

A Comprehensive Review of Intraoperative Parathyroid Hormone Monitoring

¹Marlon A Guerrero, ²Orlo H Clark

¹Department of Surgery, University of Arizona, Arizona

²Department of Surgery, University of California, San Francisco

Correspondence: Orlo H Clark, Department of Surgery, University of California, 1600 Divisadero Street, Box-1674, San Francisco CA 94143, USA, Phone: 415-885-7616, e-mail: orlo.clark@ucsfmedctr.org

INTRODUCTION

Intraoperative parathyroid hormone monitoring (IOPTH) has changed the surgical approach to primary hyperparathyroidism (PHPT). The traditional approach for the treatment of PHPT is a bilateral neck exploration (BNE), which entails the identification of all parathyroid glands and resection of the abnormal glands. However, with the advent of improved surgical adjuncts, including preoperative ultrasound and sestamibi scintigraphy, and IOPTH monitoring, the pendulum has swung from bilateral exploration to minimally invasive parathyroidectomy. Minimally invasive parathyroidectomy (MIP) encompasses a myriad of “minimally invasive” procedures and includes focused, unilateral, videoscopic, endoscopic, and robotic parathyroidectomies. The standard that MIP is measured against is the traditional bilateral neck exploration which results in a >95% success rate in experienced hands.¹⁻⁴

The most common and widely accepted adjuncts used with MIP are ultrasound (US) scanning, sestamibi (MIBI) scanning, and IOPTH. The reported accuracy for identifying a single adenoma is 71 to 80% for US and 74 to 88% for MIBI, and 64 to 95% when both are combined.⁵⁻⁸ On the other hand, the accuracy for identifying multigland disease is lower with either single (69% for US and 49% for MIBI) or combined (62%) imaging modalities.⁶ IOPTH is reported to have an overall accuracy of 80%.⁵ Similar to preoperative localizing studies, the best results of IOPTH occur in patients with single gland disease (87 to 99%),^{5,8} but IOPTH assay is less accurate in patients with multigland disease (58%).⁵ Others, contend that IOPTH is accurate and allows for the successful operative treatment of patients with both single gland and multiple gland parathyroid disease, and rely on parathyroid gland function rather than morphology or histology.⁹

Not many issues in surgery have been debated as extensively as the use of IOPTH during parathyroid surgery. Proponents supporting IOPTH (in conjunction with localizing studies) propose that the use of IOPTH allows for a less invasive approach, while providing the same operative success and risk of recurrence as a BNE.^{10,11} On the other hand, opponents of IOPTH argue that a minimally invasive approach underestimates the rate of multigland disease and can potentially lead to operative failure.⁶ A minimally invasive approach also allows for a shorter hospital stay, although most patients having a bilateral approach can be discharged within 24 hours, a more cosmetic appealing incision, and less postoperative pain are also reported. The risk of surgical complications can be argued to occur less frequently with MIP since only one side of the neck or two parathyroid glands and one recurrent laryngeal nerve are at risk. However, this argument is hard to defend because the complication risk during BNE is already nominal (1%) in the hands of experienced parathyroid surgeons. The contention surrounding the use of IOPTH is centered on the potential risk of operative failure. This comprehensive overview outlines the use of IOPTH during parathyroid surgery and outlines the arguments for and against the use of routine IOPTH.

IOPTH CRITERIA

IOPTH was introduced as an adjunct for parathyroid surgery in 1988.¹² Several criteria have been proposed to confirm the adequacy of parathyroid resection and the success of IOPTH. The purpose of these criteria is to improve operative success by reducing the number of failed explorations. The ideal criterion should be highly accurate and have a low rate of false-positive and false-negative results.

