The role of intraoperative quick PTH measurements in primary hyperparathyroidism

Ann. Ital. Chir., LXXIV, 4, 2003

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Riassunto

RUOLO DEL DOSAGGIO INTRAOPERATORIO DEL qPTH NELL'IPERPARATIROIDISMO PRIMARIO

Nei pazienti con iperparatiroidismo primario i livelli di ormone paratiroideo intatto (PTH) si riducono drasticamente entro pochi minuti dopo l'asportazione del tessuto paratiroideo iperfunzionante. L'entità di tale riduzione è correlata con la completezza dell'asportazione del tessuto paratiroideo patologico e può essere monitorata intraoperatoriamente con il dosaggio del qPHT. Con il presente studio sono stati utilizzati i dati ottenuti con il monitoraggio del PTH rapido intraoperatorio in più di 350 pazienti operati per iperparatiroidismo primario, prestando la massima attenzione all'interpretazione dell'entità della riduzione del qPTH intraopertorio in rapporto ai valori basali ottenuti prima dell'escissione della ghiandola patologica.
Il monitoraggio del qPTH è in grado di differenziare una malattia a coinvolgimento unighiandolare da una malattia multighiandolare. Il monitoraggio del qPTH in caso di chirurgia mininvasiva è indispensabile al fine di ottenere gli stessi risultati dell'esplorazione bilaterale del collo, ma soltanto la corretta interpretazione dei valori qPTH è in grado di determinare dei risultati eccellenti.
Tuttavia è necessario collezionare ancora più dati sulla dinamica dei dosaggi del qPTH per rendere l'interpretazione più attendibile nei pazienti con iperparatiroidismo primario
Parole chiave: Iperparatiroidismo primario, dosaggio intraoperatorio del PTH rapido.

Introduction

Preoperative localization studies (1) and intraoperative measurements of parathyroid hormone (PTH) seem important prerequisites for minimally invasive parathyroid surgery. Intraoperative PTH measurements may be helpful in patients without definitive preoperative localization of the hyperactive parathyroid tissue to reduce the extent of primary and re-explorations and their complications (permanent hypoparathyroidism; paralysis of the recurrent laryngeal nerve) (2).

The role of this new technology, its advantages, disadvantages and pitfalls are reviewed.

PTH – assays

The early generation of PTH-radioimmunoassays was restricted to N-, midregion, or C- terminal fragments which circulate in rather high concentrations due to their low clearance rates (3, 4). An exciting advance in the diagnosis and treatment of parathyroid disease was the development of immunoradiometric assays (IRMA) (5-7) employing two monoclonal antibodies specific for the N- and C- terminal regions of the hormone consisting of 84 amino-acids (8).
By these assays measurement of intact [1-84] PTH is feasible within several hours. Sensitivity of tests was further improved by substitution of the radio-label by

Abstract

Background: *In patients with primary hyperparathyroidism (PHPT), circulating concentrations of intact parathyroid hormone (PTH) decline dramatically within minutes following surgical excision of hyperfunctioning parathyroid tissue. The magnitude of this decay correlates with the completeness of resection of hyperfunctioning parathyroid tissue and can be monitored during the operation.*
Method: Intraoperative Quick PTH (QPTH) monitoring and pitfalls of more than 350 patients, who were operated because of primary hyperparathyroidism are analyzed. Special attention is given to correct baseline values and interpretation of QPTH values.
Results: *QPTH monitoring is able to distinguish reliably*

between single and multiple gland disease and is an indi - spensable prerequisite for any form of limited parathyroid exploration. Experience with QPTH monitoring is neces - sary to achieve the excellent results known from bilateral neck exploration.
Conclusion: *Applying correct baseline values and cautious interpretation of QPTH values results in excellent results. Nevertheless more data must be collected to allow reliable interpretation of QPTH monitoring in all patients with PHPT.*
Key words: Primary hyperparathyroidism, intraoperative quick parathyroid hormone assay, standard interpretation.

chemiluminescent groups (ICMA) (9, 10). Special assay formats allow a rapid detection within a quarter of an hour, a time-span suitable for intra-operative PTH monitoring (9). The rapidly available results are based on the short 3 to 4 minute half life of the intact molecule of PTH.
Although the clinical usefulness of IRMA was demonstrated in several series (5-7), the disadvantage of IRMA consists of the radioisotopes limiting its use in the operating room. Compared with IRMA the ICMA (quick PTH assay [QPTH assay]) is highly accurate and safe for operating room personnel; it may be applied during the operation "online", delivering the intraoperative results within 15 to 20 minutes of beginning the test. The results reported about this QPTH assay as a «biochemical frozen section» (11) render routine examination or biopsy of the remaining glands unnecessary, thus shortening the duration of surgery (11).

