



## Original research

# Intraoperative measurement of parathyroid hormone: A Copernican revolution in the surgical treatment of hyperparathyroidism



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## ABSTRACT

Intraoperative parathyroid hormone (PTH) monitoring in the setting of the operating room represents a valuable example of the rationale use of the laboratory diagnostic in a patient-oriented approach. Rapid intraoperative PTH (ioPTH) assay is a valid tool for an accurate evaluation of the success of parathyroid surgery. The reliability of the user-friendly portable systems as well as the collaboration between operators and surgical staff allow the one-site monitoring of the ioPTH decrements on the course of the surgical management of hyperparathyroidism.

The rapid answer provided by an effective decrement of PTH during parathyroidectomy contributes dramatically to the efficacy of parathyroid surgery and the reduction of the number of re-operations. Therefore the dose of ioPTH is a valid and reliable support for the success of the intervention of parathyroidectomy at controlled costs.

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## 1. Introduction

Hyperparathyroidism is a disease characterized by the excessive secretion of PTH, accompanied in the most of patients with hypercalcemia, and hypophosphatemia (present only in one third of cases). The diagnosis of hyperparathyroidism became more frequent with the introduction of the routine assay of serum calcium; this allowed the identification of a greater percentage of patients with mild or even asymptomatic hyperparathyroidism. This fact caused a radical change in the clinical scenario, leading to near the total disappearance clinical findings frequently observed in the past such as fibrosclerotic osteitis, nephrocalcinosis, and nephrolithiasis.

Primitive hyperparathyroidism is caused by a parathyroid adenoma in the 80% of cases, followed by 15% of hyperplasia, sometimes related to inherited syndromes such as MEN-1 and MEN-2, a 4.5% arising from multiple adenomas, and the 1% by carcinomas.

Secondary hyperparathyroidism originates instead as a compensatory response to the chronic hypocalcemic stimulus. These mechanisms are the basis of a special parathyroid hypertrophy-hyperplasia characterized by resistance to medical therapy and need surgery in 25% of cases.

The introduction of intraoperative parathyroid hormone (ioPTH) assay has profoundly changed the surgical approach in both primitive and secondary hyperparathyroidism.

This method was introduced for the first time in 1988 [1] and then modified during the years up to the most recent application of third-generation immuno-chemiluminescent (ICMA) system with an incubation time of about 5 min and a rapid dosage of PTH within 10 min after removal of the hyperfunctioning parathyroid tissue [2].

### 1.1. Intraoperative assessment of PTH

The intact PTH is a polypeptide produced by parathyroid and composed of 84 amino acids.

Only parathyroids produce PTH; its half-life is of about 5 min in plasma. Once a surgical resection of hyperfunctioning tissue is performed, PTH levels are usually lower in the first days due to the suppressed production in the residual normal glands. The PTH kinetics of decrement after parathyroidectomy is characterized by a

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biphasic pattern with a very rapid initial decrement (2–4 min) and a subsequent curve with a lower elimination speed (21–82 min).

The test is easy to perform and simply to read the results.

At least four different systems, manufactured and marketed by four separate companies, have been proposed and used for the determination of ioPTH: QuiCK-Pak Nichols, STAT-IO-I-PTH Future, Immulite Turbo PTH DPC, Elecsys 1010 Roche [3]. All apply the principle of detection of chemiluminescence signal; the first two are easily transportable in the operating room whereas the other two are multiparametric analyzers difficult to transport. The time of response ranges from 7 to 12 min (QuiCK-Pak and STAT-IO-I-PTH) to 15–20 min (Immulite Turbo and Elecsys).

The module used for QuiCK-Pak dosing on portable cart contains a small bench-top micro-centrifuge, an incubator-shaker thermostat, a single reading cell luminometer and an automatic washing system. The instrument can be utilized directly inside the operating room or close to it. The total time of the analysis, from blood sampling to the communication of results to the surgeon, is about 12 min (3 min for the dispensation of the sample, the ball containing the first antibody and antibody conjugate with the substrate for chemiluminescence, 1 min for sample spinning, a 7-min incubation, 1 min for the washing of the samples and 30 s for reading the result) [4].

