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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.

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 fibrosocistic 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 accusphere 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