Which intraoperative QPTH Assay?

In a recently published paper (12) two automated QPTH assays were compared with an established manual method. PTH was analyzed manually with a test from Nichols and by two automated assays from Diagnostic Product Corp (DPC) and Roche, respectively. PTH-half-life and residual concentrations were calculated by two kinetic models. Despite of good overall correlation between PTH results, marked inter-individual deviations were observed.
The interactive kinetic model failed with a non-uniform PTH decrease, but the interpolative model produced valid results. Average half-life of 3.7±1.4 minutes with DPC differed significantly from 4.3±1.6 minutes with Roche (Nichols: 4.0±1.6 minutes).
DPC produced significant lower average residual PTH (15 pg/ml) versus Roche (27 pg/ml), Nichols results were between them (20 pg/ml). However, these differences were clinically irrelevant. Automated methods are likewise suitable as the manual test, but facilitate procedure and lower the costs.

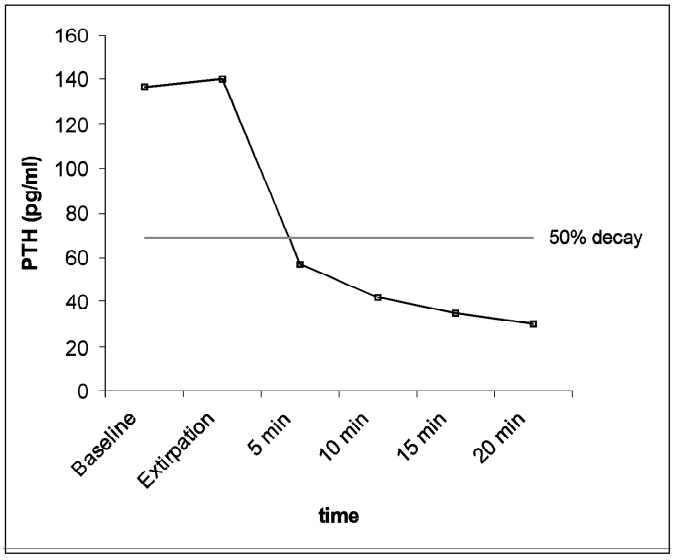

Figure 1: Typical decay of QPTH in a patient with Single Gland Disease 10 min after extirpation of the parathyroid adenoma [QPTH] has to be <50%.

Baseline value and standard interpretation of PTH decline

A ≥ 50% decline of QPTH (compared to a "baseline value", drawn at the very beginning of the operation) 10 minutes after parathyroidectomy documents the surgical success (Figure 1).

«Single gland disease» suspected by preoperative localization studies allows the surgeon to direct the dissection to the anatomical location of the suspected parathyroid adenoma. The adenoma can be removed without wide field exploration.
The fall of PTH signals whether all hyperfunctioning parathyroid tissue is excised or if further dissection is necessary. A predicted accuracy of 97% of QPTH is reported, influencing the surgical approach with changing the tactics in 13% of patients (13). In case of a QPTH decay less than 50% a bilateral neck exploration has to be performed to visualize all parathyroid glands and to remove enlarged ones.

a) The decrease of less than 50% of PTH compared to the "baseline value" shows persisting hyperfunctioning parathyroid tissue. After excision of a second, contralateral adenoma the cure of the patient could be predicted (Figure 2).
b) The typical PTH curve in a patient with four gland disease. Standard interpretation of the PTH decline (Figure 3).

A standard definition of the "baseline value" and a "standard interpretation of the PTH decline" after the excision of the hyperfunctioning parathyroid tissue help to reduce an unsatisfactory postoperative outcome (Table I).

