

QUICK INTRAOPERATIVE PTH ASSAY IMPROVES CURE RATE OF MINIMALLY INVASIVE SURGERY IN PATIENTS WITH PRIMARY HYPERPARATHYROIDISM

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Abstract

Purpose. We checked the advantage of intraoperative quick PTH (iqPTH) for improving cure rate of patients operated for primary hyperparathyroidism (PHPTH) by using minimally invasive surgery.

Methods. We compared two groups of patients diagnosed with PHPTH by preoperative localized single parathyroid adenoma (PA) submitted to minimal invasive surgery with histological confirmation. Patients from a control group (C) were operated without measuring intraoperative PTH, whereas in the second group iqPTH was assessed after adenoma excision and before wound suture. When quick PTH dropped less than 50%, conversion to open surgery and bilateral exploration followed.

Results. Six of the 40 patients from the C group (15%) had persistently elevated postoperative PTH, needing reintervention. High intraoperative PTH levels persisted in two of the 13 patients from the iqPTH group (15.4%), but conversion to open surgery allowed localizing and excision of preoperative undetected supplementary PA, increasing success rate to 100% ($p < 0.05$).

Conclusions. Assessment of iqPTH in PHPTH before wound suture provides reliable confirmation of accurate adenoma removal. Persistence of high PTH levels after adenoma removal suggests multiple gland disease and requires conversion to bilateral neck exploration in order to increase cure rate.

Key words: quick PTH, primary hyperparathyroidism, surgery, minimally invasive, cure.

INTRODUCTION

Primary hyperparathyroidism (PHPTH) is a disease caused by the intrinsic increase in parathyroid cell activity accompanied by excessive parathyroid hormone (PTH) secretion and subsequent modifications of calcium and bone metabolism (1). PHPTH has a higher incidence than previously thought, because many patients are diagnosed with milder, paucisymptomatic

or even asymptomatic forms of the disease, due to routine calcium measurement, evaluation of bone mass and turnover and cervical ultrasound check (2). Parathyroid surgery remains the only definitive therapy of choice (3). Surgery is frequently prescribed also in the asymptomatic forms of PHPTH, because normalization of PTH seems to decrease cardiovascular and neurological morbidity, as well as fracture risk (2).

The classical approach for the surgical cure of PHPTH was bilateral neck exploration for finding enlarged parathyroid gland or glands suspected of having adenomatous or hyperplastic modifications, in order to be excised by open neck surgery (ONS). The most frequent cause of PHPTH is represented, however, by a solitary, sporadic parathyroid adenoma (PA) (4). Presurgical localization of the PA with various techniques (scintigraphy with ^{99m}Tc-SestaMIBI, ultrasound, CT, PET) allowed therefore the switch from bilateral neck exploration to minimally invasive parathyroidectomy (MIP) in many cases of PHPTH (4-6). Open MIP through a small incision decreases operative time, the risk of complications, hospitalization time and hospital cost, improving patient satisfaction (7). The proper excision of the diseased parathyroid gland can be promptly proven by quick histological investigation of frozen sections (8).

Almost one of ten patients with sporadic PHPTH has more than one, sometimes ectopically located PA. In these particular cases, if multiple locations were not detected before surgery, histological confirmation of the excision of just one PA is not sufficient for attesting cure (9). Intraoperative quick measurement of PTH (iqPTH) is a more recent tool improving the diagnostic accuracy of surgical cure (9, 10). There are several criteria for interpreting iqPTH results, the Miami criteria being the ones most commonly used (11). A drop in PTH level to less than 50% the initial value and/or within the normal range after at least 10

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minutes from adenoma resection is diagnostic for cure, whereas the persistence of high PTH levels is highly suggestive for multiple gland disease (5,9-13). Serial measurements of iqPTH at 10, 20 and 30 minutes after adenoma excision increases sensitivity, but delays the diagnosis of hyperparathyroidism persistence, making conversion to ONS difficult when needed (14).

Other authors consider that accurate preoperative localization of the PA followed by MIP provides a high percentage of cure without needing iqPTH (15, 16). Preoperative localization techniques have, however, specificity and sensitivity limits. Both 99mTc-SestaMIBI scintigraphy and neck ultrasound may falsely localize a solitary lesion in cases of multiple parathyroid adenomas (17-19). Certain authors suggest that MIP of preoperative localized PA increases relapse rate with (19) or without (20) evaluation of iqPTH and advocate for ONS in all cases.

The purpose of our study was to evaluate the importance of PA preoperative localization and the advantage of iqPTH evaluation for optimizing surgical cure rate in patients with sporadic PHPTH.

