



The Significance of Determining The Intraoperative Level of Parathormone During Surgical Treatment of Hyperparathyroidism

Stefan D. Janičić^{1,2}, Kristina M. Stepanović^{1,2}, Mia S. Manojlović^{1,2},
Dean P. Bjelajac^{1,3}, Slađana M. Pejaković^{1,2}, Milan R. Mirković²,
Dragana D. Tomić-Naglić^{1,2}, Ivana A. Bajkin^{1,2}, Tijana S. Ičin^{1,2}

¹ University of Novi Sad, Faculty of Medicine in Novi Sad, Novi Sad, Serbia

² Clinic for Endocrinology, Diabetes and Metabolic Disorders, Clinical Center of Vojvodina, Novi Sad, Serbia

³ Clinic for Abdominal, Endocrine and Transplantation Surgery, Clinical Center of Vojvodina, Novi Sad, Serbia

SUMMARY

Introduction: Surgical treatment is the method of choice for treating primary hyperparathyroidism. Determining parathyroid hormone (PTH) levels intraoperatively allows for real-time monitoring of the functional activity of parathyroid gland tissue and facilitates minimally invasive parathyroidectomy.

Aim: Our study aimed to investigate the significance of intraoperative parathyroid hormone level determination in achieving physiological parathyroid hormone levels and cure.

Material and Methods: A retrospective academic study analyzed 70 patients from the Clinic for Endocrinology, Diabetes, and Metabolic Disorders at the University Clinical Center of Vojvodina who underwent parathyroidectomy. Participants were divided into control and study groups based on whether intraoperative parathyroid hormone levels were determined. Demographic and laboratory-clinical data from medical records were statistically analyzed.

Results: In the study group, the median of parathyroid hormone level was 104.30 pg/mL, while in the control group, it was 128.09 pg/mL; no statistically significant difference was observed ($p=0.380$). There was no statistically significant difference between groups regarding the number of reoperations indicated and the diagnosis of persistent hyperparathyroidism ($p=0.355$). A statistically significant difference in treatment outcomes was found among participants who met the *Miami* and *Dual* protocol criteria.

Conclusion: Determining parathyroid hormone levels during surgical treatment while meeting the criteria of current protocols can contribute to a higher cure rate. A more extensive prospective study is required for a more in-depth analysis of our healthcare center's experience.

Keywords: Primary Hyperparathyroidism, Intraoperative Parathyroid Hormone Monitoring, Parathyroidectomy

Corresponding author:

Associate Professor Tijana S. Ičin, MD, PhD

Specialist in Internal Medicine, Subspecialist in Endocrinology

Clinic for Endocrinology, Diabetes and Metabolic Disorders, Clinical Center of Vojvodina, Hajduk Veljkova 1-9, 21000 Novi Sad, Serbia

E-mail: tijana.icin@mf.uns.ac.rs

INTRODUCTION

The prevalence of primary hyperparathyroidism is approximately 20 cases per 100,000 inhabitants, with postmenopausal women being most commonly affected. Based on the clinical presentation, primary HPT can be classified into three forms: the biochemical form, characterized by isolated laboratory confirmation of excessive parathyroid hormone (PTH) secretion without accompanying clinical manifestations; the „asymptomatic form”, with atypical clinical manifestations; and the symptomatic form with typical clinical manifestations and complications. The well-known and proven complications of untreated hyperparathyroidism target the kidneys, bone tissue, and the gastrointestinal system [1-2]. The treatment of primary hyperparathyroidism can be surgical or conservative; surgical treatment is the method of choice to achieve permanent remission. Traditional parathyroidectomy is commonly practiced, while endoscopic minimally invasive surgery is an alternative [1-4].

Determining the level of parathormone (PTH) during the surgical procedure, intraoperative PTH (ioPTH) monitoring (IPM) enables real-time assessment of parathyroid gland tissue functionality, aiding surgeons in confirming the success of the procedure and removing hyperfunctional tissue. Moreover, ioPTH levels can raise suspicion of a multiglandular disease or additional hyperfunctional foci, which may prompt further exploration, expanding the scope of the surgery. IPM is included in current international endocrine surgery guidelines emphasizing minimally invasive parathyroidectomy [5]. IPM is considered significant because it can guide targeted surgical approaches and reduce the need for exploratory surgery. Current guidelines suggest that when the localization of hyperfunctioning parathyroid tissue is confirmed with preoperative imaging, IPM reduces the rate of unsuccessful surgeries and achieves a cure rate exceeding 97% [5]; moreover, it also proves valuable in cases with inconclusive preoperative imaging results [5-6]. IPM could lead to reduced duration of surgery and hospitalization and a decrease in the rate of reoperations in these patients. This valuable diagnostic tool could further reduce treatment costs and improve the quality of life for patients undergoing surgery [6].

