

Evaluation of Intraoperative Parathormone Measurement for Predicting Successful Surgery in Patients Undergoing Subtotal/Total Parathyroidectomy Due to Secondary Hyperparathyroidism

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Objectives/Background: The aim of this study is to investigate the predictive value of intraoperative parathormone measurement addressing successful surgical resection in patients with secondary hyperparathyroidism.

Methods: The study included 42 consecutive patients operated on between May 2006 and July 2008. Patients were grouped according to successful surgery (Group 1, $n = 36$) and persistent postoperative hyperparathyroidism (Group 2, $n = 6$). Serum phosphorus (P), total calcium (tCa), ionized calcium (iCa), intact parathormone (iPTH), and alkaline phosphatase (ALP) were drawn preoperatively and intraoperatively upon 15 minutes after completion of resection (iPTH₁₅). The rate of decrease of pith detected by iPTH₁₅ compared to preoperative values was calculated (iPTH%).

Results: Preoperative P, tCa, iCa, iPTH, and ALP were comparable. Subtotal parathyroidectomy (sPx) ($n = 27$) and total parathyroidectomy with autotransplantation (tPx) ($n = 15$) were performed. Mean iPTH₁₅ value, iPTH% rates were 145.9 ± 12.3 pg/mL, % 91.6 ± 0.7 , and 522.5 ± 85.4 pg/mL, % 75.1 ± 2.0 ($P = .001$) in Groups 1 and 2, respectively. Mean se-

rum tCa and iCa at POD#1 in Group 1 were 7.6 ± 0.1 mg/dL, 0.910 ± 0.4 mmol/L, and Group 2 were 8.3 ± 0.3 mg/dL, 1.050 ± 0.4 mmol/L ($P < .05$), respectively. ALP levels were similar.

Conclusion: iPTH₁₅ value and iPTH% rate accurately predicts the completeness of resection in secondary hyperparathyroidism. The rate of decrease in serum iPTH detected intraoperatively compared to preoperative baseline levels exceeding 90% in sPx, 95% in tPx, accurately predicts the success of surgery. Postoperative normocalcemia without calcium replacement would raise a suspicion about completeness of surgical resection.

Key Words: Intraoperative parathormone, successful parathyroidectomy, secondary hyperparathyroidism.

Level of Evidence: A.

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INTRODUCTION

Secondary hyperparathyroidism (SHPT) is one of the most commonly encountered complications of end-stage renal failure (ESRF). Diet regulation, sufficient hemodialysis, and medical treatment produce effective control in most cases.^{1,2} However, resistance to medical treatment and insistent symptoms may necessitate surgical treatment in 10% of patients.³ Surgical treatment alternatives of SHPT include subtotal parathyroidectomy (sPx) and total parathyroidectomy (tPx) with autotransplantation.^{4–7} No matter which surgical technique is preferred, reoperation as a result of persistent hyperparathyroidism following initial surgery in patients demonstrating serum PTH greater than 300 pg/mL, with persistent symptomatology becomes necessary in 15% of patients.^{8–12} Persistent hyperparathyroidism has been encountered most commonly in patients with supernumerary/ectopic parathyroid gland(s) or the remaining

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half of one of the parathyroid glands exceeding the suggested volume in the sPx technique. Intraoperative PTH measurement for determination of the proper surgical resection was been performed in 1988 for the first time. Subsequent studies have demonstrated the efficacy of the intraoperative iPTH measurement in patients undergoing surgery for primary hyperparathyroidism with a 95% positive prediction of sufficient surgical removal.^{13–17} These studies were conducted in patients' series with normal renal function with primary hyperparathyroidism by using the first-generation quick intact PTH immunometric measurement technique, which is based on detection of the biologic active N-terminal concomitant with the detection of an inactive C-terminal. As a result of decreased glomerular filtration rate in patients with renal dysfunction, the C-terminal is accumulated in plasma and misinterpreted by the technique of quick intact PTH (qPTH) measurement, and thereby criticized for being unreliable. The reliability of intraoperative iPTH measurement in patients with SHPT as a result of ESRF is not clear.

