

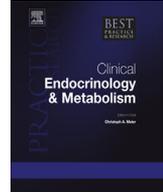


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The role of intraoperative parathyroid hormone (IOPTH) determination for identification and surgical strategy of sporadic multiglandular disease in primary hyperparathyroidism (pHPT)



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ARTICLE INFO

Article history:

Available online 8 August 2019

Keywords:

primary hyperparathyroidism
intraoperative PTH monitoring
multiple gland disease

Intraoperative PTH monitoring (IOPTH) made minimally invasive parathyroidectomy in patients with primary HPT possible. However, with the increasing accuracy of preoperative localization studies there is a growing discussion if IOPTH is necessary in patients with localized single gland disease (concordant preoperative localization studies). Different interpretation criteria have been developed – each with their particular advantages and disadvantages, but the “perfect” criterion is still missing.

Despite several pitfalls, which can be recognized intraoperatively and do not necessarily lead to a more extensive surgery, IOPTH seems to be a useful adjunct in surgery for PHPT. However, according to current guidelines, selected patients may be operated without IOPTH but need to be informed about the possibly increased risk of recurrent disease.

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Introduction

Before the introduction of intraoperative PTH (IOPTH) monitoring, bilateral neck exploration with visualization of at least four parathyroid glands was the standard surgical procedure. It was therefore

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possible to directly detect all macroscopically enlarged parathyroid glands and thus to remove them. In 1991, Irvine et al. described the technique of IOPTH determination using a PTH assay with a reduced turnover time [1]. The IOPTH- values were available to the surgeon intraoperatively and, due to the short half-life of PTH, the curve of the PTH decay was analyzed almost in “real-time”. This made the intraoperative prediction of cure possible or, otherwise, the recognition of multiple gland disease which was the prerequisite for minimally invasive techniques. In the last 20 years, the IOPTH- assays have been enhanced, new interpretation models developed and endoscopic techniques (like video assisted, transoral endoscopic and/or robotic surgery) established. However, the technique and the underlying concept has not been changed much but the accuracy of preoperative localization studies using modern techniques like PET-CT have been improved enormously. Consequently, there is an emerging discussion about the value of IOPTH monitoring. This article aims to clarify if, according to the latest literature, IOPTH- monitoring is still of value for patients with PHPT to detect multiple gland disease intraoperatively.

Technical aspects of IOPTH- determination

Blood samples are regularly drawn after induction of anesthesia, right after excision of the enlarged gland, 5 min and 10 min later. Different assays are reported to be comparable and have a turnover time of 15–45 min [2]. A promising new assay based on a handheld system with results within 10 min has, unfortunately, never been commercially available [3]. Besides the assay turnover time, the lab is not next to the OR in most institutions and additional transportation time has to be taken into account. Portable analyzing systems, however, can be brought into the OR and are therefore able to reduce total turnover time. Nevertheless, costs for acquisition and consumable supplies are high with these systems.

Criteria for interpretation

The intraoperative parathyroid hormone (IOPTH) determination is highly valuable in surgery of primary hyperparathyroidism (PHPT) as it rules out the presence of a multiple-gland disease. The macroscopic presentation of all parathyroid glands is generally waived in minimally invasive surgical procedures and unilateral explorations for which IOPTH is particularly important. Although, IOPTH enables to reflect the current biochemical picture intraoperatively, it is unable to make long-term statements on the functional state of the remaining parathyroid glands, meaning it cannot predict PHPT recurrence [4].

In practice, various commercial and in some institutions also customized assays are in usage for IOPTH monitoring. The validity of IOPTH in PHPT is measured by the degree of correspondence between intraoperative and postoperative biochemical status. Various performance criteria are described in the literature, which not only differ regarding the time of PTH assessment before and after excision of the suspected adenoma, but also regarding the percentage of decrease in PTH after parathyroid gland removal [5–9]. To provide an actual number, it is necessary to have a defined referral value [10]. This PTH “basal value” or PTH- baseline is defined differentially in the current literature, e.g. as “the pre-operative value on the day before the operation”, “after induction of anesthesia and before the incision” [11], “at the start of operation”, “after exposure of the adenoma, but before excision”, “at the time of the parathyroid gland excision” or “the highest of these PTH values”. Importantly, any surgical manipulation of the parathyroid gland may potentially induce an artificially transient PTH surge and therefore influence the subsequent IOPTH determination (see chapter “pitfalls”) [12]. Hence, baseline PTH values from the preceding day may well diverge significantly from the values on the day of surgery. PTH assessment directly before surgery (“pre-incision” instead of “pre-excision”) is recommended as a basal value to avoid manipulation-induced PTH increases [5,11,13–15].

