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An intraoperative serum parathormone level study in patients with chronic renal failure that underwent subtotal parathyroidectomy. What extent of decrease is sufficient at which moment?

AIM: *The aim of this study is to determine when to perform intraoperative parathormone (ioPTH) measurement and what extent of decrease in intraoperative serum PTH concentrations indicate success in the operations performed on patients with SHPT associated with chronic renal failure.*
MATERIAL AND METHODS: *50 consecutive patients who underwent subtotal parathyroidectomy between January 2012 and January 2019 were retrospectively included in this study. Patients were grouped according to persistent hyper parathyroidism (Group1, n:6) and curative surgery (Group 2, n:44). Preoperative serum PTH, calcium, phosphorus and ALP concentrations, intraoperative serum PTH concentrations; and serum PTH, calcium, phosphorus and ALP concentrations of 24th hour after surgery were included to the study. Intraoperatively, 20 minutes after parathyroid gland removal, blood was drawn for PTH assay. The changes in PTH levels between preoperative and intraoperative serum samples were calculated in percentage (ioPTH%) and postoperative 6th month serum PTH and ALP concentrations were included in the study.*
RESULTS: *No significant differences were found by gender, BMI, elapsed period of dialysis treatment and preoperative laboratory values between Group 1 and Group 2. The meanage of Group 1 was 35 years which is lower than Group 2. With the second group, the mean decrease in PTH levels between intraoperative and preoperative serum samples (ioPTH%) was about 90%, which was higher than Group 1.*
CONCLUSIONS: *In conclusion, we believe that, to encounter fewer persistent SHPT cases, it is essential that surgeons monitor ioPTH concentration 20 minutes after gland removal and confirm a decrease of 90% or more in ioPTH concentration. And we should not forget that young patients may tend to develop persistent SHPT.*

KEY WORDS: Chronic renal failure, Intraoperative parathormone, Secondary hyperparathyroidism, Parathyroidectomy, Subtotal patathyroidectomy

Introduction

In patients with chronic renal failure, secondary hyperparathyroidism (SHPT) develops as a result of hyperplasia and over activity of the parathyroid glands related to phosphorus retention and hypocalcemia. Medical treatment is effective in the early stages of SHPT associated with chronic renal failure, but later stages require surgeryParathyroidectomy (PTX) is considered for patients with severe SHPT who do not respond to calcimimetic treatment, develop adverse effects associated with the treatment, have poor parathyroid hormone (PTH) reduction despite calcimimetic treatment, or exhibit poor compliance to the medical intervention [1]. Recovery of anemia after parathyroidectomy is a secondary gain in patients with secondary hyperparathyroidism due to chronic renal [2]. Although it has com-

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plications such as facial nerve damage and Frey's syndrome, parathyroidectomy is preferred in many patients [3]. Subtotal parathyroidectomy (SPTX) is a preferred method of surgical treatment for patients with SHPT associated with chronic renal failure [4,5]. A decrease in serum PTH concentration after removal of the diseased parathyroid gland or glands is considered to indicate a successful surgery [5], so intraoperative parathormone monitoring has been adopted to help the surgical team determine whether to stop searching for possible glandular tissue remaining after the parathyroid glands are excised, but the optimal final intraoperative serum PTH (ioPTH) concentration to end the operation remains a matter of debate. The development of persistent SHPT after PTX can be a surgeon's nightmare. The literature suggests that persistent SHPT after PTX may occur in 0.4%–25% of patients [7-9], which is a high rate, indeed.

This study analyzed clinical data to determine when to perform ioPTH measurement and to determine what decrease in ioPTH concentration indicates success in operations on patients with SHPT associated with chronic renal failure [7-9].

Materials and Methods

General Information

We performed a retrospective analysis of 50 consecutive patients who underwent SPTX by the same team (C.P.) due to increased SHPT associated with chronic renal failure in the General Surgery Clinic of the Ondokuz Mayis University Faculty of Medicine between 2012 and 2019. All the patients were diagnosed with SHPT according to the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines.

Medical treatment was given to the patients by the Divisions of Nephrology and Endocrinology and Metabolism, and our consultation was requested for the surgical treatment. Our evaluations found that the patients had indications for surgery according to the K/DOQI guidelines [4].

