



## Original Research

# Intraoperative Parathyroid Hormone Monitoring-Guided Subtotal Parathyroidectomy is an Effective and Valid Surgical Procedure for Secondary Hyperparathyroidism

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### ABSTRACT

**Objectives:** Secondary hyperparathyroidism (sHPT) is a prevalent complication of end stage renal disease in which serious morbid conditions and mortality can be encountered. Although the best solution of this severe problem is renal transplantation, because of the huge demand and limited resources, this cannot be possible most of the time. Initial treatment alternative is medical treatment in patients with sHPT and parathyroidectomy (PTX) should be applied if does not help. Subtotal PTX, total PTX and total PTX together with autotransplantation are the current surgical options preferred for sHPT. Intraoperative parathyroid hormone (IO PTH) monitoring can increase surgical success in sHPT. We aimed to determine the ideal surgical technique and relation of IO PTH monitoring with surgical success in patients with sHPT through our study.

**Methods:** We analyzed all the data of the 35 patients who had PTX and follow up between January 2001 and December 2021 because of sHPT at General Surgery Department of Akdeniz University Medical Faculty Hospital in retrospective manner.

**Results:** Twenty-seven of the patients had been applied subtotal PTX while six of the cases had experienced limited surgery and two of them had undergone total PTX. Persistence happened to be present in the follow-up of nine patients and recurrence in one of them. Four persistent and one recurrent cases were present in 23 patients with IO PTH monitoring (78.3% surgical success), while there were persistences in each of the three patients with no IO PTH monitoring (0% success of surgery) ( $p=0.022$ ). IO PTH monitoring data of nine patients could not be reached. In this study, 20 patients had IO PTH decline of 80% or more (90% surgical success) and three patients had IO PTH decline below 80% (0% surgical success) ( $p=0.006$ ). Subtotal PTX was applied to 17 (94.1% surgical success) of these 20 patients.

**Conclusion:** In surgical treatment of patients with sHPT, IO PTH monitoring should be maintained and operation should not be finished until 80% or more decline in IO PTH level had been detected. Among the surgical alternatives for sHPT, subtotal PTX appears as an effective and valid method when performed together with IO PTH monitoring, provided that there is a decline in PTH level of 80% or more.

**Keywords:** Intraoperative parathyroid hormone monitoring, parathyroidectomy, secondary hyperparathyroidism

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In patients with chronic renal failure and end stage renal disease (ESRD), due to the imbalance of calcium (Ca) and phosphate (P) metabolism, adoptive hyperplasia of the parathyroid glands resulting in an increase of parathyroid hormone (PTH) level contributing many important problems such as bone fractures, neurologic impairment, anemia, and cardiovascular morbidity and mortality can be encountered (secondary hyperparathyroidism [sHPT]).<sup>[1,2]</sup> sHPT is a prevalent complication of ESRD<sup>[1]</sup> and the best solution of this severe condition is renal transplantation (RTX).<sup>[3,4]</sup>

However, because of the huge demand and limited resources, RTX may not be feasible in most cases and most of the patients may not be suitable candidates for RTX.<sup>[5,6]</sup>

Phosphate restriction in the diet and usage of phosphate binding derivatives, Vitamin D and its analogues, calcium, and calcimimetics (cinacalcet) may improve imbalances and reduce symptoms to a tolerable extent.<sup>[1,4,7]</sup>

When conservative approach does not help and symptomatology worsens or PTH level resists to be above 600–800 pg/mL together with or without Ca level being >10.0–10.2 mg/dL and P level above 6.0–6.5 mg/dL after medical treatment for 6 months, surgical treatment should be applied.<sup>[7–9]</sup> If the volume of the parathyroid tissue is more than 500 mm<sup>3</sup> or the diameter of the tissue is more than 1 cm in ultrasonography (USG), it is also accepted as an indication for parathyroidectomy (PTX).<sup>[7,10]</sup> Intolerable side effects of cinacalcet and patient's non-compliance with the use of the medicine can also be regarded as indications of surgery for sHPT.<sup>[9,10]</sup>

Among the patients having hemodialysis (HD), it had been observed that approximately 15% of those with HD more than 10 years and 38% of those with HD more than 20 years had been requiring PTX.<sup>[11]</sup>