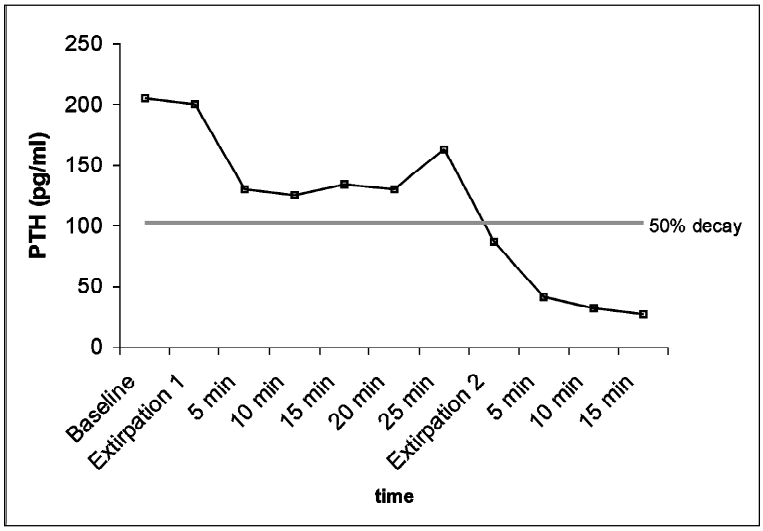

Figure 2: QPTH decay in case of Double Adenoma.
10 min after extirpation of an enlarged parathyroid gland QPTH drop is less than 50%. A contralateral double adenoma was removed by bilateral neck exploration.

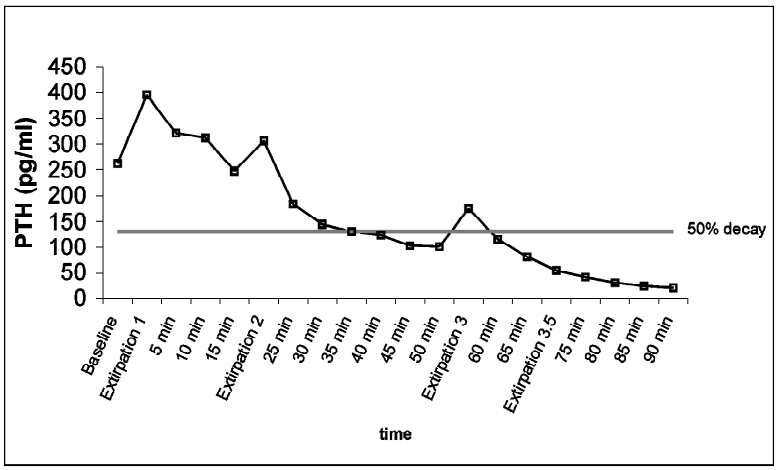

Figure 3: QPTH monitoring in a patient with primary hyperplasia (4 gland disease) and subtotal parathyroidectomy.

Table I – INTERPRETATION OF INTRAOPERATIVE QPTH MONITORING AND LONG-TERM OUTCOME

	iPTH decrease >50%	Postoperative serum calcium
True positive	+	Normal
True negative	-	Elevated
False positive	+	Elevated
False negative	-	Normal

Misinterpretation of QPTH

Unintended squeezing of the adenoma during preparation will result in a QPTH peak (Figure 4). Taking the "highest preexcision value" as the baseline value as recommended by Irvin (6), the interpretation of the QPTH curve would lead to persisting disease (false positive interpretation, manipulation of the single gland increases PTH levels).

On the other hand early clamping of effluent vessels will result in a precocious QPTH decay without removal of hyperfunctioning parathyroid tissue.

The blood sample serving as a "*baseline value*" must be drawn at the very beginning of the operation, prior to any manipulation of the neck to avoid an (artificial) increase of PTH. Taking the "highest preexcision value" as recommended by Irvin (6) will lead to misinterpretation. Further blood samples beside the baseline value are drawn prior to extirpation of the putative parathyroid adenoma ("Extirpation value"), 5 and 10 min after the removal. In some patients a delayed decay of QPTH due to a high percentage of a cross-reacting non 1-84 PTH fragment can be observed. In these patients further samples (at 15 and 20 min) can help in interpreting the QPTH results.