An ultrasound scan and parathyroid scintigraphy (Tc 99m sesta MIBI SPECT) were performed before every operation as routine imaging procedures. When needed, some patients were further evaluated by magnetic resonance imaging.

All the patients received heparin-free dialysis on the day before surgery and underwent bilateral cervical exploration and bilateral cervical thymectomy alongside SPTX. During SPTX, one half of one of the glands (which was macroscopically observed as the healthiest) was marked with a titanium clip, and the other half was excised. The excision material was always confirmed by the frozen section procedure. Twenty minutes after parathyroid gland removal, blood was drawn from the peripheral venous system and transported to the central laboratory in a +4°C container for PTH assay. The surgeries were terminated when the ioPTH concentration declined at least 50% from the preoperative serum PTH concentration.

Included in the study were preoperative serum PTH, calcium, phosphorus, and alkaline phosphatase (ALP) concentrations; ioPTH concentrations (which were tested 20 minutes after gland removal); and serum PTH, calcium, phosphorus, and ALP concentrations at the postoperative 24th hour. The change in PTH level between preoperative and intraoperative serum samples was calculated as a percentage (ioPTH %) for all patients. In the postoperative 6th month, PTH and ALP concentrations were included in the study. The patients' ages, body mass indexes (BMI), elapsed period under dialysis treatment, and follow-up times were analyzed. A number of parathyroid glands in the surgical specimens were examined.

Six patients with high serum PTH concentrations (≥250 pg/ml) 6 months after SPTX were accepted as persistent hyperparathyroidism cases and were selected as Group 1 in the study while 44 patients with normal PTH concentrations (<250 pg/ml) at postoperative 6 months were included as Group 2. The data of the two groups were compared to reveal why surgical treatment failed in patients in the persistent hyperparathyroidism group.

All the patients in Group 1 underwent both preoperative parathyroid scintigraphy and cervical ultrasound scans, which were collaboratively observed by the radiologist and the surgeon. No ectopic parathyroid gland was detected in any of the preoperative scintigraphy or ultrasound scans of Group 1 patients. All the Group 1 patients were medically treated postoperatively following K/DOQJ guidelines.

Statistical Analysis

The data were analyzed with IBM SPSS V23. The normal distribution fitness of the data was examined with the Shapiro-Wilk test. The Mann-Whitney U test was performed to compare quantitative values that did not fit the abnormal distribution. The chi-square test was performed to compare qualitative data. The statistical significance threshold was accepted as $p<0.05$.

Results

Seventeen patients (34%) were female, and 33 (66%) were male. Three patients (6%) had only peritoneal dialysis, one (2%) had both hemodialysis and peritoneal dialysis, and the remaining 46 patients (92%) had only hemodialysis. The patients' mean age was 43.5 ± 12 years and the median BMI was 23 (16-44) kg/m^2. The median elapsed period of dialysis treatment was 7 (2-16) years. The preoperative laboratory values are shown in Table I. The patients' median postoperative follow-up time was 40 (10-85) months (Table I).

As shown in Table II, no significant differences were found by gender, BMI, elapsed period of dialysis treatment, or preoperative laboratory values between the groups. Although there was no significant difference between the mean ages of the groups (Table II, p = 0.084), the mean age of Group 2 (45 ± 12) was higher than that of Group 1 (35 ± 8).

In the serum samples collected 20 minutes after parathyroid gland removal, the mean values of ioPTH concentration differed between the groups but not to a statistically significant degree. The mean value in Group 1 was 576± 431pg/ml whereas the value was 192 ± 162 pg/ml in Group 2 (Table III; p = 0.081). The decrease in ioPTH level compared to the preoperative value was calculated as a percentage (ioPTH %). The median decrease in Group 1 was 72% (54%–89%) while that in Group 2 was higher at 88% (48%–99.7%) (Table III; p = 0.025).