Subtotal PTX, total PTX, and total PTX together with autotransplantation (AT) are the current surgical options preferred in surgery for sHPT.<sup>[1,12,13]</sup> Thymectomy can also accompany these procedures.<sup>[7,14]</sup>

Furthermore, some authors define less invasive procedures such as limited surgery (LS) and subtotal PTX as choice of operation type in sHPT when possibility of RTX is highly probable.<sup>[4,15]</sup>

Another important issue for better surgical success is the use of intraoperative PTH (IO PTH) monitoring in surgery for sHPT.<sup>[15]</sup>

Considering that living donor and cadaveric kidney transplantation operations are performed in the institution where we work with a quite high rate (4656 RTX in the time frame in the scope of the study), we aimed to determine

the ideal surgical technique and the relation of IO PTH monitoring with success of surgery in patients with sHPT by means of our retrospective study.

## Methods

We documented and analyzed all the pre-operative and post-operative data of the 35 patients who had PTX and follow-up between January the 2001 and December the 2021 because of sHPT at General Surgery Department of Akdeniz University Medical Faculty Hospital in retrospective manner. Patient demographics (like age and sex), symptomatology of the patients (whether they were asymptomatic or if they had symptoms such as bone pains and fractures, arthralgia, mental status changes, anemia, dyspepsia, itching, calyphlexia, and weakness in the proximal muscles; such as disability of getting up from a chair and every kind of complaints due to cardiovascular disorders),

administration of medical treatment conservatively before surgery (use of phosphate binding agents, Vitamin D analogs, and cinacalcet), whether the patients had HD or peritoneal dialysis (PD) (if they did; the duration), pre-operative radiologic localization investigations about the parathyroid pathologies (such as USG, Tc99m Sestamibi scintigraphy [MIBI] and single photon emission tomography [SPECT]), operation types (subtotal PTX, total PTX, and LS), intact PTH and serum Ca, P, and creatinine values in the pre-operative and post-operative (before discharge from the hospital after the operation, at the end of the 1<sup>st</sup>, 6<sup>th</sup>, 12<sup>th</sup>, 24<sup>th</sup>, and 36<sup>th</sup> months postoperatively) periods, periodic intact PTH measurement values during the PTX procedure, complications due to the surgeries, results of the pathologic examinations, success of the operative procedures (status of persistence and recurrence), and post-PTX follow-up periods' durations were all collected and examined.

IO PTH measurements were done in the central laboratory of our hospital through Roche and Siemens systems, which have been preferred over each other from time to time during the study interval of approximately 21 years. Electrochemiluminescence was the method of PTH measurement considering Roche system and chemiluminescence was so for the Siemens immulite. Roche PTH STAT kits suitable for IO PTH measurement were in charge at 2007–2014 period and at the years of 2020 and 2021 at our hospital.

While applying IO PTH monitoring during PTX, we obtained the intact PTH level at the beginning of the operation after incision before any excision (initial measurement) and we repeated the measurement of PTH level 10 min after excision of each parathyroid gland. When calculating the percentage of decrease in IO PTH level, the initial measurement and the measurement made 10 min after the completion

of the whole PTX were taken as the basis. Final decisions about finishing the operations were made according to the percentage of IO PTH decline levels by the surgeons in the cases with IO PTH monitoring. Furthermore, we confirmed each lesion (including supernumerary and ectopic glands) to be parathyroid gland through pathologic examinations of the frozen sections meanwhile.

All of the PTXs were the first operations of our patients with sHPT.

In this study, total PTX means excision of four parathyroid glands completely while subtotal PTX stands for resection of 3.5 glands and LS refers to removal of one or two glands.

We handled persistence terminology as PTH elevation above 300 pg/mL within the first 6 months period after PTX and recurrence as PTH elevation of more than 5 times of the normal range after the 6<sup>th</sup> post-operative month.<sup>[16-18]</sup>

Success of PTX is also considered as lack of persistence and recurrence in our study.

This research, which was approved by Ethics Committee of Akdeniz University Faculty of Medicine Hospital, Approval No: 24.08.2022/498, was conducted in accordance with the Declaration of Helsinki.

