The role of intraoperative quick PTH measurements in primary hyperparathyroidism

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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

Riassunto

RUOLO DEL DOSAGGIO INTRAOPERATORIO DEL qPTH NELL’HIPERPARATIROIDISMO PRIMARIO

Nei pazienti con iperparatiroidismo primario i livelli di ormone paratiroidico intatto (PTH) si riducono drasticamente entro pochi minuti dopo l’asportazione del tessuto paratiroidico iperfunzionante. L’entità di tale riduzione è correlata con la completezza dell’asportazione del tessuto paratiroidico patologico e può essere monitorata intraoperatoriamente con il dosaggio del qPTH. 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 intraoperatorio in rapporto ai valori basali ottenuti prima dell’escisione della ghiandola patologica.

Il monitoraggio del qPTH è in grado di differenziare una malattia a coinvolgimento unghiandolare da una malattia multigiandolare. 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 i 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.

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 indispen-
sable 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, intraopera-
tive quick parathyroid hormone assay, standard inter-
pretation.

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 moni-
toring (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 demon-
strated in several series (5-7), the disadvantage of IRMA
consists of the radioisotopes limiting its use in the oper-
ating 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 “bio-
chemical frozen section” (11) render routine examination
or biopsy of the remaining glands unnecessary, thus short-
ening 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.

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 sur-
gical success (Figure 1).
«Single gland disease» suspected by preoperative local-
ization 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 chang-
ing 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, contra-
lateral adenoma the cure of the patient could be predic-
ted (Figure 2).
b) The typical PTH curve in a patient with four gland
disease. Standard interpretation of the PTH decline (Fi-
gure 3).
A standard definition of the “baseline value” and a “stan-
dard interpretation of the PTH decline” after the exci-
sion of the hyperfunctioning parathyroid tissue help to
reduce an unsatisfactory postoperative outcome (Table I).
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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 1 – INTERPRETATION OF INTRAOPERATIVE QPTH MONITORING AND LONG-TERM OUTCOME

<table>
<thead>
<tr>
<th>iPTH decrease &gt;50%</th>
<th>Postoperative serum calcium</th>
</tr>
</thead>
<tbody>
<tr>
<td>True positive</td>
<td>+</td>
</tr>
<tr>
<td>True negative</td>
<td>-</td>
</tr>
<tr>
<td>False positive</td>
<td>+</td>
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<tr>
<td>False negative</td>
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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 Irving (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 Irving (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 Irving criteria (“50% decrease compared to the highest preexcision

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.

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References


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