STAT-IO-I-PTH kit consists on an instrument on a trolley in the actual or immediate proximity of the operating room. The assay utilizes two affinity-purified goat polyclonal antibodies against PTH. One anti-PTH antibody (39–84) is coated onto the surface of a microtiter well; the N-terminal anti-PTH antibody (1–34) is labeled with isoluminol and lyophilized in the form of an accsphere and seeded in the wells. During the 5 min incubation time in the STAT-Shake, intact PTH in the sample is bound and antibody-antigen-antibody complex is formed. The STAT-Read automatically injects the activators initiating the chemiluminescence reaction. The light emission is proportional to the concentration of intact PTH in the sample. The time needed to perform the assay is 7 min.

The majority of commercial kits dose the PTH fragment 7–84 that has a half-life of a few hours, unlike PTH 1–84 which has a half-life of 2–5 min, producing false negatives. For this reasons our preferred method is the STAT-IO-I-PTH produced by Future Diagnostics [5].

Blood samples are taken from a dedicated peripheral vein cannula (e.g. vein of the foot) at four different times: at the induction of anesthesia but before the incision of the neck (baseline sample or zero time), during the manipulation of suspicious hypersecreting glands, 10 and 15 min after the last gland excision [6].

The criterion for evaluation of results in primary hyperparathyroidism is based on a cut off of 50% of the decrease of PTH in plasma levels, while the evaluation of the results in secondary hyperparathyroidism is based on a cut off of 70% of the decrease of PTH levels in plasma after 10 min from the resection of the last gland or of 85% after 15 min. In both cases there is a sensitivity of 85% and a specificity of 100% when it is applied after 10 min from surgical resection; sensitivity increases to 97% when sample is taken after 15 min [7].

For an optimal success of the technique, different organizational aspects must be considered. Staff must be properly trained for knowing the function of each part of the system and the possible drawbacks. It is preferable to have a sufficient notice of at least one week, whereas parathyroidectomy is almost never an emergency measure.

The dose of ioPTH during surgery is a good example of the use of laboratory services oriented towards the patient and is therefore important a relationship between the laboratory and surgical staff.

## 1.2. The role of ioPTH assay in the surgical timing of hyperparathyroidism

Preoperative localization of pathological parathyroid glands was a topic of debate for a long time. Indeed, while for some authors it was necessary, for others it was quite superfluous, and accurate bilateral neck exploration was the surgical strategy applied.

Until a few years ago the instrumental investigation tools available had an insufficient diagnostic accuracy, or were characterized by considerable invasiveness with a low cost-benefit ratio. The disappointing results, especially when compared with those obtained from surgery performed without preoperative localization, showed that these investigations were not helpful.

Technological advances in recent years, however, led to a significant improvement in the diagnostic methods, even if they are burdened by an increase in costs.

Currently sestaMIBI scintigraphy is the imaging method of choice to localize parathyroids before surgery; the ultrasound scan is useful in providing more information in the case of cervical localization, while the CT scan and MRI are more useful in ectopic localizations [8]. The diagnostic accuracy increases when the ultrasound is associated with scintigraphy, with a sensitivity of over 95%; such association, in fact, in case of dubious areas and hyperfixation scintigraphy, allows to differentiate between thyroid and parathyroid tissue origin. It is not possible to differentiate between adenoma and hyperplasia with US scan. However, a parathyroid gland increased in volume in more than one typical localization allows suspecting the presence of a multiglandular involvement [9].

Although anesthetic progress and the opportunity to practice parathyroidectomy in regional anesthesia, intra and post-operative morbidity has to be taken into account in the programming of assistance.

Significant changes in surgical strategy were made possible, in recent years, thanks to the progress of diagnostic laboratory that has allowed determining the level of PTH in the operating room during surgery rapidly.