METHODS

After approval by the University Ethical Committee, a retrospective review of a prospective parathyroid surgery database at an academic endocrine surgery practice was performed. A total of 53 patients with a biological diagnosis of PHPTH and with a preoperative image of solitary parathyroid adenoma obtained on 99mTc-SestaMIBI and overlapped on its ultrasound image were submitted to MIP. Excision of the parathyroid adenoma was histologically confirmed by frozen section analysis performed during surgery. Forty patients between 20 and 78 years at the moment of surgery (32 females and 8 males, group control, C) were operated without evaluation of iqPTH. A second group, formed out of 13 patients between 18 and 64 years (10 females and 3 males, group iqPTH) benefited of iqPTH and calcium evaluation from blood extracted from the ipsilateral internal jugular vein (IJV) ten minutes after minimally invasive excision of the presurgical localized parathyroid adenoma and before wound suture. The STAT IntraOperative-Intact-PTH Chemiluminescence immunoassay semiautomated mobile system (Future Diagnostics, Wijchen, Netherlands) was used for the intraoperative quantitative determination of PTH levels in EDTA plasma, while serum calcium was assessed by a standard photolorimetric technique (Sigma-Aldrich, St Louis, USA). We adapted the Miami

criteria of cure (decrease of PTH levels with more than 50 % than preoperative levels and/or within the normal range). When the above mentioned criteria were not fulfilled, MIP was converted to ONS and bilateral exploration of all parathyroid glands. Patients from both groups were followed up by measurement of serum PTH and calcium the first day after surgery (day 1) and at one, three and six months after surgery. We considered disease relapse when total serum calcium rose and/or remained above 10.5 mg/dL within the context of discrepantly high serum PTH levels.

Statistical analysis

The incidence of surgical failure was compared between the two groups by using the Chi-square test. Differences were found significant when $p < 0.05$.

RESULTS

Preoperative 99mTc-SestaMIBI and ultrasound accurately localized a histologically confirmed parathyroid adenoma in all 53 operated cases. Six out of the forty patients submitted to MIP but without intraoperative measurement of PTH (group C) showed, however, elevated levels of both serum PTH (above 55 pg/mL, Fig. 1 a) and calcium (above 10.5 mg/dL, Fig. 1 b) the next day after surgery. The two parameters remained elevated at one, three and six months after surgery, suggesting disease persistence despite clear histological description of an excised parathyroid adenoma (Fig. 1). All six patients were called for further investigation and a second surgical intervention. Serum calcium, but not PTH was increased in other three patients, but decreased to normal levels after one month. Mild transitory hypocalcemia was also observed at other six patients in the first day after surgery, but calcium levels normalized during the follow-up (Fig. 1).

Circulating PTH measured in the blood extracted from the IJV at the same side with the excised parathyroid adenoma showed a rapid decrease to levels lower than 50% of the preoperative value in eleven out of the 13 patients from the iqPTH group (Fig. 2) and even to levels within the normal range in nine patients (Fig. 3 a) but did not modify significantly in two patients. The rapid intraoperative decrease of serum PTH was immediately followed by a drop in the circulating calcium. The two patients with intraoperative persisting elevated levels of PTH had also intraoperative hypercalcemia (Fig. 3 b) and were, therefore, considered uncured while still being under

general anesthesia. Our rate of therapeutic failure of MIP consecutive to preoperative adenoma localization was therefore similar in groups C and iqPTH at the particular intraoperative time point (Fig. 4 a).

The parathyroid adenoma was localized in the inferior left thyroid pole in one case and in the inferior right thyroid pole in the other case of persisting intraoperative hyperparathyroidism and were histologically confirmed in both cases. Surgical approach was changed to open surgery and bilateral neck exploration in the two cases with persisting intraoperative hyperparathyroidism. A previously undescribed second parathyroid adenoma was discovered in the inferior pole of the contralateral thyroid lobe in one case and in the region of the ipsilateral thyroid lobe superior pole in the other case. The second parathyroid adenomas were excised. Postoperative PTH and calcium levels were therefore

normalized also in these two cases and all thirteen patients from group iqPTH had normal postoperative PTH and calcium levels. Normal levels of the two parameters persisted at one, three and six months after surgery, all patients from the iqPTH group being considered cured on long-term basis (Fig. 3). Quick intraoperative evaluation of PTH allowed the detection of previously undescribed supplementary parathyroid adenomas in two cases and their excision through open surgery, thereby increasing cure rate to 100 % in the iqPTH group ($p < 0.05$ compared to group C, Fig. 4 b).