## Statistical Methods

Continuous variables are reported as medians and interquartile ranges, and categorical variables as counts and percentages. Pearson Chi-square and Fisher's exact tests were used for comparative analysis in between the variables (p-value relative to expected value). Statistically significant value was  $p < 0.05$ . All statistical analyses were performed using IBM SPSS Statistics for Windows, version 23 (IBM Corp. Armonk, N.Y., USA).

## Results

Twelve (34.3%) patients were male while 23 (65.7%) were female and median age was 39 (18–73) (Table 1). Asymptomatic status was observed in 22 (68.8%) out of 32 patients (symptomatology condition could not be documented in three patients) (Table 1). Asymptomatic status was encountered approximately 2.7 times more in female patients (72.7%/27.3%) (Table 1). Within the symptoms we searched, the most common symptoms were anemia (53.1%), bone pain (51.5%), and arthralgia (51.5%) with close percentages, followed respectively by dyspepsia (34.3%) and weakness in proximal muscles (33.3%). Other symptoms had been observed with a much lower extent. About 65.5% (19/29) of the patients had HD for 9.0 (1.0–28) years whereas 34.5% (10/29) had PD for 2.5 (1.0–20) years before surgery (Table 1). Medical treatment rate was 87.5% (21/24) throughout the patients, we could reach enough data and treatment

**Table 1.** Demographic features, pre-operative laboratory values, IO PTH monitoring status, operative methods, HD/PD status, and pre-operative medical treatment modalities of 35 patients

Age, years (IQR)	39 (18–73)
Gender, n (%)	
Male	12 (34.3)
Female	23 (65.7)
Median Follow-up, months (IQR)	30 (3–72)
Asymptomatic patients/Female Patients, n (%)	22 (68)/16 (72.7)
Median Pre-operative Calcium, mg/dL (IQR)	9.6 (7.8–12)
Median Pre-operative PTH, pg/mL (IQR)	1944 (299–2830)
Median Pre-operative Phosphate, mg/dL (IQR)	9.6 (7.8–12)
Median Pre-operative Creatinine, mg/dL (IQR)	5.9 (1.6–12.5)
IO PTH Monitoring, n (%)	23 (65.5)
Operation Types, n (%)	
Subtotal PTX	27 (77.1)
Total PTX	2 (5.7)
Limited Surgery	6 (17.1)
HD Patients n (%) / Median years (IQR)	19 (65.5) / 9 (1–28)
PD Patients n (%) / Median years (IQR)	10 (34.5) / 2.5 (1–20)
Medical Treatment, n (%)	21 (87.5)
Phosphate Binders, n (%)	16 (66.7)
Vitamin D Analogs, n (%)	14 (58.3)
Cinacalcet, n (%)	17 (70.8)

n: Number of patients; IQR: Interquartile range; PTH: Parathyroid hormone; mg/dL: milligram/deciliter; pg/mL: picogram/milliliter; IO PTH: Intraoperative parathyroid hormone; PTX: Parathyroidectomy; HD: Hemodialysis; PD: Peritoneal dialysis.

was consisted of P binding derivatives, Vitamin D analogs, and cinacalcet with similar ratios (66.7%, 58.3%, and 70.8%, respectively) (Table 1).

Median pre-operative values were 9.6 (7.8–12) mg/dL for Ca, 9.6 (7.8–12) mg/dL for P, 1944 (299–2830) pg/mL for intact PTH and 5.9 (1.6–12.5) mg/dL for creatinine (Tables 1 and 2).

Pre-operative radiologic localization studies had been done to all of the patients except for two. We used mainly USG and MIBI. Furthermore, we established USG, MIBI, and SPECT meantime in two out of 32 patients (we could not reach enough radiologic data in three patients).