At postoperative 24th hour, the median serum PTH concentration in Group 1 was 239 (40–562) pg/ml while in Group 2 it was lower at 22 (3–498) pg/ml (Table III; p = 0.001). It was noted that two patients in Group 1 had postoperative 24th hour serum PTH concentrations below 250 pg/ml (i.e., 40 pg/ml and 109 pg/ml). In those patients, the postoperative 6th month serum PTH concentrations were 327 pg/ml and 406 pg/ml, respectively.

In Group 1, the postoperative 6th month median serum PTH concentration was 402(274–933) pg/ml whereas this concentration was lower in Group 2 at 46(4–168) pg/ml (Table III; p<0.001). As shown in Table III, the median number of parathyroid glands in surgical specimens; the postoperative 24th hour serum calcium, phosphorus, and ALP concentrations; and the postoperative 6th month serum ALP concentrations did not differ between the groups.

There was no significant difference between demographic characteristics and preoperative laboratory values of groups (Patients in group 1 were younger, although not significant). In the persistant hyperparathyroidism group (Group 1), the mean value of ioPTH concentration and the median value of postoperative 24th hour serum PTH concentration was high, while the median ioPTH% was low.

Discussion

SPTX with cervical thymectomy or total PTX with or without parathyroid auto-transplantation are the preferred methods of surgical treatment of SHPT associated with chronic kidney disease. In our clinic, we prefer SPTX in the surgical treatment of SHPT associated with chronic kidney disease. Regardless of the surgical method, the question of when the surgeon should end the surgery is critical.

In the K/DOQI clinical practice guidelines, a postoperative 6th month serum PTH concentration of less than 250 pg/ml is accepted as indicating a curative surgery [4], but another opinion holds that a postoperative 6th month serum PTH concentration of less than 300 pg/ml indicates a curative surgery [9]. In our study, the serum PTH concentration threshold was set at 250 pg/ml for the postoperative 6th month. Six patients with postoperative 6th month serum PTH concentrations of 250pg/ml and above (Group 1) were accepted as persistent hyperparathyroidism cases. Forty-four patients (Group 2) with postoperative 6th month PTH concentrations of less than 250 pg/ml were accepted as curative surgery examples.

In our study, no ectopic parathyroid gland was detected in the preoperative localization studies in patients who underwent surgery for SHPT associated with chronic renal failure. The preoperative mean serum calcium, PTH, ALP, and phosphorus concentrations of these patients were elevated as shown in Table I. The median postoperative follow-up time of the patients was 40 (7–85) months.

As shown in Table II, there was no difference between Group 1 and Group 2 in terms of gender, BMI, duration of dialysis, or preoperative serum PTH, calcium, phosphorus, and ALP concentrations. Although there was no significant difference between the mean ages of the groups (35 and 45 years; p = 0.084) (Table II), the mean age was higher in Group 2. Although not statistically significant, this may suggest that young patients tend to develop persistent SHPT. In a literature review from PubMed, we found no information on an association between persistent hyperparathyroidism in the postoperative period and younger patients who underwent PTX as a result of SHPT associated with chronic kidney disease. This should be confirmed by a larger number of case series and meta-analyzes.

Again, although not statistically significant, there was a difference in ioPTH concentrations between the groups. The mean ioPTH concentration was higher in Group 1 than in Group 2 (576 pg/ml vs.192 pg/ml; p=0.081) (Table III). Similarly, when we examined the percent-

TABLE I - *Demographics and preoperative laboratory findings of the patients.*

	Value
Gender, no (%)#Male	33 (66%)
Female	17 (34%)
Age (years), mean ± SD*	43.5 ± 12
BMI(kg/m²), Median (min–max)**	23 (16 - 44)
Dialysis duration (years) Median (min–max)**	7 (2 - 16)
PTH (pg/ml), mean ± SD*	1670 ± 1114
Calcium (mg/dl), mean ± SD*	10.35 ± 1
Phosphorus (mg/dl), mean ± SD*	4.78 ± 2
ALP (IU/L), Median (min–max)**	310 (10 - 2288)
Follow up time (months), Median (min–max)**	40 (7-85)

#chi square test; *data expressed as mean ± SD, Student test; **data expressed
As median (min–max), Mann Whitney U test

Table II - *Demographic characteristics and preoperative laboratory values of groups*