DISCUSSION

The most frequent cause of primary hyperparathyroidism is a sporadic, solitary parathyroid adenoma (4). The incidence of parathyroid hyperplasia and of multiple parathyroid adenomas seems to be, however, higher than previously thought, summarizing around 10% in several series (21). Minimally invasive parathyroidectomy should be a curative solution in up to 90% of the cases of primary hyperparathyroidism if the solitary parathyroid adenoma is accurately

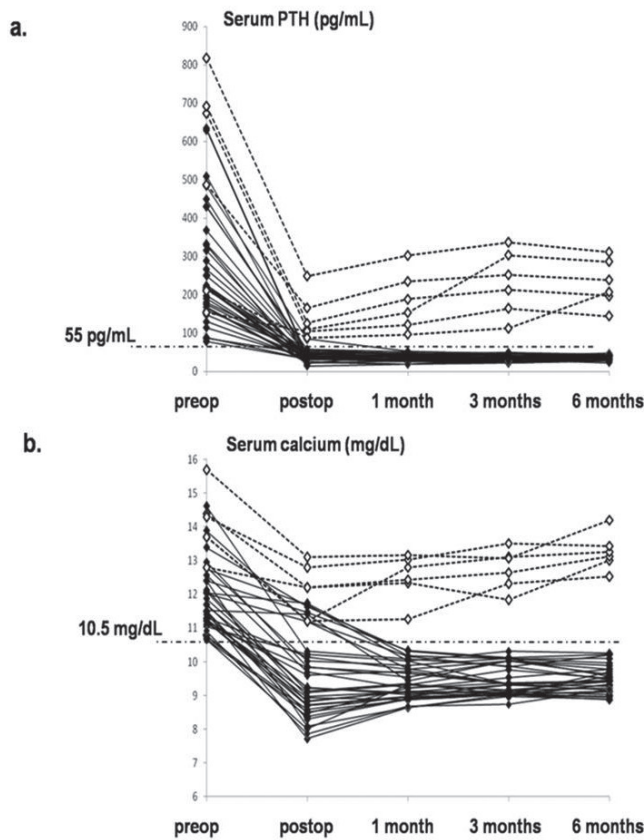


Figure 1. The evolution of serum PTH (a) and serum calcium (b) at 40 patients operated by minimally invasive surgery for preoperative localized solitary parathyroid adenoma before (preop), the next day (postop), at 1, 3 and 6 months after surgery. Long term normalization of PTH (< 55 pg/mL) and calcium (< 10.5 mg/dL) levels was achieved in 34 out of 40 patients, who were considered cured (black diamonds, continuous lines). Six patients persisted, however, having high PTH and calcium levels, and second intervention was considered after 6 months (white diamonds, dotted lines).

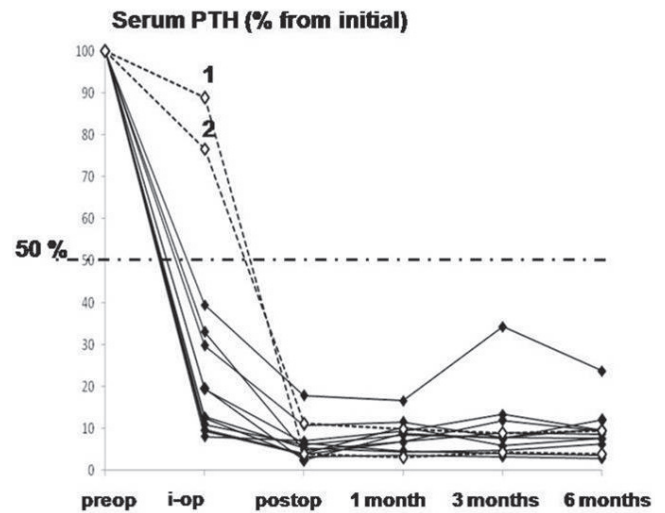


Figure 2. The evolution of serum PTH (% from preoperative levels) during minimal invasive parathyroidectomy at 13 patients where intraoperative (i-op) quick PTH was measured from the ipsilateral internal jugular vein ten minutes after excision of the preoperative localized parathyroid adenoma. Serum PTH was also measured in the peripheral blood the next day (postop), at 1, 3 and 6 months after surgery. Cure was considered when quick PTH dropped with more than 50% from preoperative levels (preop) in 11 patients (adaptation of the Miami criterion, black diamonds, continuous lines). Quick intraoperative PTH did not drop in two patients (1 and 2, white diamonds and dotted lines). Minimal intervention was switched to open surgery, a second parathyroid adenoma being found and excised, accompanied by cure also in these two cases, increasing success rate to 100%.