The most widely accepted and readily used is the *Miami criterion*.⁹ This protocol requires both a preincision and pre-

excision PTH level. A $\geq 50\%$ PTH fall from either the highest preincision or pre-excision hormone level at 10 minutes after all hypersecreting glands are excised denotes a successful operation in most patients. The preexcision PTH is required because manipulation of the parathyroid tumor can dramatically decrease or increase the IOPTH level. The IOPTH assay can result in either true positive or negative, or false-positive or negative (Table 1). Surgical cure is confirmed when eucalcemia is achieved for at least 6 months postoperatively.⁹ The Miami criterion establishes a success by assuring that calcium normalization persists beyond 6 months. By using the postoperative calcium level, IOPTH has a sensitivity of 98%, specificity of 96%, positive predictive value of 99%, negative predictive value of 90%, and accuracy of 98%.¹³

The *Rome criterion* requires a $\geq 50\%$ fall from the highest preexcision PTH level, and/or a PTH level within the reference range at 20 minute postexcision, and/or a PTH level 7.5 ng/L lower than the 10 minutes postexcision level.¹⁴ The *Halle criterion* requires the IOPTH to fall into the low normal range (< 35 ng/L) within 15 minutes of removing all hyperfunctioning parathyroid glands.¹⁵ The *Vienna criterion* requires baseline preincision PTH sample acquired before neck manipulation. A PTH fall $\geq 50\%$ from the baseline PTH level at 10 minutes from gland resection indicates a successful operation.¹⁵ The fact that so many criteria are proposed indicates that expert surgeons are not completely comfortable with the IOPTH results.

A recent study compared the accuracy of each criterion in predicting operative success in 260 patients with PHPT.¹⁶ This study demonstrated that the *Miami criterion* had the highest overall accuracy (97%), while the *Halle criterion* had the lowest (65%). The *Miami* and *Vienna criterion* had the highest true positive rate of 91.9% and 86.9%, respectively. However, both the *Halle* and *Rome criterion* had no false-positive results, compared to the 0.4% rate for

Table 2: Comparative results between studies evaluating individual IOPTH criterion			
Criterion	Sensitivity %	Specificity %	Overall accuracy %
Halle			
Barczynski, et al ¹⁶	62.9	100	65
Riss, et al ¹⁵	69.8	88.6	71.9
Miami			
Barczynski, et al ¹⁶	97.6	93.3	97.3
Riss, et al ¹⁵	97.8	54.3	92.9
Vienna			
Barczynski, et al ¹⁶	92.2	93.3	92.3
Riss, et al ¹⁵	92	88.6	91.6

both the *Miami* and *Vienna criterion*, but at the cost of higher false-negative results (35% and 16.2%, respectively). Overall, the *Miami criterion* produced the best results as an adjunct for parathyroid surgery with a sensitivity, specificity, positive predictive value, and negative predictive value of 97.6%, 93.3%, 99.6%, and 70%, respectively.¹⁶

Interestingly, this recent study¹⁶ contradicts a previous comparative study that analyzed the utility of the *Miami*, *Vienna*, and *Halle criteria* in 310 patients with PHPT.¹⁵ This study found that although the overall accuracy was similar between the *Miami* (93%) and *Vienna* (92%) criteria (Table 2), accuracy significantly dropped when the *Miami criteria* (57%) was used in patients with MGD, compared to the *Vienna* (91%) and *Halle* (91%) criteria. Using the *Miami* criteria resulted in a lower false-negative rate (2%, vs 8% for *Vienna* and 29% for *Halle* criterion). However, the false-positive rate was higher when the *Miami* criterion (39%) was used in patients with MGD, compared to both the *Vienna* and *Halle* criterion (9%) (Table 3).

