

Applicability of Tissue Aspirate for Quick Parathyroid Hormone Assay to Confirm Parathyroid Tissue Identity During Parathyroidectomy for Primary Hyperparathyroidism

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Hypothesis: Intraoperative quick parathyroid hormone (PTH) assay for tissue aspirate facilitates the confirmation of parathyroid tissue identity and allows a more selective use of frozen section examination during parathyroidectomy for primary hyperparathyroidism.

Design: A retrospective review of a prospective protocol of the applicability and accuracy of quick PTH assay for tissue aspirate as a biochemical frozen section tool.

Setting: A university hospital department of surgery.

Patients: Quick PTH assay for aspirate obtained from suspected parathyroid gland excised during parathyroidectomy for primary hyperparathyroidism.

Main Outcome Measures: The accuracy of this biochemical identification of parathyroid tissue identity was correlated with histological examination and outcome.

Results: Quick PTH assay was performed for aspirate from at least 1 excised parathyroid gland in 122 (98%) of 125 patients while 13 patients (10%) had PTH aspirate for nonparathyroid tissues including thyroid (n=10), thymic (n=2) and lymphatic (n=1) tissues. Frozen section examination was performed for 15 patients (12%), including the 3 patients who did not undergo tissue aspirate for quick PTH assay. All except 3 patients had an aspirate assay value of greater than 1500 pg/mL (range, 625 to >1500 pg/mL) for parathyroid tissue while the value of PTH aspirate for nonparathyroid tissue ranged from 27 to 229 pg/mL (median, 72 pg/mL) in 13 patients. The median size of abnormal parathyroid gland was 70 to 15000 mg (median, 775 mg).

Conclusions: With the availability of quick PTH assay, tissue aspirate for PTH assay can be adopted as an alternative to traditional frozen section examination to confirm parathyroid gland identity. Frozen section examination can be employed more selectively.

Arch Surg. 2005;140:146-149

MINIMALLY INVASIVE parathyroidectomy has been shown to be as effective as bilateral neck exploration in achieving a surgical cure¹⁻³ and it has become an accepted means of surgical treatment for patients with primary hyperparathyroidism (pHPT).⁴ The adoption of minimally invasive parathyroidectomy has revolutionized the standard practice and operative strategies of bilateral neck exploration during parathyroidectomy for pHPT. The shift of operative strategy toward minimally invasive parathyroidectomy depends on an accurate preoperative localization and the availability of intraoperative quick parathyroid hormone (PTH) assay³ to provide a rapid and accurate confirmation of surgical success as well as to facilitate the removal of all hyperfunctioning parathyroid tissues.

In the era of bilateral neck exploration, frozen section examination was routinely employed to confirm the identity of tissue excised to be abnormal parathyroid tissue.⁵⁻⁷ Frozen section is a highly reliable means of identifying tissue type during parathyroid exploration.^{6,8} On the other

See Invited Critique at end of article

hand, tissue aspiration for PTH assay has been applied in preoperative confirmation of parathyroid tissue identified during imaging.⁹⁻¹² However, this technique has not been viable for intraoperative confirmation before the availability of quick PTH assay because of the long turnover time required during the standard PTH assay. With the adoption of quick PTH assay, we have attempted to apply this technique as a biochemical assay tool to

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confirm the identity of excised parathyroid tissues and to employ frozen section examination more selectively. This study evaluates the applicability and accuracy of this tool in confirming parathyroid tissue identity, and in conjunction with intraoperative quick PTH assay, its impact in reducing the number of frozen section examinations.

METHODS

Since 1999, our institution has routinely employed quick PTH assay to confirm surgical success and to facilitate the adoption of either focused parathyroidectomy or minimally invasive parathyroidectomy for pHPT.³ The quick PTH assay was measured with a commercially available 2-site antibody immunochemiluminometric assay (QuiCK-Pak System; Nichols Institute Diagnostics, San Clemente, Calif) and was carried out in the operating room by a trained technician using a portable laboratory contained on a cart. Blood samples were collected at induction, immediately after the excision of the parathyroid gland (zero minutes) and repeated at 10 minutes postexcision. A delayed sample at 30 minutes would be obtained in addition if the assay at 10 minutes failed to show a greater than 50% decline in PTH compared with that of induction or at zero minutes. Suspected parathyroid tissues were aspirated for quick PTH assay immediately after excision to determine their identity. A 23-gauge needle connected to a 2.5-mL syringe was punctured into the suspected parathyroid gland or adenoma (**Figure 1**). It was then moved back and forth to aspirate its content into the needle, which was then rinsed with a 2-mL aliquot of saline solution. The sample was sent for quick PTH assay together with the zero-minute postexcision blood sample. The result of the quick PTH assay for the tissue aspirate is available 15 minutes after sampling. Frozen section examination is then performed more selectively in cases of diagnostic difficulty or challenging decision-making situations. Patients with multiglandular hyperplasia revealed during preoperative imaging as well as those with multiple endocrine neoplasia syndromes diagnosed preoperatively based on characteristic family history or concomitant syndrome manifestations were excluded because frozen section examination was routinely performed in these cases. Informed consent was obtained from all patients prior to the procedure.

Patients with sporadic pHPT who underwent parathyroidectomy were selected for minimally invasive parathyroidectomy with preoperative localizations utilizing technetium Tc 99m sestamibi scintigraphy and ultrasonography. Routine intraoperative quick PTH assay was performed for all patients under a standard protocol and excised abnormal parathyroid gland tissue underwent aspirate for quick PTH assay. In case of diagnostic difficulty, aspiration was performed for suspected parathyroid tissue to facilitate parathyroid tissue identification. Data were collected prospectively with regard to the following patient specifications: demographics, indications of operation, preoperative biochemistry, operative details, intraoperative quick PTH assay results, use of frozen section examination, histological examination of excised tissues, and postoperative outcome. The accuracy of quick PTH assay in confirming the identity of parathyroid and nonparathyroid tissue was studied and the potential impact of application of this technique in reducing the number of frozen section examinations was evaluated.