The second-generation chemiluminescent immunometric (Bio-iPTH; Nichols Institute Diagnostics, Chantilly, VA) measurement technique detecting the biologic active part (N-terminal) of iPTH has produced reliable results in patients with ESRF.^{18–20} The aim of this study is to evaluate the sufficiency of surgery performed for SHPT based on intraoperative Bio-PTH measurement.

PATIENTS AND METHODS

Between May 2006 and November 2008, 44 parathyroidectomies were performed in 42 patients with ESRF for SHPT. Our surgical indications included: (1) persistently high PTH (PTH > 10× ULN and rising); (2) hypercalcemia (serum Ca > 10.2 mg/dL) and/or hyperphosphatemia (serum P > 6.0 mg/dL) that cannot be controlled by medical treatment, and calcium phosphorus multiplication greater than 55; (3) at least one enlarged parathyroid gland (largest dimension > 1 cm, as estimated by ultrasound). Moreover, patients with radiography showing osteitis fibrosa, high turnover bone, severe symptoms of SHPT (itching, bone pain, and fractures).²¹

Preoperative evaluation included neck ultrasonography and parathyroid scintigraphy (Tc99m sestamibi) for demonstrating the number, size, and location of parathyroid glands.

Surgical Procedure

All patients received hemodialysis treatment without heparin 1 day before operation. Following the induction of general anesthesia antibiotic prophylaxis was used with routine administration of cefazoline 1 gram intravenously. Bilateral cervical exploration and parathyroidectomy with bilateral cervical thyrectomy was performed routinely. In the case of not being able to identify a parathyroid gland ipsilateral thyroidectomy was performed. Parathyroid autotransplantation was performed by implantation of 12–15 parathyroid gland slices of resected specimen with a size of 1 mm³ in the subcutaneous pockets prepared on the proximal ventral forearm²² in patients with total parathyroidectomy. Subtotal parathyroidectomy (sPx) was performed by leaving half of one of the most macroscopically normal-appearing gland aimed to leave a 60–90-mg remnant gland and marked with titanium clips. In patients with all parathyroid glands demonstrating increased gland volume, sPx aimed to

achieve a remnant gland volume of 60–90 mg, which may necessitate a more than three and a half gland resection. Two patients were operated on as a result of persistent hyperparathyroidism because of failure of a primary operation. Intraoperative frozen section analysis was routinely performed to verify that the resected specimen was the parathyroid gland. Macroscopically healthy appearing parathyroid glands were cryopreserved (–80°C) for possible future need of reimplantation.

Peripheral vein blood was drawn for iPTH measurement (Chemiluminescent Immunometric Assay, Bio-iPTH; Nichols Institute Diagnostics) and transferred to the laboratory with containers under +4°C, which was completed within an average of 35 minutes.

The normal range of serum PTH among healthy individuals varied between 12 and 88 pg/mL, whereas in patients with ESRF 150–300 pg/mL is accepted as a normal range of serum PTH.²³ Blood samples were drawn for measurement of iPTH, preoperatively (iPTH_p), after 15 minutes upon completion of resection (iPTH₁₅) and postoperatively at postoperative months 1, 3, 6, and 12. The rate of decrease in iPTH measured intraoperatively compared to preoperative levels were calculated (iPTH%). Serum ionized calcium (iCa), total calcium (tCa), phosphorus (P), and alkaline phosphatase (ALP) were measured at the first postoperative week and months 1, 3, 6, and 12.