These facts emphasize the impor-

tance of research in this area and the need to evaluate and summarize our healthcare center's experience in the clinical application of IPM.

AIM

Our study aimed to investigate the significance of IPM in achieving physiological/optimal PTH levels postoperatively, as well as its relevance in reducing the number of required reoperations and persistent hyperparathyroidism cases.

MATERIAL AND METHODS

The academic non-commercial research retrospectively included 70 patients with primary hyperparathyroidism of both genders who were treated and monitored at the Clinic for Endocrinology, Diabetes, and Metabolic Disorders of the Clinical Center of Vojvodina from January 1, 2010, to February 2023. The inclusion criteria were a diagnosis of primary hyperparathyroidism in patients who underwent parathyroidectomy at the Clinical Center of Vojvodina.

The study design involved a control group and a study group of 30 and 40 participants, respectively. The study group consisted of subjects whose intraoperative parathyroid hormone levels were determined during surgical treatment. The control group consisted of subjects who underwent surgery without intraoperative monitoring of parathyroid hormone levels. Demographic and laboratory-clinical data included gender, age, comorbidities, complications of primary hyperparathyroidism, preoperative morpho-functional diagnostics, preoperative and postoperative levels of serum total calcium, ionized calcium, and phosphorus, as well as preoperative and postoperative PTH levels. For both groups, through medical history overview, the extent of surgical treatment, established indications for reoperation, and confirmed diagnosis of persistent hyperparathyroidism with hypercalcemia were recorded.

Apart from the abovementioned data, ioPTH levels were noted and assessed for the study group using Miami and Dual protocol criteria for IPM [6]. Miami protocol requires blood sampling and PTH value analysis at specific times (at least thrice), obtaining a pre-incision level, pre-excision level, and a PTH level

10 minutes after parathyroidectomy; collecting a 5-minute level after parathyroidectomy is nonobligatory. A decline in PTH levels by more than 50% from the highest, either pre-precision or pre-excision value, 10 minutes after the parathyroidectomy is considered a criterion for cure [6]. Dual protocol requires collecting blood samples at two specific times, thus obtaining a pre-incision, and a PTH value 10 minutes after parathyroid gland removal. The criterion for cure is considered to be a decrease in 10-minute PTH value for more than 50% compared to the pre-incision value [6]. For PTH value assessment in our study, reference values were proposed by the Center for Laboratory Medicine, Clinical Center of Vojvodina (15.0-68.3 pg/ml). At our research center, a 'modified Miami protocol' was used, which did not include three blood samples collected at the specific time; instead, either the PTH value sampled before surgery or pre-incision value and an ioPTH value was used.

Relevant data were obtained using the Clinical Center of Vojvodina's clinical information system (electronic charts).

Exclusion criteria were the absence of relevant patient medical history data.

The study was approved by the Ethics Committee of the Clinical Center of Vojvodina on July 28, 2023 (No 6/00-131).

Demographic and laboratory-clinical variables were quantitatively described and analyzed using descriptive statistics techniques in the JASP software (Jeffreys's Amazing Statistics Program), version 0.17.2.1. The Shapiro-Wilk test was used to evaluate the normality of continuous variables. Data were presented as mean \pm standard deviation for normally distributed continuous variables and median

for non-normally distributed continuous variables. Categorical data were expressed as absolute values and percentages. Statistical analyses included parametric tests (t-test) for normally distributed variables and non-parametric tests (Mann-Whitney test) for non-normally distributed variables. The chi-square test (χ^2) and Fisher's exact test were used for analyzing categorical variables. The results were presented in tables and graphically.

RESULTS

The demographic characteristics of the participants included in the research

The research included a total of 70 participants, 60 females and 10 males.

The mean (\bar{X}) age of the participants was 57.63 years (SD = 13.35), with the youngest participant being 31 years old and the oldest 80 years old. The median age of the participants was 60 years.