ARGUMENTS FOR IOPTH

IOPTH is widely accepted for use during MIP because of its reported utility to help guide the extent of surgery.¹⁷ The

Table 1: IOPTH results using the Miami Criterion	
True-positive	IOPTH adequately decreases by $> 50\%$ from either preincision or pre-excision levels at 10 minutes after removing abnormal parathyroid gland(s) and the patient remains normocalcemic at 6 months
False-positive	IOPTH decreases by $> 50\%$ from either preincision or pre-excision levels at 10 minutes despite all abnormal glands not being removed
True-negative	IOPTH fails to decrease by $> 50\%$ from either preincision or pre-excision levels at 10 minutes after removing parathyroid gland(s), indicating an incomplete resection
False-negative	IOPTH fails to fall $> 50\%$ from either preincision or pre-excision levels at 10 minutes despite adequately removing the abnormal parathyroid gland(s)

Table 3: Comparative results between studies analyzing the efficacy of individual IOPTH criterion

<i>Criterion</i>	<i>Total</i>	<i>TP n(%)</i>	<i>TN n(%)</i>	<i>FP n(%)</i>	<i>FN n(%)</i>
Halle					
Barczynski, et al ¹⁶	260	154(59.2)	15(5.8)	0(0)	81(35)
Riss, et al ¹⁵	310	192(62)	31(10)	4(1.3)	83(26.8)
Miami					
Barczynski, et al ¹⁶	260	239(91.9)	14(5.4)	1(0.4)	6(2.3)
Riss, et al ¹⁵	310	269(86.8)	19(6.1)	16(5.2)	6(1.9)
Vienna					
Barczynski, et al ¹⁶	260	226(86.9)	14(5.4)	1(0.4)	19(7.3)
Riss, et al ¹⁵	310	253(81.6)	31(10)	4(1.3)	22(7.1)

value of IOPTH is derived from the reported improvement in surgical outcome when used in conjunction with preoperative localizing studies in some, but not all patients. For instance, operative success when MIBI shows a single adenoma is increased from 83 to 92% with the use IOPTH.⁵ Similarly, when US shows a single adenoma the success rate is increased from 71 to 86%.⁵ Furthermore, IOPTH has been reported to identify 87% of patients with multigland disease when MIBI identified only a single adenoma.⁷

A single adenoma is the cause of PHPT in about 85% of cases, but one of the most important aspects of parathyroid surgery is accurately identifying or excluding multiglandular disease. Preoperative localizing studies are often used to help differentiate single and multigland disease. It is reported that concordant, independently evaluated US and MIBI imaging studies accurately identifies up to 99% of single adenomas.⁸ Additionally, the use of IOPTH in patients with concordant imaging studies has been shown to increase the success of surgery from 95 to 97-99%.^{5,18-20} The limitation, however, is that preoperative imaging studies are only concordant in 52 to 64%.^{6,8,10,19} This means that about half to two-thirds of the patients will have discordant studies, making the use of minimally invasive techniques extremely difficult. It is therefore important for IOPTH to be accurate in guiding the extent of surgery in patients with discordant preoperative imaging studies when any procedure short of a BNE is attempted.

The use IOPTH has been reported to accurately guide the operative management in 74% of patients with discordant imaging studies. The reported operative success rate in this cohort of patients is 93%.¹⁰ Also, 66% of patients with discordant imaging studies successfully underwent a unilateral neck exploration when IOPTH was used, rather than a BNE.¹⁰ Since it is reported that the vast majority of

patients with concordant imaging studies have a single adenoma, identifying MGD in patients with discordant imaging is essential to prevent operative failure. This is important since MGD accounts for about 15% of PHPT cases. IOPTH is reported to accurately distinguish MGD in 78% of patients with discordant imaging studies and in 83% of all patients.¹⁰ Others report that IOPTH can accurately predict the success or failure of parathyroidectomy in 97.5% of patients with MGD.¹¹ The sensitivity and positive predictive value of IOPTH in these patients with MGD is 97% and 100%, respectively.¹¹ Even strong advocates of IOPTH testing do not recommend it for patients with familial PHPT and multiple endocrine neoplasia type 1 when multiple abnormal parathyroid glands are common.^{9,21}

