



Role and Recent Trend of Intraoperative Parathyroid Hormone Monitoring During Parathyroidectomy in Patients With Primary Hyperparathyroidism

Dongbin Ahn^{ID} and Ji Hye Kwak

Department of Otolaryngology-Head and Neck Surgery, School of Medicine, Kyungpook National University, Daegu, Korea

일차성 부갑상선 기능항진증에서 수술 중 부갑상선 호르몬 감시의 역할과 최근 경향

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경북대학교 의과대학 이비인후-두경부외과학교실

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Address for correspondence

Dongbin Ahn, MD

Department of Otolaryngology-

Head and Neck Surgery,

School of Medicine,

Kyungpook National University,

130 Dongdeok-ro, Jung-gu,

Daegu 41944, Korea

Tel +82-53-200-5781

Fax +82-53-200-4524

E-mail godlikeu@naver.com

In the last few decades, the standard surgical treatment for primary hyperparathyroidism (PHPT) has shifted from bilateral neck exploration to focused/minimally invasive parathyroidectomy (FMIP). This shift was accelerated by the introduction of intraoperative parathyroid hormone (IOPH) monitoring, which can provide intraoperative information regarding the localization and complete excision of the pathological parathyroid gland during FMIP. Since the first clinical application of the IOPH assay in 1991, IOPH monitoring has substantially improved to date to increase its performance and availability. In addition, the clinical applications of IOPH changed with the needs of actual clinical practice, although the fundamental concept and technique remained unchanged. In this review, we discuss the role of IOPH monitoring in the surgical management of PHPT based on the results of contemporary studies and summarized the major issues regarding IOPH.

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Introduction

Primary hyperparathyroidism (PHPT) is a common endocrinopathy that primarily causes bone and kidney disorders, the prevalence of which increases with age.^{1,2)} In addition, with an increased number of health examinations and the introduction of osteoporosis screening guidelines, the overall incidence of PHPT in the United States has increased from 27.9 cases per 100000 person-years in 1985–1997 to 50.4 cases per 100000 person-years in 1998–2010.^{3,4)} Surgical removal

of the pathological parathyroid gland (PTG) is currently the only curative treatment method for PHPT; accordingly, the number of parathyroidectomies performed has also increased in recent decades.⁵⁾

Since the first parathyroidectomy performed in 1925, bilateral neck exploration (BNE) has been the gold standard for surgical treatment of PHPT, with a surgical cure rate of >95%.⁶⁾ In recent decades, however, improvements in preoperative localization techniques such as Tc-99m sestamibi (MIBI) scintigraphy, high-resolution neck ultrasonography (US), and computed tomography (CT) have meant that focused/minimally invasive parathyroidectomy (FMIP) has been performed more commonly, as this technique allows a shorter hospital

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stay and lower complication rates without compromising surgical outcomes.^{7,8)}

In addition to advances in imaging modalities, intraoperative parathyroid hormone (IOPTH) monitoring has been applied as an important component of FMIP, which helps surgeons to quantitatively detect the excision of all hyperfunctioning parathyroid tissue, predicting the final surgical cure.^{6,9)} In 1988, Nussbaum, et al.¹⁰⁾ initially introduced the post-excision measurement of parathyroid hormone (PTH) as an adjunct to indicate cure. In 1991, Irvin, et al.¹¹⁾ introduced a rapid IOPTH assay to assess the adequacy of surgery. For the first time, a series of 21 patients underwent parathyroidectomy guided by IOPTH using an immunoradiometric method. Since then, IOPTH monitoring has been enhanced, developing new interpretation models, although the underlying concept and fundamental technique have not changed considerably.^{9,12)} Furthermore, there are emerging controversies regarding the true added-value of IOPTH to increase surgical outcomes, given that parathyroidectomy usually shows excellent success rates regardless of IOPTH monitoring, particularly when performed by an experienced surgeon based on an accurate preoperative imaging study.^{13,14)}

Consequently, there is a recent need to discuss the current role of IOPTH monitoring in clinical practice. Therefore, this article reviews the role of and trends in IOPTH monitoring in the surgical management of PHPT, based on the results of contemporary studies.