We monitored PTH levels during PTX in most of the patients (Tables 1–3). We also documented serum Ca, P, creatinine, and intact PTH values before hospital discharge after PTX and Ca, P, and PTH levels several times in the post-operative follow-up period (Table 2). Median values were 7.9 (5.3–9.9) mg/dL for Ca, 2.4 (1.1–8.67) mg/dL for P, 48 (1.9–1477) pg/mL for intact PTH and 6.95 (2.5–20) mg/dL for creatinine before hospital discharge after PTX and as 9.3 (6.3–10.3)

**Table 2.** Pre-operative and post-operative laboratory data of 35 patients

	PREOP	BD	PO1M	PO6M	PO12M	PO24M	Final
Calcium, mg/dL (IQR)	9.5 (7.8–12)	7.9 (5.3–9.9)	8.1 (6.6–10.2)	7.85 (5.1–11.6)	8.35 (7.9–10.9)	8.8 (7.0–9.9)	9.3 (6.3–10.3)
PTH, pg/mL (IQR)	1895 (299–2830)	48 (1.9–1477)	40 (3.7–1548)	67.5 (1.2–1900)	66 (1.6–1933)	108.5 (0.7–2902)	267 (1.0–1860)
Phosphate, mg/dL (IQR)	9.6 (7.8–12)	2.4 (1.1–8.67)	2.8 (1.5–9.5)	3.65 (1.3–9.3)	4.7 (1.7–8.9)	4.3 (1.5–8.9)	5.1 (2.5–8.2)
Creatinine, mg/dL (IQR)	5.95 (1.6–12.5)	6.95 (2.5–20)					

PTH: Parathyroid hormone; BD: After parathyroidectomy before discharge; IQR: Interquartile range; mg/dL: milligram/deciliter; pg/mL: picogram/milliliter; M: Months; Final: Final follow up values; PREOP: Pre-operative; PO: Post-operative.

**Table 3.** Success of surgery according to the operative methods and usage of IO PTH monitoring

	n, Total	Group 1	Group 2	Group 3	Success of Surgery, n (%)			
					General Success Rate	Group 1	Group 2	Group 3
Subtotal PTX	27	17	1	3	22 (81.5)	16 (94.1)	0 (0)	0 (0)
Total PTX	2	1	-	-	2 (100)	1 (100)	-	-
Limited surgery	6	2	2	-	1 (16.7)	1 (50)	0 (0)	-
						18* (78.3)		0* (0)
						18** (90)	0** (0)	

n: Number of patients; IO PTH: Intraoperative parathyroid hormone; PTX: Parathyroidectomy; Group 1: Patients with IO PTH decline of 80% or more; Group 2: Patients with IO PTH decline below 80%; Group 3: Patients with no IO PTH monitoring; \*Success of surgery according to the usage or not usage of IO PTH monitoring; \*\*Success of surgery when IO PTH decline is 80% or more and when it is below 80%.

mg/dL for Ca, 5.1 (2.5–8.2) mg/dL for P, and 267 (1.0–1860) pg/mL for intact PTH at the end of the whole follow-up (Table 2).

Median post-operative follow-up period was 30 (3–72) months (Table 1).

Among the 35 patients, 27 of them had been applied subtotal PTX, six of the cases had experienced LS whereas two of them had undergone total PTX (Tables 1-3). Pathology results of 22 patients were reported as hyperplasia whereas four of them were documented to be adenoma and one as parathyroid carcinoma (results were unavailable in eight patients). We detected a fifth parathyroid gland inside thymus of a patient with sHPT whom we applied subtotal PTX. This patient developed recurrence at the end of the follow-up period of 24 months suggesting a supernumerary gland. Furthermore, in another patient in whom we established total PTX without IO PTH monitoring guidance, we excised a supernumerary gland (proven to be parathyroid gland through frozen sections) which we found incidentally.

Persistence happened to be present in the follow-up of nine patients and recurrence in one of them in the whole patient group (Table 3). Globally, we documented 81.5% of surgical success rate among 27 patients whom we applied subtotal PTX, 100% of success rate in two patients with total PTX, and 16.7% surgical success in six patients with LS (Table 3). Four persistent and one recurrent case were pres-

ent in 23 patients with IO PTH monitoring leading 78.3% of surgical success while there were three persistences in three patients with no IO PTH monitoring contributing 0% success of surgery (Table 3) ( $p=0.022$ ). We could not reach the IO PTH monitoring data of nine patients (whether monitoring was done or not); therefore, we omitted them in comparative analysis.

In this study, 20 patients had IO PTH decline of 80% or more (one persistent and one recurrent cases; recurrent case was with subtotal PTX and the other one was with LS) and three patients had IO PTH decline below 80% (three persistent cases; two of them with LS and one with subtotal PTX) leading to 90% surgical success in the former group and 0% in the latter (Table 3) ( $p=0.006$ ). Subtotal PTX was applied to 17 (94.1% of surgical success) of these 20 patients (Table 3).