LIMITATIONS OF IOPTH

In spite of reports advocating the routine use of IOPTH during parathyroid surgery, other studies question its utility, especially in patients with concordant imaging studies.^{5,8,19,22} Although, IOPTH has the theoretical benefit of guiding the extent of surgery, IOPTH seems to only confirm what localizing studies find in most patients. When the MIBI and US are concordant and identify the same single adenoma their combined accuracy is 95%.⁵ This is comparable to the traditional BNE approach. Using IOPTH with concordant imaging studies is reported to increase the success rate of surgery to 97%, but with the disadvantage that 9 to 13% of patients undergoing a MIP needlessly undergo further exploration, requiring considerable more time in the operating room.^{5,22} In another study, IOPTH was found to only identify MGD in 1% of patients with concordant studies. In the same study, the reported failure rate of surgery in patients with concordant MIBI and US was 2% without IOPTH and 1% with the use of IOPTH,

which was not statistically significant.⁸ These results raise the issue of whether incurring additional costs with the routine use of IOPTH in patients with concordant imaging studies is worth the nominal benefit.

An overall estimate of the cost of parathyroid surgery is difficult to accurately predict due to practice differences, regional reimbursement differences, differences in the use of localizing studies, differences in the accuracy of localizing studies, and differences in the use of IOPTH amongst medical centers. It has been suggested that the use of IOPTH results in an average saving of \$1000 per patient.²³ However, a recent cost analysis study estimated that IOPTH became cost saving only when the cost of reoperation for failed parathyroidectomy exceeded \$12,000 or three times the initial MIP.²⁴ The use of IOPTH results in an overall increase in operative cost of 4% when compared to MIP alone without IOPTH.²⁴ This study, however, did not factor in the costs of the preoperative localizing studies, nor did it compare the costs to the traditional BNE. One may deduce, that when factors such as preoperative imaging studies, IOPTH, and operative time are added to the cost of the procedure, there would be increased cost and little gain compared to 95% success rate of BNE. This, however, needs to be validated with a study that performs a cost analysis on the use surgical adjuncts and the operative time with MIP compared to the traditional BNE.

Another limitation is that MIP may underestimate the rate of MGD. PHPT may result from double adenomas, 4-gland hyperplasia, and rarely triple adenomas. Differentiating between these is vital in ensuring operative success. However, it has been shown that IOPTH is accurate in only 43% of cases of double adenoma.²⁵ IOPTH is also associated with a high false-positive rate (55 to 57%) in patients with double adenomas.^{25,26} Furthermore, it has been reported that when a BNE is routinely performed, unsuspected multigland disease is identified in 20 to 22% of patients who had preoperative localizing studies identifying a single adenoma.⁶ Adding IOPTH only reduced the rate of identifying unsuspected multigland disease to 16 to 17% and correctly predicted multigland disease in only 22% of patients.⁶ Others, however, report that adding IOPTH to preoperative imaging studies improves the detection rate of MGD to 89%.²⁷ Regardless, these data indicate that IOPTH fails to accurately predict MGD in about half of patients and may potentially lead to operative failures.

The limitation of IOPTH stems from factors that result in false-positive or false-negative results. For instance,

hemolysis of intraoperative blood samples has been reported to falsely lower the IOPTH level. A study evaluating the effects of hemolysis on 226 IOPTH samples from 47 patients found that hemolysis occurred in 7.5% of the samples, and that hemolysis resulted in a median IOPTH decrease of 39%.²⁸ The authors' suggested that hemolysis of the pre-excision samples could result in false-negative IOPTH results, and that hemolysis of postexcision specimens could result in false-positive IOPTH results.²⁸ Regardless of which specimen is affected (preincision, pre-excision, or post-excision), the consequences of hemolysis is to potentially result in failed parathyroidectomies.