Role of IOPTH and Current Guidelines

The traditional role of IOPTH can be summarized as follows: 1) confirming complete excision of all hyperfunctioning PTGs before surgery completion; 2) indicating the presence of additional hyperfunctioning parathyroid tissue based on an insufficient IOPTH drop, thereby guiding the surgeon to perform further neck exploration; 3) differentiating parathyroid tissue from non-parathyroid tissue; 4) lateralizing the side of the neck harboring the hyperfunctioning PTGs through differential jugular venous sampling when preoperative localization studies are equivocal; and 5) safely allowing FMIP along with preservation of the normal PTG in patients with PHPT.^{6,15,16)}

Because of its many advantages, the American Association of Endocrine Surgeons (AAES) Committee strongly suggests the use of IOPTH monitoring in image-guided FMIP to reduce the risk of operative failure.¹⁷⁾ However, when IOPTH moni-

toring is not possible, BNE remains the preferred surgical approach. Similar to the AAES guidelines, the European Society of Endocrine Surgeons guidelines recommend the use of IOPTH monitoring 1) when targeted parathyroidectomy is performed based on a single preoperative localization study, 2) when preoperative localization with MIBI scintigraphy and US is not concordant, and 3) in cases of reoperation.¹⁸⁾ In contrast to these recommendations by two major endocrine surgeons' societies, the National Institute of Clinical Excellence recommends against the routine use of IOPTH for first-time parathyroid surgery because of its cost and minimal surgical benefit.¹⁹⁾

IOPTH Monitoring Techniques

The half-life of PTH is approximately 3–5 min, allowing PTH decay to be measured quickly and quantitatively during parathyroidectomy.²⁰⁾ Although the detailed protocol is different according to several IOPTH interpretation criteria, PTH measurement is required before and after excision, and is usually performed preoperatively, before excision (just before excision of pathological PTG during surgery), and 10–20 min after excision.^{6,12,15)} At least four different systems have been proposed and used for the determination of IOPTH: the QuiCK-Pak system (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA), STAT-IntraOperative-Intact-PTH Immunoassay (Future Diagnostics, Wijdien, Netherlands), Immulite Turbo PTH assay (Diagnostic Products, Los Angeles, CA, USA), and Cobas Elecsys PTH assay (Roche, Mannheim, Germany).^{16,21)} All these assay apply the principle of detection of chemiluminescence signal; the turnaround times were approximately 10 min for the QuiCK-Pak system and STAT-IntraOperative-Intact-PTH Immunoassay and 15–20 min for Immulite Turbo PTH assay and Cobas Elecsys PTH assay.^{16,22)} However, to estimate the total time to obtain IOPTH levels in actual clinical practice, additional transportation time has to be taken into account if the laboratory is not located next to the operating room.

Interpretation Criteria

In 1993, Irvin, et al. first established that a 50% decline from a pre-excision IOPTH level best predicted postoperative normocalcemia.^{23,24)} The "Miami criterion" was later refined to decrease $\geq 50\%$ from the highest PTH level at 10 min after excision of presumed pathological PTG.^{24,25)} If this criterion is met, the procedure can be terminated. Otherwise, the neck

is re-explored and the protocol for IOPTH monitoring is repeated for each additional excision until a sufficient drop in IOPTH can be demonstrated, which indicates that the entire pathological PTG was excised. The overall accuracy of the Miami criterion in predicting postoperative calcium values has been reported to be 97%–98%.^{12,24)}

Several groups have made modifications to the Miami criterion, including a larger IOPTH level percent drop (>65%–80%), decrease in IOPTH level to a specific value or within the normal range, and/or a IOPTH decrease at 5 min after gland excision.^{12,26)} Table 1 shows the definition and performance of the commonly used IOPTH criteria for predicting surgical success of parathyroidectomy.^{6,9,12,24,27)} In a retrospective study evaluating the diagnostic performance of Halle, Miami, Rome, and Vienna criteria in 260 patients with PHPT, the Miami criterion followed by the Vienna criterion was found to be the best balanced, with the highest accuracy in intraoperative prediction of cure.¹²⁾ However, the Rome criterion followed by the Halle criterion was found to be the most

useful for the intraoperative detection of multiglandular disease (MGD).¹²⁾ Similarly, in another study, the Vienna and Halle criteria were found to be better predictors of MGD than the Miami criterion.²⁸⁾