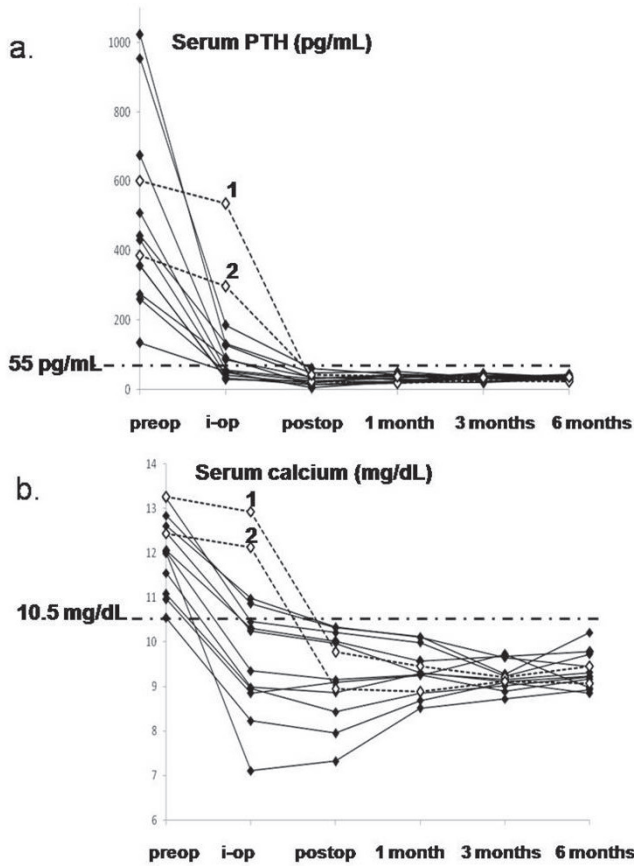


Figure 3. The evolution of serum PTH (absolute values, **a**) and serum calcium (**b**) during minimal invasive parathyroidectomy at 13 patients where intraoperative (i-op) quick PTH and calcium were also measured from the ipsilateral internal jugular vein ten minutes after excision of the preoperative localized parathyroid adenoma. Serum PTH and calcium were also measured in the peripheral blood the next day (postop), at 1, 3 and 6 months after surgery. Cure was considered when PTH dropped under 55 pg/mL and serum calcium decreased under 10.5 mg/dL. At the two patients where quick intraoperative PTH did not drop with more than 50% from preoperative levels (1 and 2, white diamonds and dotted lines), minimal intervention was switched to open surgery and a second parathyroid adenoma being found and excised, accompanied by long term normalization of serum calcium and PTH in both cases and increasing success rate to 100%.

localized before surgery (15). We used ONS in all three cases with primary hyperparathyroidism and multiple parathyroid lesions detected by imagistic investigation. These patients were, therefore, not included in our study. Other 40 patients diagnosed with solitary parathyroid adenomas localized by 99mTc-SestaMIBI and ultrasound, were operated by MIP and formed the C group. Six of these patients (15%) were however not cured, showing persistently high levels of PTH and calcium. The accuracy of MIP was confirmed by histology investigation that described an excised parathyroid adenoma in all six cases of surgical failure. The persistence of hyperparathyroidism should

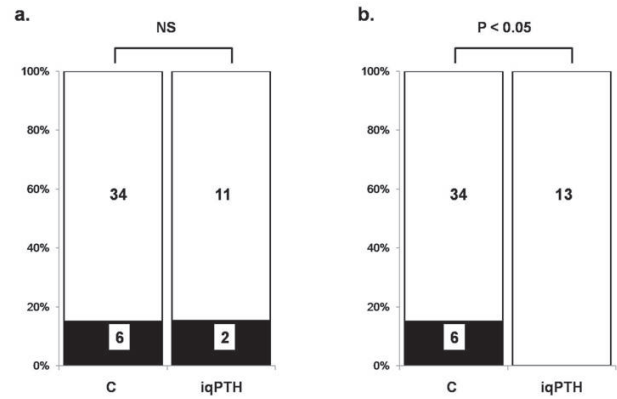


Figure 4. a - the distribution of cured patients (white bars) and patients with persisting high PTH levels after surgery or immediately after the excision of the parathyroid adenoma (groups C and iqPTH, respectively, black bars). No difference in the incidence of cure failure between the two groups at the intrasurgical time point was observed (non-significant chi-square test). **b** - the distribution of cured patients (white bars) and patients with persisting high PTH levels after surgery in both groups. Conversion to open neck surgery increased success rate to 100% in the iqPTH group ($p < 0.05$ when compared to the incidence of cure failure in the C group by the chi-square test).