Localization of performed parathyroidectomies

Upon reviewing the medical documentation, the localization of the parathyroidectomies performed on the participants included in the research was recorded. The lower right parathyroid gland was the most frequently removed parathyroid gland, with 38 participants, with more than one parathyroid gland surgically removed in 16 participants.

Table 1. Preoperative and postoperative electrolyte values

Electrolyte	Group	Valid	Median	\bar{X}	SD	p
Total calcium - preoperatively	Study group	38	2.760	2.763	0.189	0.219
	Control group	29	2.700	2.714	0.191	
Ionized calcium - preoperatively	Study group	40	1.450	1.480	0.110	0.019
	Control group	30	1.410	1.427	0.090	
Phosphorus - preoperatively	Study group	38	0.825	0.820	0.206	0.463
	Control group	28	0.820	0.782	0.180	
Ionized calcium - postoperatively	Study group	40	1.290	1.312	0.123	0.179
	Control group	29	1.290	1.358	0.233	
Total calcium - postoperatively	Study group	35	2.400	2.436	0.272	0.439
	Control group	22	2.335	2.311	0.414	
Phosphorus - postoperatively	Study group	34	0.965	0.926	0.206	0.214
	Control group	22	1.040	0.999	0.219	

Preoperative and postoperative values of serum electrolytes and the extent of surgical intervention

The values of ionized calcium, total calcium, and phosphorus, both preoperatively and postoperatively, were compared between the control and the study group (Table 1). The Mann-Whitney U test showed a statistically significant difference between the compared groups regarding the preoperative value of ionized calcium, with higher values observed in the study group (1.45 vs. 1.41, $W = 798.00$, $p = 0.019$).

Six participants in each group underwent exploratory surgery during the surgical procedure. The chi-square test did not detect a statistically significant difference in frequencies between the groups ($p = 0.583$).

Postoperative values of parathyroid hormone among the groups

The median postoperative level of PTH in the study group was 104.30 (IQR = 76.65), and in the control group, 128.09 (IQR = 67.60) (Figure 1). Using the Mann-Whitney U test, no statistically significant difference was found between the groups ($W = 674.50$, $p = 0.380$).

Intraoperative measurement of parathormone levels and treatment outcomes

Reoperation for primary hyperparathyroidism or indication for such a procedure was established in 5 participants in the control group and 4 in the study group. Diagnosis of persistent hyperparathyroidism was made in 3 participants from both the control and study groups (Table 2). The analysis did not reveal a statistically significant difference in the fre-

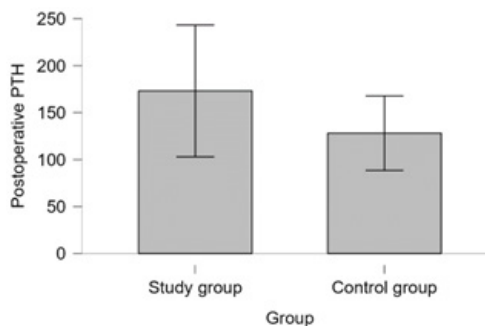


Figure 1. Postoperative values of parathyroid hormone among the group

Reoperation/Persistent primary hyperparathyroidism			
Group	Yes	No	Total
Study group	7	33	40
Control group	8	22	30
Total	15	55	70

Table 2. The outcome of surgical treatment of primary hyperparathyroidism among the groups

quencies of reoperations and persistent hyperparathyroidism between the compared groups ($\chi^2 = 0.856$, $p = 0.355$).

Meeting the Miami and Dual protocols criteria in the intraoperative determination of parathormone levels and treatment outcomes

Contingency tables were used to cross-tabulate categorical variables related to the fulfillment of criteria for ioPTH determination protocols and the outcome of surgical treatment (Table 3). Due to the small sample size and the insufficient number of subjects in certain cells of the contingency table, Fisher's exact test was performed. A statistically significant difference in treatment outcomes was found among participants who met the protocol criteria.