Although there is some evidence to suggest that the use of stricter criteria may decrease the risk of operative failure, it should be noted that as the IOPTH criteria become stricter, unnecessary BNE would be performed more frequently without improving surgical success.^{28,29)} Therefore, the choice of IOPTH criteria should be individualized based on surgical difficulties and probabilities of MGD, as suggested by the results of preoperative imaging studies, such as US and MIBI scintigraphy.

Time and Cost

Despite the previously mentioned advantages and applications of IOPTH, there are several barriers to its adoption. Compared with BNE without IOPTH, IOPTH-guided FMIP is sig-

Table 1. Definition and performance of commonly used IOPTH criteria for prediction outcomes of parathyroidectomy

Criteria	Definition	Performance
Miami	A $\geq 50\%$ IOPTH decrease from the highest measurement (pre-incision or pre-excision) at 10 min after excision of all hyperfunctioning PTG(s)	Sensitivity 98% Specificity 54%–93% PPV 99%–100% NPV 70%–88% Accuracy 92%–97%
Halle	An IOPTH decay to < 35 ng/L within 15 min after excision of all hyperfunctioning PTG(s)	Sensitivity 63%–70% Specificity 87%–100% PPV 98%–100% NPV 14%–27% Accuracy 65%–72%
Rome	A $\geq 50\%$ IOPTH decrease from the highest pre-excision level and/or IOPTH level within normal range at 20 min after excision, and/or ≤ 7.5 ng/L less than the value at 10 min after excision	Sensitivity 83% Specificity 90%–100% PPV 99%–100% NPV 21%–26% Accuracy 84%
Vienna	A $\geq 50\%$ IOPTH decrease from the pre-incision value within 10 min after excision of all hyperfunctioning PTG(s)	Sensitivity 82%–92% Specificity 89%–93% PPV 97%–100% NPV 56%–61% Accuracy 80%–92%
Rotterdam	IOPTH value between 100 and 200 ng/L and IOPTH decrease of $\geq 70\%$ 10 min after parathyroidectomy or IOPTH decrease of ≥ 200 ng/L and $\geq 80\%$ 10 min after parathyroidectomy	Sensitivity 100% Specificity 88% Accuracy 100%
Charleston	Decay $> 50\%$ from the highest baseline value 10 min after resection and return to normal range or decay $> 65\%$, or decay $> 50\%$ and return to normal range within 20 min after resection	Sensitivity 97% Specificity 98% Accuracy 97%

The percentage of performance was rounded off to one decimal point. IOPTH, intraoperative parathyroid hormone; PTG, parathyroid gland; PPV, positive predictive value; NPV, negative predictive value

nificantly associated with shorter operative times, almost certainly related to the extent of dissection.^{27,30)} However, when FMIP is performed, the addition of IOPTH can increase operating time.²⁷⁾ In a study of 240 patients with PHPT who underwent surgery, the duration of surgery was approximately 20-min longer when IOPTH monitoring was used than when it was not used ($p<0.001$).¹⁵⁾ A recent meta-analysis involving 2290 patients from 12 studies also showed a trend toward increased length of operation in the IOPTH group, with a weighted mean difference of 21.6 min, although this trend did not reach statistical significance ($p=0.06$).²⁰⁾ This extra time could be attributed to sample transportation from operating room to the laboratory of the institution, as well as the turnaround time of the assay.^{9,27)} Extra time resulting from sample transportation would be negligible if a Point-of-Care (POC) system for IOPTH assay is established, allowing measurement of IOPTH in the operating room. However, the necessary equipment is bulky and occupies space. Importantly, this would also require the presence of trained laboratory personnel.²⁷⁾

It is not surprising that IOPTH incurs additional costs during parathyroidectomy. This extra cost is primarily derived from the cost of the PTH assay, which includes 4–5 IOPTH measurements in most protocols. Therefore, the added-value of IOPTH monitoring should be balanced against assay-related costs in terms of cost-effectiveness.