Serum iPTH levels detected at the first postoperative week < 300 pg/mL were defined as a successful resection group (Group 1) and in patients with iPTH levels > 300 pg/mL at a given period were accepted as an insufficient surgical resection group (Group 2). Medical treatment were assigned for patients in Group 2 according to K/DOQI clinical practice guidelines (CKD stage-5 Guideline 9b) based on postoperative levels of iPTH, Ca, and P.²³ Treatment aimed to prevent postoperative symptomatic hypocalcemia was initiated in the recovery room by a rate of 0.5–1.5 mg/kg/hr calcium gluconate infusion for all patients. Upon initiation per oral feeding 0.50–2.0 µg active vitamin D concomitant with 4,000–6,000 mg/day calcium carbonate was started. Serum tCa was drawn every 6 hours for determining the dosage of calcium replacement. Intravenous calcium replacement treatment was withdrawn after detection of a serum tCa level of 8 mg/dL and oral calcium replacement treatment was continued.

Statistical analysis was performed by SPSS version 17.0. Data were expressed as mean and standard error of mean (SEM).

RESULTS

Twenty-seven subtotal and 15 total parathyroidectomies with autotransplantation were performed during the study period. Thyroid lobectomy was performed in two patients as a result of not being able to locate the ipsilateral parathyroid glands intraoperatively. Persistent hyperparathyroidism was detected in six patients (Group 2) in follow-up. Medical treatment was initiated during the early postoperative period in given patients. Reoperation was performed in two patients as a result of persistent increased serum iPTH and unremitting symptoms during follow-up. Demographic data is presented at Table I according to the grouping of the patients.

Preoperative evaluation with ultrasonography detected median 1.62 (range: 0–3) parathyroid glands with a mean size of 12.5 ± 3.0 mm (range: 7–18 mm). Scintigraphy revealed median 2.2 (range: 2–3) parathyroid glands. Inferior parathyroid glands were the most commonly detected ones by both ultrasonography and scintigraphy, whereas neither investigation detected any

TABLE I.
Demographic data of the patients.

	n (n=42)	Group 1 (n=36)	Group 2 (n=6)
Age (mean $\pm$ SE, y)	41,48 $\pm$ 1,9	41,5 $\pm$ 2,1	41,3 $\pm$ 3,9
Gender (F/M)	16/26	15/21	1/5
Duration of dialysis dependence , (mean $\pm$ SE,y)	8.8 $\pm$ 0,6	8,8 $\pm$ 0,7	8,8 $\pm$ 1,5
Symptoms, No. of patients			
Bone pain	41	35	6
Bone fracture	6	5	1
Pruritus	23	19	4
Calciophylaxis	1	1	
SHPT, Duration of medical treatment (m)	9,47 $\pm$ 0,67	9,3 $\pm$ 0,5	10,5 $\pm$ 0,6
Operative procedure			
sPx	27	22	5
tPx	15	14	1

SE: standart error, y: year, F: female, M: male, SHPT: secondary hyperparathyroidism, m: month, sPx: sub-total, tPx: total parathyroidectomy

ectopically located parathyroid gland. Operative explorations demonstrated median four (range: 3–5) parathyroid glands per patient. Three parathyroid glands were identified in 2.4% of patients, whereas the rates of demonstrated five glands were 7.2%. Ectopic localization were present in 7 (4%) out of 170 resected parathyroid glands. Ectopic parathyroid localizations were as follows: intrathyroidal (n = 2), carotid sheath (n = 2), thymus (n = 2), and upper mediastinum (n = 1) (Fig. 1). In our study, preoperative imaging with ultrasonography and