In hyperparathyroidism, surgical removal of hypersecreting glands involves a rapid decrease in plasma levels of PTH and its speed and precocity can immediately show a biological healing. In this way the intraoperative dosage of PTH can confirm the success of surgery or change the surgical strategy in time.

For many years the main limitation of ioPTH assay was due to the times needed to perform radioimmunoassay and immunoradiometric methods, sometimes exceeding the 24 h.

The development of portable analyzers and the immunochemiluminescence technique allowed to perform the PTH assay directly in the setting of the operating room.

The main advantage of the ioPTH assay is represented by the ability to predict an efficient surgical removal of hyperfunctioning glands, excluding the possible persistence of residual affected tissues. This provides to the surgeon information not only on what has been excised, but above all on what instead has not been possibly even removed, suggesting real-time changes in surgical tactics. This element is of fundamental importance, especially because the most of the failures in hyperparathyroidism surgery are due to incomplete removal, resulting in inadequate or insufficient persistent or recurrent hyperparathyroidism.

The failures are in fact related to the impossibility to find an adenoma or removal of non-parathyroid tissue (lymph nodes, thyroid nodules), whose can simulate the appearance of a parathyroid pathology [10]. The second cause of failure is the presence of multiglandular hyperparathyroidism, as in the case of a double adenoma or hyperplasia that interests the four glands or eventual ectopic glands. For this reason the surgical technique of choice for

years, in the absence of other facility capable of assessing the completeness of parathyroidectomy, was represented by complete bilateral cervical exploration. The latter implicates the identification of at least four parathyroid, to rule out or confirm the presence of a multiglandular disease, and removal of the glands of pathological appearance (with the possible extemporaneous histological examination [11]).

The rapid ioPTH assay, represents a kind of “extemporaneous histological biochemical examination”: a significant reduction of PTH levels, in fact, is able to predict healing in almost 100% of the cases, demonstrating the complete exeresis. On the contrary, the finding of elevated PTH values at the end of the intervention is a sign of persistent disease and suggests to continue the surgical exploration until the identification and removal of all the pathological tissue.

Therefore this method of investigation not only “certifies” the nature of the parathyroid tissue removed, but also documents the absence of residual hyperfunctioning tissue, thus making the exploration of not easily identified parathyroids not always necessary. The protocol adopted for the ioPTH assay provides four measurement: one baseline at the induction of anesthesia; a second at the identification of pathological glands; a third at 10 min and a quarter at 15 min after the removal of the glands. A decreased value of PTH post-ablation greater than 50% (the so-called “cut-off”) compared to the value pre-ablation (the baseline value) is able to predict the biological healing with a sensitivity of 98% and a specificity of 94% and an accuracy of 97%. Failure to decrease PTH indicates the persistence of hyperfunctioning parathyroid tissue [4].

Recently, the international literature reported results and opinions often widely divergent regarding the accuracy and usefulness of this method. There are, in fact, still not finally resolved issues regarding the use of ioPTH assay: they are of economic nature (costs and cost-effectiveness), biological (different PTH kinetics decay in single adenoma and multiglandular hyperplasia) and technique. The problems of technical nature are due to the sensitivity and the specificity of the type of method used and the protocol used: there is not an unanimous agreement on the number and timing of withdrawals, the definition of withdrawal baseline and cut-off [12]. As regards the timing of blood samplings pre and post-excision, the original method implicate that drawings prior to ablation are made before incision and before removal of the parathyroid pathological gland and subsequent after 5 and 10 min from excision. Other authors suggested different protocols, considering the withdrawal baseline the one made the day before, or at the time of induction of anesthesia or incision or after mobilization of the thyroid, but before parathyroid isolation; there were also proposed blood samplings post-excision performed in very variable times (from 5 to 90 min). However, it is necessary to define what is the baseline, in order to calculate the percentage of decrease post-excision. In this perspective, it has been proposed to consider as basal sample the highest value that precedes the ablation (which very often corresponds to the pre-excision, which increase is determined precisely by the manipulation of the parathyroid gland). Other authors argue that consider this value as baseline withdrawal may cause errors of interpretation. It was therefore proposed to consider only the value at the time of the incision or the one that precedes the manipulation of the gland. However it must be considered that dosages practiced at the time of the incision can present values higher than 60% compared to those measured at the induction of anesthesia, making the interpretation of results more difficult.