Two studies addressed the cost-effectiveness of IOPTH monitoring. In one meta-analysis of 17 studies involving 4280 unique patients, IOPTH reduced the overall treatment costs only when total assay-related costs decrease below \$110 per case.³¹⁾ In addition, the IOPTH strategy was cost-saving when the rate of unrecognized MGD exceeded 6%, or if the cost of reoperation exceeded \$12000 (compared with an initial FMIP cost of \$3733).³¹⁾ Another study involving 92 patients with PHPT who underwent FMIP suggested that 97% of patients will be cured regardless of IOPTH monitoring, and its false-negative rates significantly reduce the cost-effectiveness of IOPTH monitoring.³²⁾ Given these findings of the cost-effectiveness, routine use of IOPTH monitoring could not be justified in most patients with PHPT. Conversely, these findings imply that IOPTH monitoring would be most valuable in patients with inaccurate preoperative localization and at high risk of reoperation. In fact, the majority of these patients had MGD rather than single glandular disease (SGD).

However, assessment of the cost-effectiveness of IOPTH may result in different conclusions according to the institution and country, as the cost of IOPTH monitoring varies greatly

as a function of these factors. For example, in South Korea, where medical fees are regulated and the National Health Insurance covers the entire population as a compulsory social insurance system, the total cost of parathyroidectomy is only \$2000–3000, and the cost for measurement of PTH levels is only \$15–30 per assay. Furthermore, patients are charged only some of the total costs. Hence, the additional expense incurred by IOPTH monitoring may not be a critical consideration.

Recent Issues and Changed Role of IOPTH

The major controversies regarding IOPTH in FMIP include the following issues. First, is a 50% decrease in 10-min IOPTH level the best to determine the conversion of surgery to BNE? Second, is routine IOPTH monitoring necessary for successful parathyroidectomy? Lastly, in which case of parathyroidectomy does IOPTH have a true added-value?

Regarding the first issue, a 50% decrease in 10-min IOPTH level as an indicator of the need for BNE would also be associated with the protocol and interpretation criteria of IOPTH. As mentioned above, although Miami criteria has been demonstrated as the most balanced of the currently used criteria, it showed relatively low negative-predictive values (70%–88%), and occasionally involved false-negative results in patients undergoing FMIP, leading to unnecessary BNE.^{6,9,12,27)} These false-negative cases may result from individual variations in PTH clearance that have been attributed to patient-specific variability in PTH half-life associated with subclinical renal insufficiency or expanded intravascular volume during operations, concomitant use of anesthetics that slow PTH clearance, or initial spikes in PTH level due to excessive gland manipulation.^{6,9,26,27)} To avoid unnecessary BNE based on false-negative results of 10-min IOPTH, measurements of additional 20-min IOPTH has been suggested, if the criterion is not met at 10 min after suspicious PTG excision or if the decline dynamics are equivocal (e.g., borderline decrease at 50%).²⁶⁾ In a study involving 706 patients with PHPT who underwent parathyroidectomy guided by IOPTH, an additional 20-min IOPTH measurement was performed in 24 out of 72 patients who did not meet the >50% IOPTH decrease criteria. Of these, 46% (11/24) patients had a >50% IOPTH decrease at 20 min and parathyroidectomy was completed, whereas 54% (13/24) did not.²⁶⁾ These 11 patients with >50% IOPTH decrease at 20 min achieved surgical success without BNE. Therefore, measurement of the 20-min IOPTH in addition to the Miami

criteria may be a good modification to minimize unnecessary neck exploration and related time and cost. However, there are a limited number of studies addressing this additional 20-min IOPTH protocol; thus, further studies should be performed to assess its true benefits in terms of surgical outcomes, cost-effectiveness, and time-effectiveness, and to determine which patients will benefit most from routine use of 20-min IOPTH measurements.