## Discussion

There are different concerns about the efficacy, advantages, and disadvantages of the three common surgical methods (subtotal PTX, total PTX+AT, and total PTX) used in surgery for sHPT<sup>[1,7,12]</sup> LS is generally not a method of choice in surgery for sHPT<sup>[9]</sup> and is preferred by few authors under certain circumstances.<sup>[4,19]</sup>

Surgical success ratios are variable among the previous studies. Liang et al.<sup>[13]</sup> operated 63 patients with sHPT by randomly preferring subtotal PTX, total PTX and total PTX-



+AT, and observed surgical success rates of 61.9%, 95.2%, and 90.4%, respectively. Neagoe et al.<sup>[20]</sup> achieved 83.4% success of surgery with subtotal PTX and 100% for total PTX+AT on 43 patients with sHPT. However, Conzo et al.<sup>[21]</sup> detected 70% success with total PTX interestingly.

Total PTX is regarded as the one with the lowest recurrence rate while subtotal PTX appears to be with the highest recurrence rate among the three common methods accepted in surgery for sHPT.<sup>[12]</sup> On the other hand, Yuan et al.<sup>[22]</sup> defined no difference between recurrence rates of patients having subtotal PTX and total PTX+AT.

Another important point is post-operative hypoparathyroidism condition which is quite hazardous for the viability of the graft if the patient with ESRD has RTX afterward.<sup>[4]</sup>

In some of the previous researches, quite high post-operative hypoparathyroidism rates had been mentioned after PTX for sHPT.<sup>[13,21]</sup> Liang et al.<sup>[13]</sup> reported post-operative hypocalcemia rates for the three methods (subtotal PTX, total PTX, and total PTX+AT) used in their investigation as 9.6%, 57.1%, and 23.8%, respectively. Conzo et al.<sup>[21]</sup> detected 25% of hypoparathyroidism rate after total PTX and 20% after total PTX+AT. Contrary to these, Uludağ<sup>[7]</sup> defined the rate of permanent hypoparathyroidism after PTX for sHPT as below 7% in general. Furthermore, Lorenz et al.<sup>[9]</sup> stated post-operative hypoparathyroidism ratio as 2% for subtotal PTX in surgery for sHPT.

Results of our study, in terms of our 27 patients with subtotal PTX regarding success of surgery (Table 3) and post-operative hypoparathyroidism, are consistent and compatible with those of the previous investigations in the same field. According to our results (Table 3), subtotal PTX seems to be a reasonable option in surgery for sHPT with quite high surgical success (81.5%) and low post-operative hypoparathyroidism ratio (7.4%). Because of the very limited number of the patients with LS (six patients) and total PTX (two patients) in our study (Tables 1-3), trying to make comparison of their results with the correspondents in the literature would be misleading.

Measurement of PTH level in periodic manner throughout the surgery had been a great opportunity for the endocrine surgeons dealing with hyperparathyroidism.<sup>[9,23,24]</sup>

In his prospective study, Amza et al.<sup>[15]</sup> operated 55 patients with sHPT and compared the surgical success between two cohorts; one of them consisting of 34 patients in whom there had been no IO PTH monitoring (Group 1) and the other one involving 21 patients with IO PTH monitoring (Group 2). Amza et al.<sup>[15]</sup> used two surgical alternatives (subtotal PTX and total PTX). Majority of the patients in Group 2 had been operated using total PTX while the opposite was so in Group 1.<sup>[15]</sup> Amza et al.<sup>[15]</sup> also preferred subtotal

PTX for the patients eligible for RTX. In this study,<sup>[15]</sup> IO PTH decrease above 50% had been assumed as sufficient and 100% remission had been observed in Group 2 while remission rate had been 76.47% in Group 1.