be therefore related to other co-existent locations of hyperactive parathyroid tissue that were not observed at imagistic investigation, and not to a surgical mistake. The presence of multiple parathyroid adenomas was, moreover, confirmed in two of the six cases that were meanwhile re-operated (data not shown). Other authors consider that patients with concordant scans and suggestive biochemistry can be cured by MIP in such a high percentage that iqPTH measurement may have only limited importance (22). The incidence of preoperative undiagnosed multiple parathyroid adenomas was nevertheless much higher in our series, reaching 15% in both groups. This difference may be caused by specific population particularities, such as vitamin D deficiency which is widespread in Romanian territory (23). The levels of serum 25OH-D3 were, however, inconsistently evaluated in our study groups.

Classical preoperative localization techniques have some limitations in detecting all locations of multiple parathyroid disease (24-26), and this drawback limits successful cure by MIP in certain cases (17-19). The utilization of SPECT, SPECT-CT and four dimensional CT increases detection sensitivity and specificity (27,28), but these methods are not commonly available. Quick intraoperative PTH evaluation gives, therefore, additional information regarding the success of MIP (9-13). An important drop of PTH levels supports cure achievement, whereas the persistence of high PTH suggests the existence of non-excised hyperfunctional

parathyroid tissue. Evaluation of intraoperative PTH raises two important issues: accuracy and speed. In other words, appropriate definition of cure or failure must quickly lead to a therapeutic decision – completion of MIP or conversion to ONS and identification of supplementary diseased parathyroid tissue. Actual definition of cure using intraoperative PTH is still a question of debate. Timing and place of sampling, as well as the interpretation of PTH decrease vary in different studies (29). Circulating PTH has a half life of about 5 minutes. Peripheral sampling ten minutes after adenoma excision using the Miami criteria (over 50% decrease of PTH from presurgical values) has a very good, although not a 100 % specificity and sensitivity for defining cure (30). Enlarging the time span for PTH measurement to 20 minutes diagnosed cure in additional patients but delayed surgical decision (14). In order to maximize both diagnosis accuracy and speed, we measured intraoperative PTH directly from the ipsilateral IJV only once, ten minutes after the excision of the parathyroid adenoma, confirmed by histology.

We chose intraoperative blood sampling from the IJV due to the easiness and rapidity of blood sampling. Other authors describe slightly higher PTH values from the IJV than from peripheral blood when evaluated at patients with PHPTH and a similar drop at both locations at 10 and 15 minutes after adenoma excision (31). PTH was, however, not assessed in our patients immediately after surgical elimination of the parathyroid adenoma, but 10 minutes later, when PTH levels may have been similar in the IJV and peripheral blood. Literature data is also controversial regarding laterality-related differences in PTH measurement between the right and left IJV (32, 33). It could be, therefore, argued whether iqPTH assessment from the IJV is indeed as informative as peripheral evaluation for applying the Miami criteria of cure, especially since preoperative PTH cannot be routinely assessed also from the IJV. We observed, nevertheless, a clear PTH drop of over 50% from the presurgical peripheral levels ten minutes after the excision of the parathyroid adenoma in the eleven cases showing cure after MIP and even a normalization of PTH levels in nine of these patients. The short time interval between adenoma excision and PTH assessment from the IJV allowed the switch from MIP to ONS in the two cases where intraoperative PTH remained increased. A supplementary parathyroid adenoma was found in both cases and surgical cure during the same surgical intervention was also possible for these two patients, increasing surgical cure to 100%

in the iqPTH group.

There are, however, certain limitations of our conclusions. Our patient series is not very large, the number of patients from the two groups is disproportionate and the study is retrospective, including all our operated patients, without randomization. Result accuracy could be improved with a larger prospective, randomized multicentric study, under current organization.

Patients with primary hyperparathyroidism need a complex approach, including preoperative localization of the lesion and MIP when the lesion is unique and well localized. iqPTH is presently considered an intraoperative adjunct in surgery for primary hyperparathyroidism (34). Routine intraoperative evaluation of PTH levels may, however, be important especially in populations or medical centers where the incidence of undiagnosed multiple parathyroid adenomas is high, in order to testify cure, or switch to ONS. The importance of quick single sampling of PTH from the IJV should be reevaluated, since it is easy to be performed and seems to give an accurate image of surgery success or failure, fast enough for allowing a change in surgical strategy and optimize patient cure in selected cases.

Conflict of interest

The authors declare that they have no conflict of interest concerning this article.

Acknowledgements

This paper was published under the frame of European Social Fund, Human Resources Development Operational Programme 2007-2013, project no. POSDRU/159/1.5/136893.

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