Second, the necessity of IOPTH monitoring during FMIP for PHPT with positive imaging findings, is still controversial. In a study involving 240 patients with PHPT in 2010, the additional benefits of IOPTH was not significant when preoperative US and MIBI scintigraphy were performed.¹⁵⁾ A recent study involving 242 patients with PHPT who underwent FMIP based on positive US findings showed that surgical cure was achieved in 232 patients (95.9%) without routine measurement of IOPTH.¹³⁾ However, 8 out of 10 remaining patients who failed to achieve initial surgical success underwent reoperation. The cause of failure of the initial surgery was verified as MGD in 6 patients and incorrect excision (thyroid tissue) in 2 patients. Although the authors insisted that added-value of IOPTH is limited in patients with positive preoperative US based on high surgical cure rates, the findings of this study paradoxically imply the possible benefits of using IOPTH to detect MGD and differentiate parathyroid tissue from non-parathyroid tissue, as reoperation could be prevented if the initial surgery was performed under IOPTH-guidance. In fact, IOPTH monitoring could be dispensable or optional if pathological PTG is truly single and well/concordantly localized in preoperative imaging studies. However, preoperative imaging studies for the identification of MGD have significant limitations. Regardless of the type of imaging modality (US, MIBI scintigraphy, or CT), the accuracy of diagnosing and localizing MGD has been reportedly less than 50%.^{33,34)} Therefore, it is almost impossible to guarantee SGD preoperatively. Despite these limitations of preoperative diagnosis of MGD, the fact that more than 85% of PHPT is caused by a single parathyroid adenoma makes surgeons consider single disease preferentially when only one suspicious PTG enlargement is identified and localized by preoperative imaging studies.

In summary, although IOPTH monitoring does not affect surgical plans and outcomes in most patients with PHPT of SGD, IOPTH monitoring still has a role in rescuing challenging cases of FMIP and maximizing the performance of parathyroid surgery, particularly for MGD, which cannot be diagnosed preoperatively, and for PHPT cases with inaccurate or

discordant imaging results. This could answer the third issue, to define in which parathyroidectomy cases IOPTH would provide true added-value. In addition, cases of reoperation, or where surgery is performed by an inexperienced surgeon, are also suitable cases where IOPTH could provide true added-value.

Considering the conventional roles and current issue of IOPTH, we conclude that the current role of IOPTH monitoring is changing toward maximization of surgical performance during FMIP in challenging cases, rather than as a routine tool for accurate surgical localization during parathyroidectomy for general PHPT. In addition, in keeping with a recent trend toward a single-scan paradigm, which uses only a single imaging modality for preoperative localization of PHPT instead of multiple imaging modalities, compensating for the possible inaccuracy of a single-image study has been suggested as an emerging role of IOPTH, as it is better to perform intraoperative biochemical monitoring than multiple preoperative imaging studies to inform surgeons as to how many PTGs need to be removed.²⁷⁾

Personal Practice and Experience with IOPTH Monitoring

For starting IOPTH, surgeons should investigate the available equipment or system for general PTH assay in the institutional main laboratory. A minimal prerequisite should be the availability of one of the four different systems for PTH assay mentioned in the section "IOPTH monitoring techniques."

Between 2009 and 2022, 82 patients underwent FMIP for PHPT at our institution and IOPTH monitoring was used in 61 patients (74.4%). We used the Cobas Elecsys PTH assay at our main laboratory for IOPTH without the POC PTH assay system in the operating room. Therefore, blood samples drawn for IOPTH had to be transported to the main laboratory; this was usually the duty of residents or interns. Although the theoretical turnaround time of the Cobas Elecsys PTH assay is 18 min, the IOPTH results were usually obtained approximately 25–30 min after excision of the presumed pathological PTG. Oftentimes, the laboratory staff was informed about the surgical in advance and requested for early-processing of PTH assay in the main laboratory. In addition, to eliminate unnecessary lengthening of the operating time, we proceeded with wound closure while waiting for the IOPTH results. We used the Miami criteria ($\geq 50\%$ decrease in 10-min IOPTH) as the primary criteria to determine surgical success. In addition, the 20-min IOPTH level was routinely measured to minimize

the unnecessary neck exploration in some patients with a delayed IOPTH decrease of $\geq 50\%$.