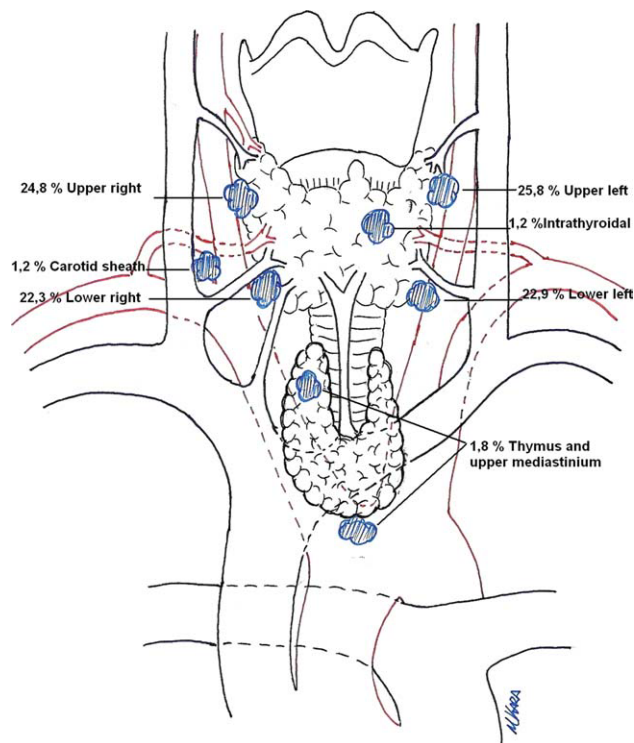


Fig. 1. Distribution of the anatomic localization of parathyroid glands. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

scintigraphy for demonstrating the number and localization of parathyroid glands were unsuccessful. There was no statistical significant difference in preoperative PTH values between two groups of patients, whereas $iPTH_{15}$ and $iPTH_{\%}$ values were significantly different ($P = .001$) (Table II). Mean serum $iPTH_{15}$ and $iPTH_{\%}$ were 145.4 ± 11.1 pg/mL and $91.8 \pm 0.6\%$, respectively, in Group 1. $iPTH_{\%}$ of 90 for sPx, 95 for tPx, were successful in predicting effective surgery (Table III).

Routine immediate postoperative intravenous calcium replacement was initiated in the recovery room and followed by oral calcium and vitamin D replacement in all patients. The patients in Group 1 was discharged with oral calcium and vitamin D replacement treatment, and gradually tapered to discontinue based on the target serum $iPTH$, tCa , and P levels (150–300 pg/mL, 8.4–10.4 mg/dL, 2.7–4.5 mg/dL, respectively). Although there was initiation of early medical treatment for patients in Group 2, postoperative follow-up during 6 months has demonstrated significantly higher $iPTH$ levels in Group 2 compared to Group 1 (Fig. 2). Postoperative imaging with scintigraphy was performed in patients with persistent hyperparathyroidism 3 months after surgery.

TABLE II.
Preoperative and intraoperative biochemical data in two groups (mean $\pm$ SEM).

	Group 1	Group 2	P
tCa (mg/dl)	10,5 $\pm$ 0,1	10,3 $\pm$ 0,4	0,585
iCa (mmol/L)	1,201 $\pm$ 0,010	1,161 $\pm$ 0,033	0,098
P (mg/dl)	6,4 $\pm$ 0,3	6,4 $\pm$ 0,2	0,386
tCa x P	71,8 $\pm$ 1,8	73,5 $\pm$ 4,1	0,847
ALP (U/L)	566,2 $\pm$ 40,8	419,5 $\pm$ 63,5	0,110
Albumin (g/dl)	3,9 $\pm$ 0,6	4,1 $\pm$ 0,4	0,754
$iPTH_p$ (pg/ml)	1991,4 $\pm$ 129,9	2050 $\pm$ 196,4	0,752
$iPTH_{15}$ (pg/ml)	145,4 $\pm$ 11,1	522,5 $\pm$ 85,4	0,001
$iPTH_{\%}$	91,8 $\pm$ 0,6	75,1 $\pm$ 2,0	0,001

TABLE III.

Correlations of iPTH₁₅ and iPTH% values with the type of surgery and distributions as groups (mean $\pm$ SEM).

	Group 1	Group 2	P
sPx-iPTH ₁₅ (pg/ml)	165,3 $\pm$ 14,4	451 $\pm$ 57,3	0,001
sPx-iPTH%	90,16 $\pm$ 0,78	76,96 $\pm$ 2,8	0,001
tPx-iPTH ₁₅ (pg/ml)	98,3 $\pm$ 15,4	572	0,001
tPx-iPTH%	95,31 $\pm$ 0,94	73,1	0,001

sPx: subtotal, tPx: total parathyroidectomy, iPTH: intact parathormon, iPTH₁₅: intraoperatively upon 15 minutes after completion of resection. iPTH%: The rate of decrease in iPTH measured peroperatively compared to preoperative levels.