False-positive

False-positive results occur when the IOPTH inappropriately falls (according to the criterion utilized) after removing a parathyroid gland or glands, despite the presence of one or more remaining hypercellular parathyroid gland. As stated above, hemolysis of postexcision blood specimens may artificially decrease the PTH level resulting in false-positive IOPTH levels.²⁸ These false-positive results inappropriately suggest a successful parathyroidectomy and may cause the surgeon to fail to recognize multigland disease. Multigland disease is the greatest risk for a failed operation. For instance, over half of patients with double adenomas are reported to have false-positive IOPTH results.^{25,26} A reason for this high false-positive rate may be due to size differences between the adenomas. A recent study demonstrated that false-positive results occurred in two-thirds of patients with double adenomas and that this occurred when the first adenoma removed was larger than the second (846 ± 226 mg vs 284 ± 177 mg, respectively; $p = 0.02$).²⁹ This finding corroborates a previous study that reported that the size of the first adenoma excised was statistically significant in predicting false-positive IOPTH results.²⁶ Gland size may also affect IOPTH results in patients with 4-gland primary hyperplasia or in patients with multiple endocrine neoplasia. It has been reported that excision of an asymmetrically enlarged parathyroid gland in patients with 4-gland hyperplasia may result in an inappropriately drop in the IOPTH, similar to the drop that occurs in a single adenoma.³⁰

False-negative

Another limitation of IOPTH monitoring is the risk of false-negative results. False-negative results can lead to needless conversion from a MIP to a BNE, increased operative time,

increased risk of operative complications, and increased costs. It has been reported that the false-negative rate is 9% at 10 minutes and 4% at 30 minutes from the highest preexcision or preincision value.²² One explanation for these false-negative results may be due to the varying half-life of parathyroid hormone.³¹ As well, the clearance of PTH may be affected by the glomerular filtration rate and therefore marginal renal function may contribute to false-negative results.³² Another potential cause for false-negative IOPTH results is the hemolysis of the blood samples, specifically the preincision or pre-excision samples.²⁸ It should be recognized that advocates for the routine use of IOPTH contend that false results may not be necessarily due to limitations of the assay, but may result from technical errors or deviation from the IOPTH criteria.⁹ It has also been recommended that obtaining additional blood sampling (at times greater than 10 minutes) may help clarify whether the result is a false- or true-negative and minimize the need for further exploration.³³ We recommend immediately sending a third postparathyroidectomy sample in patients when the PTH level does not fall more than 50%.

COMPLICATIONS

IOPTH has been widely accepted as a surgical adjunct because of its usefulness in guiding operative decision-making, but also because of its seemingly low risk of complications. The multitudes of studies on IOPTH sampling have not documented any complications resulting from IOPTH sampling. However, the inherent risks of penetrating a vessel include venous thrombosis, bleeding, and infection. The reason that complications may not be attributed to IOPTH sampling is that large cohorts of patients are needed to see these adverse events. Another explanation is that venous thrombosis from small peripheral veins and the internal jugular vein do not normally cause any deleterious effects and therefore this complication may go unnoticed. These complications, however, need to be considered by all surgeons performing IOPTH monitoring.

SITE OF PTH SAMPLING

The various IOPTH criteria utilize blood sampling to calculate the PTH drop from baseline after excising the abnormal parathyroid gland(s). Surgeon preference usually dictates the site of sampling: internal jugular vein (central) or peripheral vein. The use of peripheral sampling has a theoretical advantage of not being affected by its close

proximity to the surgical field. On the other hand, central venous sampling is more convenient because the vein is in the operative field and no other access needs to be obtained. It is, however, important to determine if the site of blood sampling affects the IOPTH results. The IOPTH level of centrally collected samples have been reported to be higher, with statistical significance, than peripheral samples.³⁴ These difference in PTH levels did not translate into a statistical difference in the percent drop. Utilizing the 10 minutes post-excision criteria, a > 50% drop from baseline was seen in 94% patients who underwent central venous sampling, compared to 97% with peripheral sampling ($p = 0.41$).³⁴ There was also no difference in percent drop between the two sample sites when the sample time was extended to 15 minutes, or when the IOPTH reached the normal range.³⁴ These findings have been corroborated by other studies that analyzed central and venous samples concomitantly drawn in the same group of patients; higher PTH levels were noted in the central venous specimens, and the accuracy of the test was not affected by sample site.^{35,36} We, however, recommend obtaining all of the blood samples from the same site.