Blood samples for IOPTH assessment are collected from central or peripheral venous blood vessels, depending on the assay. Most authors prefer peripheral venous blood sampling for IOPTH monitoring [7,15–18].

Some authors propose more stringent or, respectively, less restrictive cut-off values of IOPTH in individual cases, provided additional information of preoperative imaging is available [14,19–21]. If sonography and MIBI-SPECT scintigraphy show a concordant localization, there is a high probability for

the presence of a single-gland disease. In contrast, if sonography and MIBI scintigraphy results are negative or discordant, the risk for multiple gland disease is increased and therefore more strict IOPTH cut-off values should be applied. More stringent performance criteria are for example “Vienna” or “Halle” compared to “Miami” or “Rotterdam” criteria (Table 1). In order to reduce surgical time efforts have been made to develop “shorter” criteria [22,23]. It has been shown, that a decay of $\geq 50\%$ 5 min after excision of the gland (referred to baseline) allows discontinuing surgery (which seems to be possible in 71% of the patients) [24].

Guidelines

The ideal situation in surgery is, when the surgeon is able to remove an image-identified abnormal gland without an additional dissection. In image-guided surgery, positive preoperative localization study directs where to start exploration and the results of IOPTH monitoring, which relies on real-time assessment of gland function, help to determine the success. However, such focused operations preceded by solely imaging studies without IOPTH determination might miss multiglandular disease in up to 15% of the cases [27]. Targeted operations for PHPT guided by current IOPTH monitoring protocols have shown excellent results with high cure rates up to 97–99% [28–32]. The American Association of Endocrine Surgeons (AAES) committee strongly suggests the usage of IOPTH monitoring in image-guided focused parathyroidectomy to avoid higher operative failure rates. Furthermore, when IOPTH monitoring is not available, bilateral exploration remains the preferred surgical approach [27].

The short half-life (3–5 min) of parathyroid hormone (PTH) and the availability of a rapid immunochemiluminescence assay technique (completion time of 8–20 min) are two most essential components for IOPTH monitoring. However, IOPTH determination is very dependent upon the protocol used for blood sample collection. During the operation, blood is obtained from an arterial line, a central or a peripheral vein. Several IOPTH monitoring protocols are currently available [33].

An adequate IOPTH level drop is helpful in predicting cure and appropriate follow-up examinations remain necessary to conclude that these predictions were in fact accurate. New techniques and software have been developed to allow surgeons to perform PTH cure analysis. However, most surgeons interpret IOPTH results without mathematical models and still report excellent results.

The usage of IOPTH monitoring does add additional costs to an operation and it is not universally available [34]. However, a failed parathyroidectomy is more expensive and riskier due to the requirement of a second operation [35,36].

Similar to the AAES guidelines, the European Society of Endocrine Surgeons (ESES) guidelines recommend IOPTH monitoring for patients undergoing targeted parathyroidectomy including preoperative localization study, when preoperative localization with Sesta-MIBI and sonography is not concordant or in reoperative parathyroidectomy [7]. However, when results of preoperative imaging are concordant for single-gland disease, IOPTH monitoring is of little advantage [37,38]. The accuracy of IOPTH monitoring in detecting multiglandular disease (MGD) is highly dependent on the applied performance criteria. A

Table 1
Performance criteria of IOPTH determination.

Performance criteria	Definition
Miami [5]	IOPTH decrease of $\geq 50\%$ of the highest pre-excision value 10min after PTX
Halle [7,11]	IOPTH decrease of 50% of the highest standard value (≤ 35 pg/ml) 15min after PTX
Vienna [11]	IOPTH decrease of $\geq 50\%$ of baseline value 10min after PTX
Vienna 5 min [24]	IOPTH decrease of $\geq 50\%$ of baseline value 5min after PTX
Ann Arbor [25]	IOPTH decrease of $\geq 50\%$ of baseline value and achievement of standard range (12–75 pg/ml) 5 or 10min after PTX
Rome [19]	IOPTH value ≤ 35 pg/ml or IOPTH decrease of $\geq 90\%$ of baseline value
Aarhus [26]	IOPTH value $\leq 20\%$ of baseline value or achievement of standard range 5min after PTX
Rotterdam [6]	IOPTH value between 100 and 200 ng/l and IOPTH decrease of $\geq 70\%$ 10min after PTX or IOPTH decrease of ≥ 200 ng/l and $\geq 80\%$ 10min after PTX

IOPTH, intraoperative parathyroid hormone; PTX, parathyroidectomy.

retrospective analysis has shown that the Miami protocol followed by the Vienna protocol are the most balanced criteria, with the highest accuracy in intraoperative prediction of cure [39]. On the other hand, the Rome and the Halle criteria are most effective in detecting MGD (Table 1) [11,19,39,40]. A decrease of >50% of IOPTH is as a highly accurate predictor of cure in patients with MGD [41].