Suspicious uptake in ectopic localizations (upper mediastinum and cervical) was detected in two patients. Reoperation took place in these patients for completion of parathyroidectomy as a result of increasing iPTH levels resistant to medical treatment during 6 months of follow-up, whereas the other four patients remained stable under medical treatment in Group 2. Reexploration in two patients suggested that failure of initial surgery was possibly due to a high volume of the remnant parathyroid gland in one patient who had previous sPx and a supernumerary parathyroid gland in the other patient who also had previous sPx, and both were treated with tPx and autotransplantation. Intraoperative iPTH measurements in both reoperations demonstrated similar patterns of iPTH% compared to Group 1. There was no statistical significant difference in iPTH levels in both groups after 12 months of follow-up.

Mean serum tCa and iCa in Group 1 and Group 2 were 7.6 $\pm$ 0.1 mg/dL, 0.910 $\pm$ 0.4 mmol/L, and tCa 8.3 $\pm$ 0.3 mg/dL, 1.050 $\pm$ 0.4 mmol/L, respectively ($P < .05$) (Fig. 3). In all patients in Group 1 hungry bone syndrome was developed during immediate postoperative period. Patients in Group 1 demonstrated significant low calcium levels even though intravenous calcium replacement treatment was initiated in the recovery room. According to the selected surgical technique in Group 1,

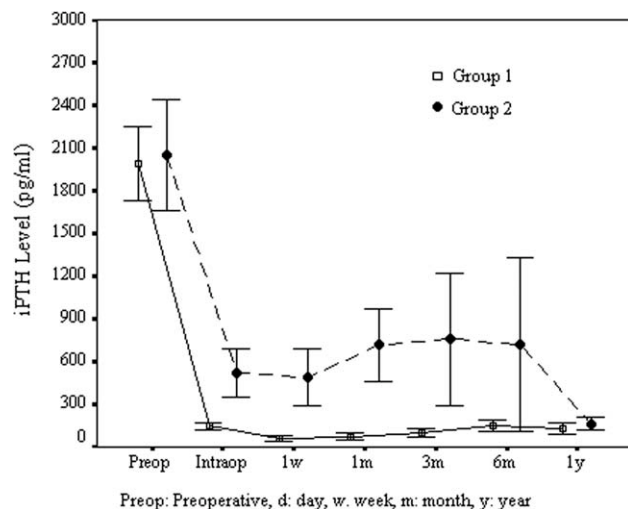


Fig. 2. Serum iPTH levels in two groups (mean $\pm$ SEM).