	Group 1 (n = 6)	Group 2 (n = 44)	p
Gender, no (%)#			
Female	3 (50%)	14 (32%)	0.378
Male	3 (50%)	30 (68%)	
Age (years), mean ± SD*	35 ± 8	45 ± 12	0.084
BMI (kg/m²), Median (min–max)**	22 (19 - 22)	24 (16 - 44)	0.245
The Duration of Dialysis (year), Median (min–max)**	11 (2 - 16)	7 (2.5 - 15)	0.252
Preoperative			
PTH (pg/ml), mean ± SD*	1940 ± 891	1634 ± 1145	0.533
Calcium (mg/dl), Median (min–max)**	10.8 (8 - 12)	10.2 (9 - 13)	0.356
Phosphorus (mg/dl), mean ± SD*	4.2 ± 1	4.9 ± 2	0.223
ALP (IU/L), Median (min–max)**	883 (67 - 2288)	291 (10 - 1896)	0.075

#chisquare test; *data expressed as mean ± SD, Student test; **data expressed as median (min–max), Mann Whitney U test.

Table III - *Intraoperative and postoperative comparison of laboratory results between groups.*

	Group 1 (n = 6)	Group 2 (n = 44)	p
ioPTH (pg/ml), mean ± SD*	576 ± 431	192 ± 162	0.081
ioPTH%# Median (min–max)**	72 (54 - 89)	88 (48 - 99.7)	0.025
Postoperative Median (min–max)**			
PTH (pg/ml)	239 (40 - 562)	22 (3 - 498)	<0.001
Calcium (mg/dl)	7.5 (4.3 - 8)	6.8 (3.4 - 10.2)	0.850
Phosphorus (mg/dl)	4 (3.1 - 4.2)	3.1 (1.5 - 7.9)	0.247
ALP (IU/L)	528 (195 – 1001)	522 (61 – 3001)	0.109
Postoperative 6th month Median (min–max)**			
PTH (pg/ml)	402 (274 - 933)	46 (4 - 168)	<0.001
ALP (IU/L)	223 (101 - 2489)	110 (50 - 740)	0.121
Number of parathyroid glands## Median (min–max)**	4 (4-4)	4 (1-7)	0,681

*data expressed as mean ± SD, Student test; **data expressed as median (min–max), Mann Whitney U test
The decrease in intraoperative serum PTH concentrations compared to the preoperative serum PTH concentrations in percentage.
Number of parathyroid glands in surgical specimens

age of decrease in ioPTH % from preoperative PTH concentrations, we found that the rate in Group 2 was about 90%, which was higher than in Group 1 (Table 3;p = 0.025).

As shown in Table III, when postoperative serum PTH concentrations were examined, Group 1 had higher values than Group 2 (239 pg/ml vs.22 pg/ml; p<0.001), but it was confusing that two patients in Group 1 had a postoperative PTH concentration of less than 250 pg/mL while their 6th month PTH concentrations were higher. This result does not exactly support the rule of the K/DOQI clinical practice guidelines that postoperative serum PTH concentration of lower than 250 pg/ml equate to a curative surgery [4]. Still, the 6th month PTH concentrations were higher in Group 1 than in Group 2 (402 pg/ml vs.46 pg/ml; p<0.001) (Table III). Like other studies, ours showed that examination of ioPTH in the central laboratory after PTX was an effective method of determining the success of the surgery [6,11], but there is no consensus on the timing of the ioPTH examination after PTX or on how much the ioPTH should decrease relative to the preoperative PTH concentration. Vulpio et al. conducted a study that examined ioPTH concentrations separately at 10 minutes, 20 minutes, and 30 minutes after PTX and reported that the measurement at 30 minutes was the most consistent indetermining the success of the surgery [11]. Richards et al. report that the success of the surgery was related to an at least 50% reduction in ioPTH concentrations 10 minutes after the parathyroid glands were excised, but Barczyński et al. report that surgical success is demonstrated by an ioPTH% decrease of at least 80% at 20 minutes after PTX [12,13]. While the examination of ioPTH is accepted as a suitable method, there is no consensus on the timing of the ioPTH examination after PTX. Unlike other results, ours suggests that PTX is adequate when there is a 90% or greater decrease in intraoperative PTH concentrations 20 minutes after PTX (Table III).