Pitfalls

Renal insufficiency

PTH is degenerated in the liver to fragment of different sizes c- and n-terminal which are subsequently excreted renally. In patients with renal insufficiency, particular c-terminal fragments cannot be excreted, accumulate and cross-react with the commercially available IOPTH- assays. Thus, the PTH-decay is prolonged and the results have to be interpreted with caution [42]. Nevertheless, IOPTH seems to be a useful adjunct even in patients with chronic kidney disease and renal impairment [43,44].

Intraoperative PTH- spikes

In up to one third of the operations, a PTH- rise (increase of PTH at excision of the enlarged gland referred to baseline value) can be observed [12]. These “spikes” are most likely caused by intraoperative manipulation of the enlarged gland during its preparation and lead to an elongated PTH- decay [45]. Furthermore, they are a common cause of false negative assay results. Risk factors for PTH- spikes have not been identified yet [46]. It has been shown, that in the case of intraoperative PTH spikes an individual interpretation of the PTH curve instead of strictly following the criterion lowers the rate of false negative assay results [47]. However, the “perfect criterion” for patients with spikes has not been defined yet. Furthermore, spikes may be associated with multiglandular disease [48].

Low or high baseline values

In patients with high normal or only slightly elevated PTH values, finding the correct diagnosis is as challenging as interpreting the intraoperative PTH course. In patients with “mild” or normocalcemic hyperparathyroidism a calcium sensing receptor disorder (familial hypercalciuric hypercalcemia) has to be ruled out [49] which can be difficult, especially in patients on thiazide diuretics [50]. Due to a more flat curve and a higher incidence of multiglandular disease it can be difficult to either reach the 50% threshold and to recognize the decay as exponential in patients with normal baseline values [51]. High baseline values may also pose a problem because, after a sufficient and fast initial drop [52], PTH values need more time to reach the normal range. Although the curve follows an exponential decay, PTH can reach a plateau with still elevated values.

Cystic adenoma

The rupture of a parathyroid cyst during preparation leads to a massive PTH- increase due to the sudden hormone release and following prolonged resorption. Consequently, the decay can be insufficient (often after an initial drop) [53].

Conclusions

Preoperative ^{99m}Tc-Sestamibi-scintigraphy and ultrasound are the widely used standard localization studies and correctly identify the enlarged gland concordantly in 66% [54]. Multiple gland disease, however, can often not be correctly identified. Methionine- or ¹⁸F-Cholin-PET/CT are promising new modalities but cannot be performed in all patients by standard. Nevertheless, due to modern ultrasound-technique and SPECT-CT, the widely used localization studies are of increasing accuracy.

Consequently, there is an increasing discussion if IOPTH is necessary in patients with positive localization of a single adenoma [54–58]. Current guidelines tend to allow abandoning IOPTH in

patients with suspected single gland disease and concordant localization studies but a clear information to the patient seems to be necessary, pointing out the possible increased risk for a reoperation.

However, there seems to be a special situation for endemic goiter regions. It has been shown that without IOPTH, even in patients with concordant localization of a single adenoma in ultrasound and Sestamibi scintigraphy, the number of missed patients with MGD would increase significantly [54].

Since the introduction of IOPTH twenty years ago the basis of the technique has not changed. Several criteria have been established which may be described as “fine tuning” but cure rates are high with up to 99% and it might not be possible to further enhance them. However, with a better understanding of IOPTH- pitfalls and advanced technical options, especially turnover time and applicability may be improved. A shorter assay turnover time and, therefore, available results earlier after blood drawing seems to be the next necessary step in enhancing IOPTH followed by automatic (software based) analysis of the IOPTH curve considering all possible pitfalls (like PTH- spikes, renal insufficiency, high/low baseline values etc.).

Practice points

- IOPTH has been developed to intraoperatively confirm complete excision of hypersecreting tissue and made minimally invasive (targeted) explorations possible.
- Localization studies like Sestamibi-scintigraphy, ultrasound, 4D-CT or PET-CT are performed to detect the enlarged gland(s) preoperatively.
- Preoperative localization studies have a low sensitivity for detecting multiple gland disease.
- In case of concordant localization of a single adenoma, minimally invasive surgery may be performed without IOPTH.
- In endemic goiter regions, the rate of patients with persisting disease is significantly increased without IOPTH in patients with concordant localization.
- The surgeon should use a defined criterion for interpretation of the PTH- values
- Nevertheless, sometimes the individual intraoperative interpretation of the PTH- decay is crucial to decrease false (negative) results.

Research agenda

- Shorter assay turnover time (handheld device?)
- Automated (software based) analysis of the IOPTH curve considering all possible pitfalls
- “Real-time” measurement of PTH (via intravasal sensors)

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