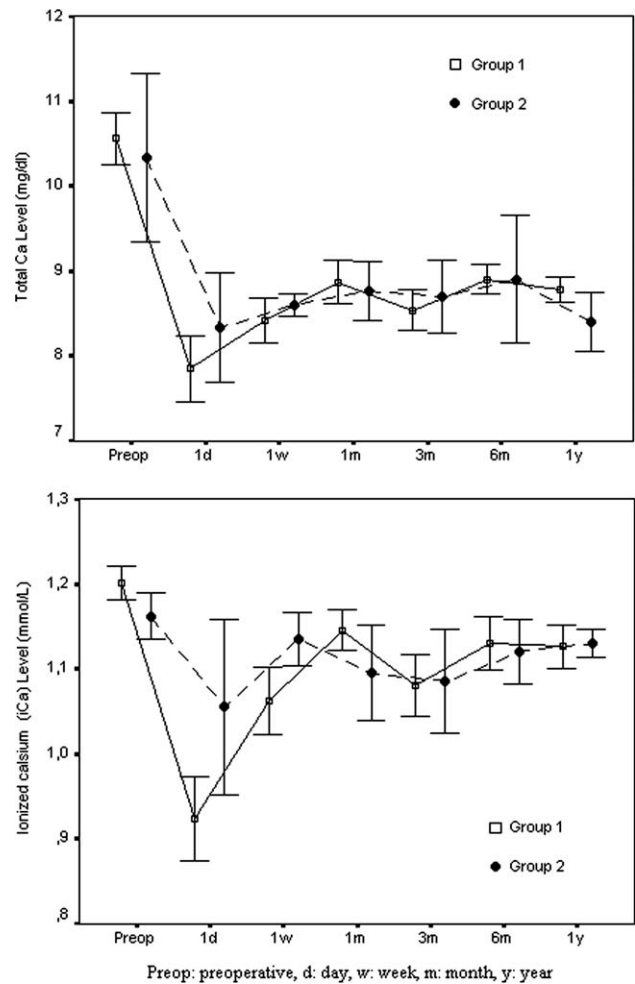


Fig. 3. Serum tCa and iCa levels in two groups (mean $\pm$ SEM).

postoperative day 1 mean serum tCa and iCa values in sPx and tPx were 7.1 $\pm$ 0.3 mg/dL and 0.88 $\pm$ 0.4 mol/L, respectively. There was no significant difference in tCa and iCa values among the groups in follow-up. Postoperative serum P and ALP levels were similar in both groups (Figs. 4 and 5).

DISCUSSION

Secondary hyperparathyroidism is one of the most encountered complications of ESRF. Although the medical treatment alternatives successfully resolve the symptoms in most of the patients, 10% of patients experience insistent itching, bone pain and fracture, metabolic complications, and are thereby referred to surgery.²⁴⁻²⁶ Secondary hyperparathyroidism significantly differs from primary hyperparathyroidism with regard to all parathyroid glands being hyperplastic, and necessitates detecting all glands including ectopic and supernumerary ones for successful surgical treatment.^{27,28} Subtotal parathyroidectomy and total parathyroidectomy with autotransplantation techniques are equally preferred and effective in the hands of experienced surgeons. No matter which surgical technique is preferred, almost 15% of patients undergo reoperation despite medical

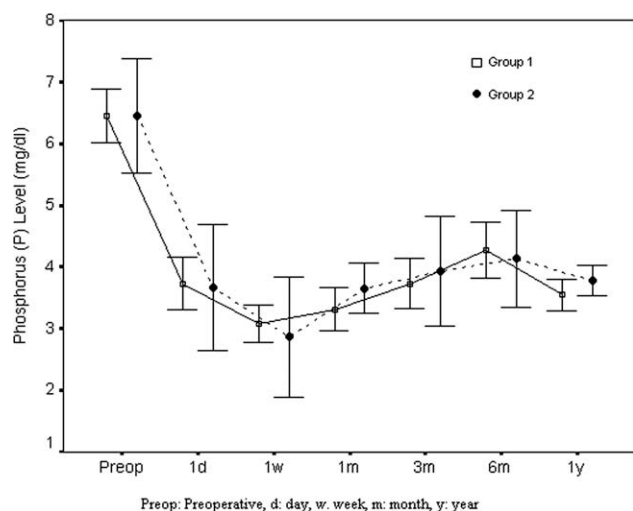


Fig. 4. Serum phosphorus levels in two groups (mean $\pm$ SEM).

