19*	0.703
	6 months	66.92*	81.66*	0.065
	1 year	68.79*	75.82*	0.379
	5 years	66.72*	82.28*	0.052

SPTX: Subtotal parathyroidectomy, PTX-AT: Total parathyroidectomy with auto-transplantation, PTH: Parathormone, *Mann-Whitney U test-mean rank level

these reasons, surgical treatment is recommended for SHPT cases in a majority of the current guidelines (4,10). So far, three surgical techniques have been defined for SHPT treatment: SPTX, TPX-AT, and TPX. Since TPX causes complications (severe hypocalcemia, adynamic bone diseases), it is avoided today as much as possible (11). Hence, we did not use the TPX technique in any surgically managed SHPT patient at our center.

After PTX operations patients may develop some complications including hypocalcemia, hoarseness due to recurrent laryngeal nerve injury, or hematoma formation. While hypocalcemia may occur at a higher rate due to the elimination of osteoclastic activity or the hungry bone syndrome at the postoperative period, other complications such as hoarseness and hematoma occur more rarely, at rates ranging between 1% and 5% (12,13). Similar with the other studies, we found that only 1-3% of the cases suffered complications like hoarseness and hematoma. Postoperative hypocalcemia is usually temporary and occurs due to ischemia of the remaining parathyroid glands. It is easily treated with intravenous Ca and vitamin D. In a study, Schneider et al. (13) investigated the relationship between the surgical procedure and postoperative hypocalcemia, but found no difference between surgical techniques. Our study similarly showed a greater rate of hypocalcemia (9-15%) than other complications although there was no significant difference. In our patients, all episodes of postoperative hypocalcemia were temporary and treated medically. Although adequate PTH lowering is usually achieved early after the surgery, PTH, Ca, and P levels may impair in the postoperative long term period. This is caused by hyperplasia of the remnant parathyroid gland secondary to long-term hemodialysis in patients undergoing SPTX; it may also occur in patients undergoing TPX-AT due to hyperplasia of the implanted parathyroid gland in the long term due to implantation of an excess amount of parathyroid tissue. In addition, regardless of the surgery, if there is an ectopic parathyroid gland, it may result in abnormalities of PTH, Ca, and P levels in later periods (14). In the other studies no significant difference was found between both methods in terms of PTH, Ca, and P levels in long term (15-18). Likewise,

our study did not show any significant difference during a 5-year follow-up period between groups.

In the literature, increased bone turnover, low preoperative serum Ca and postoperative complications are shown as the determinants of LOS (19,20). In these patients, after PTX, low serum Ca levels are detected and usually after surgery iv. Ca replacement is required. We did not find significant difference between the groups in terms of serum Ca and postoperative complications. However, we found significant difference in terms of LOS. LOS was significantly higher in the PTX-AT group. We think that this difference is due to the time required for the blood supply of parathyroid tissue, which autotransplanted during surgery, in the PTX-AT group.

In surgically treated SHPT cases persistence is defined as the lack of any postoperative fall in serum PTH level. Recurrence, on the other hand, is defined as an elevation of serum PTH level 6 months or later after surgery. Although a study by Melck et al. (21) showed somewhat higher recurrence and persistence rates in TPX-AT cases, that difference did not reach statistical significance. Higher rates in TPX-AT cases may result from a greater amount of implanted parathyroid gland (22). In accordance with the literature, our study found higher persistence and recurrence rates in the TPX-AT group despite failing to demonstrate any statistical significance.

As for the limitations of our study, the important limitations are that, number of patients is small and the unequal distribution of the groups was unequal. In addition, due to the retrospective design of our study, we could not reach demographic and follow-up datas of some patients. More detailed and effective study results may be obtained by a prospective multi-center study with a larger study population.

Conclusion

SHPT is an important, potentially fatal disorder that must be treated accordingly in patients with CKD. There is no difference between SPTX and TPX-AT techniques in treatment of SHPT. Depending on the surgeon's experience, both surgical techniques can be used safely with high success rates.

Ethics

Ethics Committee Approval: The present cohort study was designed as a survey and was approved by the Clinical Research Ethics Committee of Başkent University (no: KA20/485, date: 05.01.2021).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.K., M.E., Concept: E.K., M.E., Design: E.K., Data Collection or Processing: E.K., M.E., Analysis or Interpretation: M.E., Literature Search: E.K., M.E., Writing: E.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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