Figure 4 shows PTH values of a patient whose parathyroid adenoma was squeezed resulting in an immediate increase of PTH. After manipulation PTH returns to levels prior to manipulation. Applying the Irvin criteria ("50% decrease compared to the highest preexcision

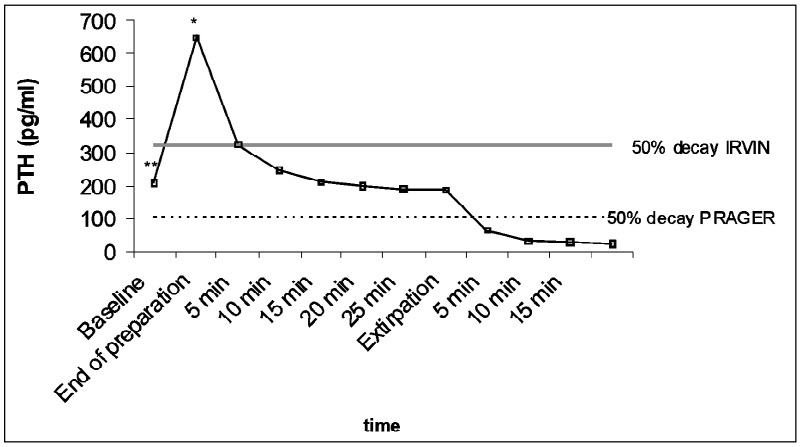

Figure 4: QPTH peak due to manipulation – importance of correct baseline value
At the end of the preparation a QPTH peak is observed, due to (unintended) manipulation. According to IRVIN a 50% decay of the highest preexcision value (*) should document cure. Without removal of the hyperfunctioning parathyroid tissue QPTH comes back (25 min) to the correct baseline level (**), drawn at the very beginning of the operation. Nevertheless only removal of the adenoma (Extirpation) leads to a >50% decay of PTH according to the correct baseline value (**).

value") this patient would be "healed" without removing the adenoma and therefore show persisting disease.
Manipulating parathyroid tissue before extirpation but also unintended clamping the effluent vessels minutes before extirpating the hyperfunctioning parathyroid tissue may lead to a misinterpretation of the QPTH curve. Only the correct "baseline value" allows correct "*standard interpretation of the PTH curve*" and avoids persisting disease or unnecessary extension of the operation. After extirpation of the hyperfunctioning parathyroid tissue any further manipulation has to be avoided to assure correct PTH decrease. The surgeon is only allowed to perform a very gentle closure of the skin avoiding any pressure to the cervical region, to enable a correct interpretation of the PTH curve.

Very high or low baseline values

Great care must be taken in case of very high baseline values, because the longer half life of a cross-reacting non 1-84 fragment can give obscure results. In those patients additional samples must be taken 15 or 20 minutes after extirpation. At this time PTH should have come down to the normal range. Alternatively kinetic calculations could give better results (12).
The same is true for extreme low baseline values (PTH < 90 pg/ml). In our experience the 50% rule cannot be applied in these patients.

Technical problems

Technical assay problems during PTH measurement itself can be best avoided by double-measurements. Nevertheless, values that do not fit the curve (exponential decay) should be interpreted cautiously and re-measured if possible (12). *Problems drawing the blood sample* can be avoided by arterial sampling (A. radialis). This enables correct timing and facilitates drawing the sample itself. In a series of more than 350 patients no problems were caused by the arterial line itself.

Renal Insufficiency

Most of the available QPTH assays show to some degree cross-reactivity with a non 1-84 PTH fragment which was detected recently 14. This fragment accumulates in patients with renal insufficiency, resulting in incorrect QPTH measurements. Thus at the moment QPTH seems of low help in patients with renal hyperparathyroidism, documenting total or sufficient subtotal parathyroidectomy

"Biochemical Frozen Section"

The QPTH assay may serve as a "biochemical frozen section" (11) in the majority of the patients, indicating the removal of all hyperfunctioning parathyroid tissue. Nevertheless, ligation of the adenoma's veins will result in a sharp decay of PTH, predicting cure although a thyroid nodule was mistaken for a parathyroid adenoma thus resulting in persisting disease. QPTH monitoring cannot replace frozen section in all circumstances. If there is any doubt about the provenience of the removed tissue, frozen section is mandatory.

Conclusions

QPTH monitoring is an indispensable prerequisite for any type of minimally invasive parathyroid exploration. It helps to distinguish between single gland and multiple gland disease and makes routine exploration or biopsy of the remaining glands unnecessary. In PHPT cautious interpretation of the intraoperative PTH decay is necessary to achieve a success rate of more than 97% (15).
Intraoperative QPTH monitoring may help the surgeon to shorten the duration of operation and to reduce morbidity of (bilateral) parathyroid exploration (permanent hypoparathyroidism) but this technology cannot replace the surgeon's skill, knowledge and experience.

The study was supported by "Jubiläumsfonds der Österreichischen Nationalbank" grant # 9307.

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