treatment after initial surgery as a result of missed supernumerary/ectopic parathyroid gland/s as well as because of hyperplasia of autotransplanted parathyroid tissue and remnant parathyroid left in situ in the subtotal technique.^{8,29} Our preferred technique has become tPx with forearm subcutaneous autotransplantation during the study period. The reason for the evolution of our preferred technique is the ease of the management of the possible autotransplanted parathyroid tissue hyperplasia in follow-up as well as precluding the morbidity of neck reexploration in case needed. The localizations and the number of parathyroid glands are the most significant predictors of successful surgical treatment. Autopsy series reports the rate of the presence of three, four, and more than four parathyroid glands are 3.4%, 84.4%, and 13%, respectively.²⁹ Our results were similar with regard to the number of parathyroid glands (2.4% for three glands, 90.4% for four glands, and 7.2% for more than four glands). The most common reported ectopic parathyroid gland locations were thymus, mediastinum, carotid sheath, carotid bifurcation, posterior tracheal, and intrathyroidal.³⁰ We have detected an ectopic parathyroid gland in 4.2% of resected parathyroid glands (Fig. 1). Preoperative imaging with ultrasonography and sestamibi (MIBI) scintigraphy has been reported to be successful, with a high sensitivity and specificity in localizing the adenoma in patients with primary hyperparathyroidism. Unfortunately, given radiologic modalities do not produce a similar success in demonstrating all parathyroid glands in patients with secondary hyperparathyroidism.^{31,32} The limitations of imaging studies in demonstrating hyperplastic parathyroid glands were reported to be due to ectopic localizations such as posterior sternum, intrathyroidal and upper mediastinum, as well as relative small size (5 mm) of the hyperplastic parathyroid glands.^{33,34} Our study demonstrated that ultrasonography and MIBI scintigraphy are not successful in detecting hyperplastic parathyroid glands sizing less than 1 cm, especially in the case of concomitant thyroidal nodularity. Preopera-

tive detection of the localization of parathyroid glands and the presence of supernumerary/ectopic glands is difficult. Based on this difficulty, some authors suggest an extensive bilateral cervical exploration combined with bilateral cervical thymectomy aiming to resect all parathyroid glands. However, extensive exploration carries a higher risk of morbidity and produces increased operative times. Our results based on the present series did not reveal any benefit of preoperative imaging studies prior to initial surgery; however, scintigraphy is a helpful diagnostic tool in locating the ectopic, supernumerary, and hyperplastic remnant gland(s) in patients with persistent hyperparathyroidism. There have been efforts in defining a validated method of intraoperative iPTH measurement predicting the completeness of surgical resection intraoperatively^{18,35,36} that would preclude unnecessary exploration and cervical thymectomy, thereby decreasing the operative times and related morbidity. The first generation of the qPTH measurement technique was reported to be effective in primary hyperparathyroidism, although second-generation Bio-intact PTH measurement in secondary hyperparathyroidism produced better results.^{37,38} Lokey and Brossard^{19,39} have reported that diminished glomerular filtration rate significantly prolongs the half-life of circulating PTH, and thereby intraoperative measurement may mistakenly detect high levels of PTH. Clary and Seehofer^{8,40} criticized this conclusion and demonstrated that active PTH N-terminal detection that is metabolized via liver successfully depicts the functioning parathyroid glands. Compromised vascular supply of the remaining half of the parathyroid gland in subtotal parathyroidectomy would also interfere with circulating PTH levels. The most important determinant of the success of parathyroid surgery is the surgeon's familiarity with the cervical anatomy as well as experience in parathyroid surgery. The deterioration of the blood supply of in situ parathyroid gland(s) would also interfere with the results of intraoperative iPTH measurements. Therefore, it is recommended that prior to extensive exploration,

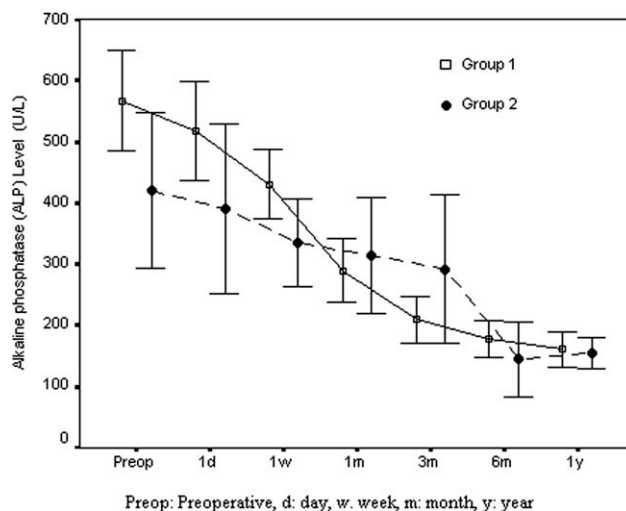


Fig. 5. Serum alkaline phosphatase levels in groups (mean $\pm$ SEM).

meticulous dissection should take place to identify parathyroid glands, with caution not to cause hemorrhage, and resection should take place. In case that a decision has been made to proceed with sPx, preferably one of half of the inferior glands should be left in situ initially and then the rest of the glands should be resected. This approach would help to identify the remaining half gland's viability prior to termination of the procedure.