Konturek et al.<sup>[19]</sup> operated 297 patients with sHPT using either subtotal PTX (268 patients; 90.2%) or incomplete PTX (29 patients; 9.8%) and established IO PTH monitoring in 207 (69.7%) patients. A decrease of more than 60% in PTH level 10 min after parathyroid excision and at least 80% drop 20 min after excision had been considered effective in this research.<sup>[19]</sup> Persistence rate was 4.5% in patients with subtotal PTX whereas it was 17.2% in patients with incomplete PTX.<sup>[19]</sup> Significant difference had been observed between the cure rates of the patients with and without IO PTH monitoring (97.8% and 87.8%, respectively).<sup>[19]</sup>

Difference of surgical success rates of the patients with IO PTH monitoring in our research (Table 3) and that of Amza et al.<sup>[15]</sup> and Konturek et al.<sup>[19]</sup> is probably because of the abundant usage of total PTX by Amza et al.<sup>[15]</sup> and due to the presence of much higher number of patients in the related cohort of Konturek et al.<sup>[19]</sup>

In our study, success of surgery was found to be significantly higher in patients who underwent IO PTH monitoring compared to those who did not ( $p=0.022$ ) (Table 3). Similarly among those who underwent IO PTH monitoring, surgical success was detected to be significantly higher in patients with a decline of 80% or more with respect to those with a decrease of <80% ( $p=0.006$ ) (Table 3). Besides we also observed that IO PTH decline of 80% and more together with the preference of subtotal PTX led us to a satisfactory result of 94.1% success of surgery (Table 3). However, we obtained unacceptable results in the patients with no IO PTH monitoring with the same operative technique (0% of surgical success) (Table 3).

Our cure rate in case of subtotal PTX guided by IO PTH monitoring (Table 3) is quite similar with that of Konturek et al.<sup>[19]</sup> who also decided to use a similar surgical approach together with a similar IO PTH cut off criteria.

Low cure rate of the patients with LS in our investigation (Table 3) can be related with the limited number of patients in this category. We also think that the great difference of the surgical success, we postulate about the patients with no IO PTH monitoring (Table 3) and Amza et al.<sup>[15]</sup> and Konturek et al.<sup>[19]</sup> interpreted is because of the big difference in the number of patients and due to the difference of the surgical methods applied.

In many studies established previously, IO PTH monitoring was defined to increase the success of secondary and tertiary hyperparathyroidism surgery.<sup>[15,19,23,24]</sup> In some of these researches, different surgical approaches including total

PTX and total PTX plus AT other than subtotal PTX, are also used.<sup>[15,23,24]</sup> Because of the limited number of patients with the other surgical techniques in our study, we are able to make inferences mainly about patients with subtotal PTX and IO PTH monitoring preference in surgery for sHPT.

The first kidney transplantation was performed in 1982 at our hospital, and we are working in one of the centers where this surgery is most intensively made in the World. Many patients with ESRD can easily undergo RTX from a cadaver or living donor in our department. Due to this situation, main treatment modality for patients with sHPT had been RTX for long years at our clinic. In addition, the nephrology department of our hospital has been applying conservative medical treatment seriously in patients with sHPT since the early 1980s. Therefore, number of patients needing PTX for sHPT had been at a lower extent. Furthermore, eligibility of RTX for patients with ESRD, enabled us to choose less invasive PTX types more often in surgery for sHPT, to avoid postoperative hypoparathyroidism which would interfere with the survival of the probable renal graft, like Van der Plus et al.<sup>[4]</sup> and Konturek et al.<sup>[19]</sup>

The limitations of our study were the retrospective nature of the study and the limited number of patients. We think that more meaningful results can be obtained with prospective and multicenter studies involving more patients in the same field.

## Conclusion

In surgical treatment of patients with sHPT, IO PTH monitoring should be maintained and operation should not be finished until 80% or more decline in IO PTH level had been detected.

Among the surgical alternatives for sHPT, subtotal PTX appears as an effective and valid method when performed together with IO PTH monitoring, provided that there is a decline in PTH level of 80% or more.

## Disclosures

**Ethics Committee Approval:** This investigation was approved by Ethics Committee of Akdeniz University Medical Faculty Hospital (No: 498, dated 24.08.2022).

**Patient Informed Consent:** Since our study was retrospective, consent forms were not required from patients.

**Meeting Information:** This study was presented at the 11<sup>th</sup> National Congress on Endocrine Surgery which was held on the 16<sup>th</sup> to 19<sup>th</sup> of March 2023 in Antalya.

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**Conflict of Interest:** None declared.

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