DISCUSSION

The first available literature data regarding IPM

Dual protocol - criteria fulfillment	Reoperation/Persistent primary HPT			Fisher's exact test
	Yes	No	Total	
Yes	1	20	21	Odds ratio 0.114 $p < 0.05$
No	6	13	19	
Total	7	33	40	

Miami protocol - criteria fulfillment	Reoperation/Persistent primary HPT			Fisher's exact test
	Yes	No	Total	
Yes	2	29	31	Odds ratio 0.062 $p < 0.01$
No	5	4	9	
Total	7	33	40	

Table 3. Criteria fulfillment of Miami and Dual protocol and treatment outcome

dates back to the eighties of the twentieth century [8]. Implementing IPM in the surgical operative rooms depended on developing rapid assays for intact PTH measurement. The first assay of this kind was an immunoradiometric assay with two binding sites, and nowadays, it is mainly replaced with immunochemiluminescence-labeled antibody (ICMA). According to the available literature, the time to obtain the results ranges from eight to twenty minutes, depending on the manufacturer [6-7]. This *point-of-care* test has had a significant impact on the surgical approach to the treatment of primary hyperparathyroidism. Until then, widely practiced bilateral surgical neck exploration, which usually lacked appropriate localizing diagnostic procedures priorly and was followed by macroscopic parathyroid glands evaluation, was the surgical treatment paradigm. One of the most significant drawbacks of previous practice was the need for a correlation between the qualitative assessment of tissue and the degree of secretion. IPM addresses primary hyperparathyroidism adequately according to its nature as a hyperfunctional disorder and does so in real time [7].

In their research in 1991, Irvin GL et al. highlighted the predictive significance of the decrease in intraoperative measured PTH levels compared to baseline values in successful parathyroidectomy and postoperative normocalcemia. In addition, they showcased the phenomenon of an initial increase in the PTH values due to the manipulation of parathyroid gland tissue during excision, a finding later confirmed by other authors [7, 9-10]. With the wide use of IPM and the availability of rapid assays, more endocrinology and endocrine surgery authors have addressed this issue. Regarding targeted parathyroidectomy guided by localization studies, there is no consensus among authors regarding the justification for intraoperative monitoring of PTH levels. Jacobson SR et al. conducted retrospective research at the Mayo Clinic in Massachusetts and emphasized the high sensitivity of the scintigraphy findings with sestamibi radiopharmaceutical, without the need for IPM. Postoperative normocalcemia was achieved in 97% of participants and 55% were discharged on the day of surgical treatment [11]. Ollila DW et al. reached a similar conclusion in their study [12]. On the other hand, in their retrospective study, which involved 100 participants, Mandell DL et al. illustrated that IPM

is relevant in the cases of uniglandular disease to perform minimally invasive surgery, even in cases where preoperative scintigraphy localized hyperfunctional tissue. Additionally, they highlighted the benefits of IPM in patients undergoing reoperation [13]. Mandell DL et al, similarly to Lew JI et al, have underlined the importance of IPM in patients with discordant morpho-functional findings, i.e., in those with unreliable preoperative localization of hyperfunctional tissue. In the first study, in 24 patients, preoperative scintigraphy finding with Tc 99m sestamibi (MIBI) radiopharmaceutical, was inaccurate, negative, or did not indicate the correct localization of hyperfunctional tissue; 96% of those participants were treated successfully using IPM [13-14]. Research by Lew JI and Irvin GL included 225 participants with preoperative scintigraphy and neck ultrasound findings. Participants were monitored for at least 6 months following parathyroidectomy, as in our research. In 85 participants (38%), the findings of morpho-visualization techniques were discordant. IPM, with an intraoperative decrease in PTH values of more than 50%, influenced the surgical course in 74% of patients with discordant findings between ultrasonography and parathyroid gland scintigraphy. In 93% of this group, the outcome of surgical treatment was successful. Conversely, in those who have concordant findings on morphological imaging, the benefit of IPM was trivial [14]. In their guideline, the American Society of Endocrine Surgeons underlines a strong recommendation for measuring ioPTH levels even in cases when minimally invasive parathyroidectomy is guided by morpho-functional findings [6].

In a retrospective-prospective study on 103 participants who underwent parathyroidectomy, Westerdah J and Bergenfelz A stressed the importance of IPM in differentiating uniglandular vs. multiglandular parathyroid gland disease [15]. In a research conducted by Carneiro-Pla DM et al. which involved 519 participants, a MIBI scan did not indicate the presence of multiglandular hyperplasia of parathyroid glands. In 13 of those 15 patients (87%), Miami protocol criteria were not fulfilled [16].