Directly related to the issue of the withdrawal is the one regarding the baseline so-called cut-off, the expected decrease of PTH after excision, to consider the patient cured. The cut-off of 50% is a purely empirical limit, which has the advantage of being easy to

calculate. In most cases of hyperparathyroidism caused by a single parathyroid adenoma and with a very high level preoperative PTH, the removal of the adenoma results in a rapid drop, significantly higher than the 50%. Instead, when there is a multiglandular involvement, or when the initial PTH values are lower, the decrease is slower and more gradual, and therefore a cut-off of 50% appears to be inadequate, because in many of them, despite a decrease of more than 50%, it was observed persistence of hyperparathyroidism, due to a multiglandular disease not adequately recognized and treated. For these reasons there were proposed higher values of cut-off, for example the 70%; these high values, however, can lead to increase the number of false negatives and thus unnecessarily prolonged cervical explorations. At present, it is not possible to identify a cut-off in the dosage of ioPTH able to predict in 100% of cases, the presence of a multiglandular disease and this is the major limitation of this method [13].

In secondary hyperparathyroidism a further problem is the abnormal metabolism of PTH (slowed catabolism, prolonged half-life) in the case of kidney failure and the need to identify a new cut-off able to predict the radicalism of the excision and then healing with an acceptable accuracy, as that of 50%, already identified for primitive hyperparathyroidism is totally inadequate. A cut-off of 70% at 10 min may be sufficient to predict the healing (defined as the absence of persistent hyperparathyroidism) with a sensitivity 85% and specificity of 100%. In some cases, however, may be needed more blood samplings at different longer times and a cut-off even above 75% [14].

Tertiary hyperparathyroidism shows the same problems as multiglandular primary forms, and then a cut-off of 50% at 10 min would be sufficient to predict the healing with a sensitivity 84% and specificity of 100%, even if sometimes further withdrawals are needed with a cut-off of 70% [15]. The rapid ioPTH assay can be also very helpful in relapses [16].

## 2. Conclusions

Despite the evolution and the different drugs available, parathyroidectomy is an essential therapeutic element in the treatment of hyperparathyroidism, particularly in patients with secondary hyperparathyroidism in hemodialysis with elevated PTH levels (>400 pg/ml) and signs of myelofibrosis associated with at least one of the following factors resistant to medical therapy (calcimimetics): hypercalcemia, hyperphosphatemia, ectopic progressive calcifications, severe clinical symptoms and calciphylaxis without excluding patients undergoing kidney transplantation [17–20]. In agreement with the international literature, the use of ioPTH assay can be considered the “gold standard” in the context of the timing of surgical hyperparathyroidism. The easily use of the portable system and reliability of analytical results, combined with a sequential approach guided by the surgeon make the intraoperative monitoring of parathyroid hormone directly into the operating room an important tool for the surgeon and induces improvements in the hospital course and in the treatment of the patient. As for the programming of the commitment of the staff, it is needed enough time to notice, taking into account that the interventions of parathyroidectomy are not considered emergency operations. Therefore it is advisable to perform multiple operations on the same day, as the cost of the assay would be amortized by producing the calibration curves only once a day.

Furthermore, the possibility to use this method in the interventions of parathyroidectomy, contributes to a considerable saving linked above all to the reduction of the number of reoperations. Therefore the dose of ioPTH is a valid and reliable support for the success of the intervention of parathyroidectomy at controlled costs.

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## Ethical approval

Not required.

## Author contribution

Maria Concetta Gioviale: Participated substantially in conception of the study and in the analysis and interpretation of data; also Participated substantially in the drafting and editing of the manuscript.

Giuseppe Damiano: Participated substantially in conception of the study and editing of manuscript.

Roberta Altomare: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

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