In our series, all 82 parathyroidectomies were completed successfully, with a 100% surgical cure rate. Among 61 patients with IOPTH monitoring, the 10-min IOPTH decreased by $\geq 50\%$ from the baseline in 58 patients (95.1%). For the remaining 3 patients (4.9%) with a $< 50\%$ decrease in 10-min IOPTH, 20-min IOPTH was measured, which revealed a decrease by $\geq 50\%$ from baseline in 2 patients (3.3%). For these 2 patients, surgery was completed without additional neck exploration. In the remaining patient (1.7%), 20-min IOPTH did not decrease sufficiently; thus, surgery was converted to BNE to excise all pathological PTGs (MGD), ultimately achieving an IOPTH decrease of $\geq 50\%$. Therefore, 20-min IOPTH prevented unnecessary BNE in 2 (66.7%) out of 3 patients who did not meet the $\geq 50\%$ decrease criteria at 10-min IOPTH. In addition, one patient with MGD was rescued with the assistance of IOPTH, which indicated the presence of additional pathological parathyroid tissue even after the excision of one pathological PTG. However, there were no differences in surgical success, vocal cord paralysis, or surgical cure between patients with ($n=61$) and without ($n=21$) IOPTH, as all parathyroidectomies were completed successfully without complications.

Interestingly, the operating time from the beginning to the end of general anesthesia was significantly shorter with IOPTH monitoring than without IOPTH monitoring (70.6 ± 20.4 min vs. 88.5 ± 22.6 min, $p=0.031$). Although IOPTH monitoring is usually considered to be associated with longer operating time because of the need to wait for the results of post-excision PTH level, we proceeded with wound closure while waiting for the IOPTH results, and assurance of successful excision of the pathological PTG ultimately lead to a reduced operating time.

Conclusion

Despite several controversies regarding IOPTH, this technique remains the most effective method to guide successful parathyroid surgery when using FMIP. The use of IOPTH could be individualized according to the characteristics of PHPT based on the preoperative evaluation (localization and number of suspicious lesions), each institution's circumstances (facilities and cost), and surgeon's preferences. However, the use of IOPTH should be strongly suggested to avoid reoperation and achieve maximal performance of FMIP if there is any possibility of MGD or risk of localization failure. In ad-

dition, although more than 85% of PHPT is SGD and improvement of preoperative imaging studies may undermine the conventional roles of IOPTH, the recent single-scan paradigm requires another role of IOPTH, the which enables surgeons to abandon the customary use of multiple preoperative image studies. Among several interpretation criteria, the Miami criterion is still believed to be the standard criterion for IOPTH, with the highest overall accuracy. The performance of the Miami criterion could be enhanced by adding the measurement of 20-min IOPTH, which could minimize the unnecessary conversion to BNE.

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Author Contribution

Conceptualization: Dongbin Ahn. Data curation: Dongbin Ahn, Ji Hye Kwak. Formal analysis: Dongbin Ahn. Investigation: Dongbin Ahn, Ji Hye Kwak. Methodology: Dongbin Ahn. Supervision: Dongbin Ahn. Validation: Dongbin Ahn, Ji Hye Kwak. Visualization: Dongbin Ahn. Writing—original draft: Dongbin Ahn. Writing—review & editing: Dongbin Ahn, Ji Hye Kwak.

ORCID

Dongbin Ahn <https://orcid.org/0000-0002-4977-7406>

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정답 및 해설

답 ③

해설 심한 코피가 있는 경우, 작은 조작에도 쉽게 출혈하는 경향이 있으므로 조직 검사를 외래에서 시행하지 않는다. 혈관이 풍부한 종양이 의심되므로 조영 증강 CT/MRI를 촬영하여 종양의 범위와 혈관 발달 정도를 확인한다. 비내시경 및 환자의 병력으로는 주로 사춘기 남자에게 호발하는 혈관이 풍부한 양성종양인 비인강 혈관섬유종이 의심된다. 수술로 제거하며 주로 내시경 수술을 시행한다. 혈관조영술을 시행하여 수술 전 영양동맥을 확인하고 색전하여 술중 출혈을 줄이는 데 도움을 줄 수 있다.