Protocols for IPM have been revised over the years; the two most commonly used currently are Miami and Dual protocols, and the results in the long-term cure rates range between 97% and 99% [5-6]. In our research,

no statistically significant difference was observed between the study and the control group regarding treatment outcomes. However, the analysis within the study group found that the participants who met the Miami and Dual protocols criteria were statistically significantly less likely to undergo reoperation. This could indicate the importance of adhering to the criteria of existing protocols, and not just to the decrease in iPTH levels, in the success of surgical treatment.

CONCLUSION

A comparison between the control group and the study group did not reveal a statistically significant difference in postoperative PTH levels or in the number of indicated or performed reoperations. However, within the study group, a statistically significant difference was observed in PTH levels and treatment outcomes among participants meeting the *Miami* and *Dual* criteria for IPM, at a significance level of $p < 0.05$. This supports the relevance of adhering to the criteria of these protocols during IPM.

The main limitation of our study was the sample size, which reduced its power and could have led to the lack of differences between groups regarding the analyzed variables. A prospective study with a larger sample size would be necessary for a more detailed evaluation and statistical analysis of our healthcare center's experience in implementing IPM.

CONFLICTS OF INTEREST

All authors declare no conflict of interest.

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Značaj određivanja intraoperativnog nivoa parathormona tokom hirurškog lečenja hiperparatireoidizma

Stefan D. Janičić^{1,2}, Kristina M. Stepanović^{1,2}, Mia S. Manojlović^{1,2}, Dean P. Bjelajac^{1,3}, Slađana M. Pejaković^{1,2}, Milan R. Mirković², Dragana D. Tomić-Naglić^{1,2}, Ivana A. Bajkin^{1,2}, Tijana S. Ičin^{1,2}

¹ Univerzitet u Novom Sadu, Medicinski fakultet, Novi Sad, Srbija

² Klinika za endokrinologiju, dijabetes i bolesti metabolizma, Klinički centar Vojvodine, Novi Sad, Srbija

³ Klinika za abdominalnu, endokrinu i transplantacionu hirurgiju, Klinički centar Vojvodine, Novi Sad, Srbija

KRATAK SADRŽAJ

Uvod: Operativno lečenje je metoda izbora u terapiji primarnog hiperparatireoidizma. Određivanje nivoa parathormona (PTH) tokom operativnog zahvata, intraoperativni PTH monitoring, omogućava praćenje funkcionalne aktivnosti tkiva paraštitastih žlezda u realnom vremenu i izvođenje minimano invazivne paratireoidektomije, doprinosi većoj stopi izlečenja i potencijalno smanjuje troškove bolničkog lečenja.

Cilj: Cilj naše studije je bio da ispitamo značaj određivanja intraoperativnog nivoa parathormona u postizanju fiziološkog nivoa parathormona i izlečenja.

Materijali i metode: Ispitivanje je retrospektivno obuhvatilo 70 bolesnika podvrgnutih paratireoidektomiji, lečenih i praćenih na Klinici za endokrinologiju, dijabetes i bolesti metabolizma Univerzitetskog kliničkog centra Vojvodine. Ispitanici su podeljeni u dve grupe, kontrolnu i ispitivanu grupu, u zavisnosti od toga da li je određen intraoperativni nivo parathormona. Demografski i laboratorijsko-klinički podaci obuhvaćeni istraživanjem dobijeni su iz istorija bolesti, a potom su statistički obrađeni.

Rezultati: U ispitivanoj grupi, medijana nivoa parathormona iznosila je 104,30 pg/mL, dok je u kontrolnoj grupi iznosila 128,09 pg/mL; nije primećena statistički značajna razlika ($p=0,380$). Nije utvrđeno postojanje statistički značajne razlike među poređenim grupama kad je reč o broju indikovanih reoperacija i postavljanja dijagnoze perzistentnog hiperparatireoidizma ($p=0,355$). Statistički značajna razlika u ishodu lečenja otkrivena je kod ispitanika koji su ispunili kriterijume *Miami* i *Dual* protokola.

Zaključak: Određivanje nivoa PTH tokom operativnog lečenja uz ispunjenje kriterijuma aktuelnih protokola može doprineti većoj stopi izlečenja. Za detaljniju analizu iskustva našeg zdravstvenog centra bila bi potrebna opsežnija prospektivna studija.

Ključne reči: primarni hiperparatireoidizam, intraoperativni PTH monitoring, paratireoidektomija

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