IDENTIFICATION OF PARATHYROID GLANDS

Identifying parathyroid tissue during a parathyroidectomy can sometimes be challenging. The surgeon should be aware of parathyroid embryology and of the common and uncommon sites of parathyroid tumors. Parathyroid operations are also more difficult in patients with diffuse lymphadenopathy, large thyroid goiters, Hashimoto thyroiditis or brown cervical fat. In addition, distinguishing an intrathyroidal parathyroid gland from a thyroid nodule can be difficult and about 3% of parathyroid adenomas are intrathyroidal in position. Ultrasound can help identify a cystic-like mass in the thyroid. The nature of the mass can be determined by aspirating the suspected nodule to determine whether the parathyroid hormone level is elevated thus confirming the presence of parathyroid tissue. It has been shown that an IOPTH value of > 1,500 pg/mL from the aspirate has a sensitivity and specificity of 100% for parathyroid tissue.³⁷ Traditionally, frozen section analysis was used to confirm parathyroid tissue. However, the accuracy of differentiating parathyroid tissue from thyroid tissue can sometimes be difficult.³⁸ Frozen section analysis can mistakenly classify parathyroid tissue as a follicular nodule, complicating the distinction from thyroid nodules.³⁸

As such, IOPTH analysis from the aspirate of a suspected nodule should be used to confirm the identity of the tumor. The application of IOPTH in this manner can be used as an adjunct to confirm the identification of a parathyroid gland preoperatively at the time of ultrasound or during surgery. Such use is especially helpful in patients with PHPT and coexisting thyroid nodules and in patients with persistent and recurrent PHPT.

TERTIARY HYPERPARATHYROIDISM

IOPTH monitoring has been considered by many to be a valuable adjunct during parathyroidectomy for primary hyperparathyroidism. The efficacy of its use remains debated. A more intense debate ensues regarding the role of IOPTH during surgery for tertiary (THPT) hyperparathyroidism. It has long been regarded that THPT results from 4-gland asymmetrical hyperplasia. For this reason, the usual approach has been a BNE with a 3.5 gland subtotal parathyroidectomy or rarely a total parathyroidectomy and autotransplantation. Some argue that THPT can result from single or double parathyroid adenomas and therefore IOPTH can successfully be used in these cases.³⁹ The use of IOPTH has been shown to alter the operative management of 16% of these patients.³⁹ However, others recommend against the use of IOPTH. Despite data showing that IOPTH has a sensitivity of 94% in patients with THPT, some argue against its use because of a 5.2 times high-risk of operative failure.⁴⁰ The argument against the routine use of IOPTH is that, unlike PHPT where the majority of cases are caused by a single adenoma, the vast majority of THPT have had secondary hyperplasia and developed residual 4-gland hyperplasia, although there is usually a marked difference in tumor size.

CONCLUSION

There is no arguing that improved preoperative localizing tests and IOPTH have created changes in our surgical treatment of patients with PHPT. Although the use of IOPTH is not required or essential, it has been shown by many to be a useful adjunct and provides an outcome that is similar to BNE. It is especially helpful when conducting a minimally invasive parathyroidectomy. It can also be useful in guiding the extent of resection during a bilateral exploration. The usefulness of IOPTH extends beyond determining adequacy of resection. IOPTH can also help distinguish parathyroid tissue from thyroid or cervical nodules. This application further exemplifies how IOPTH

has played an integral role in advancing parathyroid surgery.

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