Our study revealed that intraoperative bio-intact iPTH measurement 15 minutes after completion of resection successfully predicts the completeness of resection. The threshold of the rate of decrease in iPTH compared to preoperative values were 90% for successful subtotal parathyroidectomy, whereas it is 95% for total parathyroidectomy. Some authors have reported that a significant decrease in intraoperative iPTH compared to preoperative values successfully prevents unnecessary efforts of extensive dissection and cervical thymectomy aiming to resect the possible ectopic and/or supernumerary parathyroid glands.^{18,41} We have performed routine cervical thymectomy in all patients, and histopathologic examinations did not reveal any parathyroid gland in thymectomy specimens in all but two. In the case of typical localizations of parathyroid glands upon completion of resection demonstrating a decrease of 90% or greater for sPx, 95% or greater for tPx in iPTH values compared to preoperative baselines would prevent performing bilateral cervical thymectomy.

Further exploration should take place in case of high iPTH₁₅ exceeding 300 pg/mL and %iPTH values less than previously mentioned values to prevent reoperation. Intraoperative iPTH values in sPx unless detection of ectopic supernumerary parathyroid gland(s) may lead to decide to convert the procedure to total parathyroidectomy with autotransplantation. This approach may decrease the iPTH values, which may occur as a result of high volume of the left half of the remaining parathyroid gland. It is controversial whether this decision should be made prior to performing further dissection to detect ectopic/supernumerary parathyroid glands. The preference of the surgeon based on his/her experience defines the decision to do either one of the mentioned strategy. No doubt that extensive exploration should take place, unless converting the procedure to total parathyroidectomy would not produce a sufficient decrease in iPTH levels. Either surgical technique may be complicated with persistent postoperative hyperparathyroidism. Medical treatment is initiated in patients with persistent hyperparathyroidism. The control scintigraphy is helpful in differentiating the etiology of persistent hyperparathyroidism. Medical treatment successfully controls most of the persistent hyperparathyroidism, especially in the case of a lacking detectable focus of high uptake in control scintigraphy. It is difficult to conclude due to the limited number of patients in present series; however, postoperative detected focus of high uptake in scintigraphy may address the possible necessity of reoperation for achieving the control of persistent hyperparathyroidism. Careful postoperative follow-up in patients after initial surgery for SHPT would detect a certain group of patients with persistent

hyperparathyroidism. In this group of patients either medical treatment or surgical reoperation successfully resolves the persistent hyperparathyroidism at the end of first year of initial surgery compared with patients successfully treated initially.

Cruz et al.⁴² demonstrated that postoperative hypocalcemia does not necessarily predict the success of surgery, whereas it may predict the incomplete resection if there is no postoperative hypocalcemia. Our results demonstrating significantly high serum tCa and iCa levels in patients who had incomplete resection compared to patients who did not suggests a similar prediction as well. Additionally, as a result of an immediate decrease in iPTH level following resection, the inhibition of iPTH on osteoblastic activity resides and hungry bone syndrome occurs, presenting severe hypocalcemia. Immediate postoperative normocalcemia would raise a concern of possible incomplete surgery and direct the surgeon to take necessary steps to detect if it is the case. ALP levels return to normal subsequently.

CONCLUSION

In conclusion, intraoperative iPTH measurement upon completion of the resection is a helpful method of predicting the completeness of resection. The rate of decrease in intraoperative iPTH levels compared to preoperative baseline values exceeding 90% in sPx, 95% in tPx, seem to be a valid threshold to predict the completeness of resection that would preclude an extensive dissection and exploration accompanied with cervical thymectomy and thereby decrease the morbidity related to the surgery.

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