The metabolism of intact PTH and its remnants is extended due to impaired renal functions in SHPT in chronic renal failure. The half-life of intact PTH with normal renal function is known to be 2 minutes, but, in the case of chronic renal insufficiency, the duration

of this cycle is about 5 minutes, i.e., the intact PTH metabolism is prolonged [14,15]. In our view, the metabolisms of all patients with chronic kidney disease differ, so the half-life of intact PTH differs from patient to patient. If the interval of the ioPTH examination after PTX is short, the ioPTH concentration may be observed as high because the intact PTH has had insufficient time to break down. This means that the surgeon will waste time in re-exploration, which may unnecessarily prolong the operation and even cause complications such as recurrent nerve injury and bleeding, which may result in increased morbidity. By contrast, if an extended period passes before the PTH assay after gland removal, the intact PTH can be metabolized and a true result obtained, but this can also unnecessarily prolong the surgery. In other words, a margin of 10 minutes may lead to unnecessary re-exploration and a margin of 30 minutes may prolong the operation unnecessarily. In a prospective study with 86 patients, Ohe et al. reported that intraoperative PTH monitoring increased the success rate 20 minutes after the glands were excised [16] . In our opinion, measuring the ioPTH concentration 20 minutes after gland removal is the most appropriate method. It prevents false results, unnecessary re-exploration, loss of time, and possible morbidity as well as avoiding unnecessary prolongation of the operation. Our study was performed retrospectively, and our results can be further verified with prospective studies and with agreater number of patients in the future.

In conclusion, we believe that, to encounter fewer persistent SHPT cases, it is essential that surgeons monitor ioPTH concentration 20 minutes after gland removal and confirm a decrease of 90% or more in ioPTH concentration.

Additionally, surgeons should exercise greater caution while operating on younger patients with SHPT associated with chronic kidney disease.

Riassunto

Si intende determinare quando eseguire la misurazione intraoperatoria del paratormone (ioPTH) e quale misura di diminuzione della concentrazione sierica di PTH indica il successo nell'intervento eseguito su pazienti con iperparatiroidismo secondario (SHPT) associato a insufficienza renale cronica.

Sono stati inclusi in modo retrospettivo in questo studio 50 pazienti consecutivi sottoposti a paratiroidectomia subtotale tra gennaio 2012 e gennaio 2019. I pazienti sono stati raggruppati in base all'iperparatiroidismo persistente (Gruppo 1, n: 6) e alla chirurgia curativa (Gruppo 2, n: 44). Sono state incluse nello studio preoperatorio le concentrazioni sieriche di PTH, calcio, fosforo e fosfatasi alcalina (ALP), e le concentrazioni sieriche intraoperatorie di PTH; e le concentrazioni sieriche di PTH, calcio, fosforo e fosfatasi alcalina di 24 ore dopo l'intervento. Intraoperatoriamente, 20 minuti dopo la rimozione della ghiandola paratiroidea, è stato prelevato sangue per il test PTH. Le variazioni dei livelli di PTH tra campioni di siero preoperatorio e intraoperatorio sono state calcolate in percentuale (ioPTH%) e nello studio sono state incluse le concentrazioni sieriche di PTH e ALP al 6° mese postoperatorio.

Risultati: non sono state riscontrate differenze significative per sesso, BMI, periodo di dialisi trascorso e valori di laboratorio preoperatori tra il Gruppo 1 e il Gruppo 2. La media del Gruppo 1 era di 35 anni, che è inferiore al Gruppo 2. Con il secondo gruppo, la media la diminuzione dei livelli di PTH tra i campioni di siero intraoperatorio e preoperatorio (ioPTH%) è stata di circa il 90%, che era superiore al gruppo 1.

In conclusione, riteniamo che, per incontrare meno casi di SHPT persistente, sia essenziale che i chirurghi controllino la concentrazione di ioPTH 20 minuti dopo la rimozione della ghiandola e confermino una diminuzione del 90% o più della concentrazione di ioPTH. E non dobbiamo dimenticare che i giovani pazienti possono tendere a sviluppare SHPT persistente.

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