RESULTS

From 2000 to 2003, 133 patients underwent surgical treatment for pHPT with intraoperative quick PTH assay per-

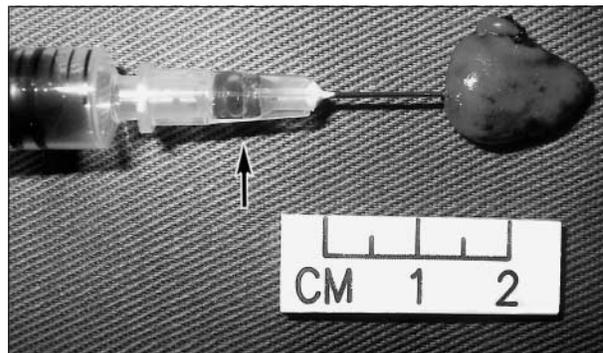


Figure 1. A 23-gauge needle connected to a 2.5-mL syringe was punctured into the suspected parathyroid adenoma. It was then moved back and forth to aspirate its content into the needle (arrow), which was then rinsed with a 2-mL aliquot of saline solution.

formed. Eight patients with multiglandular hyperplasia diagnosed before the operation were excluded. Quick PTH assay for tissue aspirate was attempted in 125 patients who were subsequently proven to have abnormal parathyroid tissue during histologic examinations.

There were 41 men and 84 women with a median age of 56 years (range, 19-93 years). Forty (32%) of 125 patients underwent open exploratory surgery, while endoscopic-assisted or focused minimally invasive parathyroidectomy was accomplished in 78 (92%) of 85 patients. One patient underwent mediastinal exploratory surgery for a mediastinal adenoma located at the aortopulmonary window, while another underwent reexploratory surgery for a recurrent adenoma after a previous incomplete excision. Aspiration was not attempted in a patient with a negative preoperative localization, and multiglandular hyperplasia was diagnosed during the operation. In addition, this technique was not used for 2 patients; one whose intrathyroidal parathyroid adenomas failed to be recognized after hemithyroidectomy, and another whose 125-mg adenoma was ruptured during dissection. This assay was successfully performed in 122 (98%) of 125 patients.

Intraoperative frozen section examination was performed on specimens from 13 patients (10%), including the 3 patients without quick PTH assay for tissue aspirate. Frozen section examination was requested for other patients because of the failure to identify the parathyroid adenoma during the initial exploration ($n=8$) and the surgeon's need for tissue confirmation ($n=2$). The final histological results revealed a solitary adenoma in 123, multiglandular hyperplasia in 1, and double adenomas in 1 patient. All patients had a decline of quick PTH assay of greater than 50% at 10 minutes after excision of the adenoma or at the end of the procedure compared with that at induction or immediate postexcision.

Of the 123 parathyroid aspirates, the value of quick PTH assay ranged from 625 to greater than 1500 pg/mL. The quick PTH result was greater than 1500 pg/mL in all except 3 aspirates; the results of 3 other aspirates were 625, 754, and 929 pg/mL. The median size of the adenomas was 775 mg (range, 70-15000 mg) and 78 adenomas (63%) were 1000 mg or smaller. Thirteen patients underwent aspiration of nonparathyroid tissue with quick PTH assay value of 27 to 229 pg/mL (median, 72.7 pg/mL). The nonparathyroid tissue included thyroid nodule

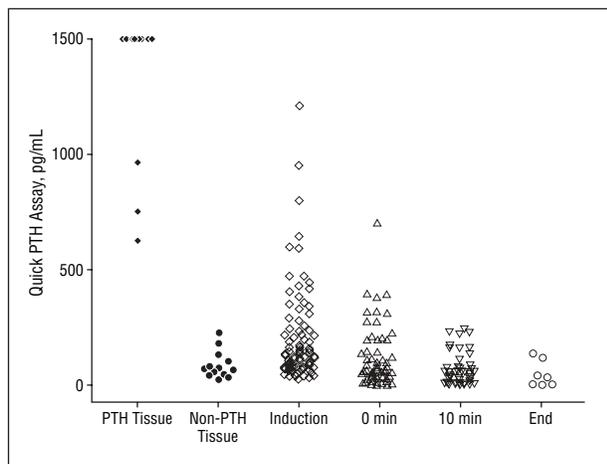


Figure 2. A scatterplot showing the quick parathyroid hormone (PTH) assay aspirate values of parathyroid compared with nonparathyroid tissues. The quick PTH assay for blood samples at different time intervals is illustrated. A delayed assay at 30 minutes (end) was performed for patients who failed to show a greater than 50% decline in the 10-minute assay compared with that at induction or at 0 minutes.

(n = 10), lymphatic tissue (n = 1) and thymic tissue (n = 2). **Figure 2** shows a scatterplot of the quick PTH levels from parathyroid adenomas compared with nonparathyroid tissue aspirates as well as those from serum at different time intervals with reference to the excision of adenomas. During a median follow-up of 10 months, all patients remained normocalcemic.

COMMENT

Parathyroid aspirate for PTH assay or cytologic examination under imaging guidance has been applied to confirm the identity of the imaged parathyroid adenoma as shown in preoperative localizations.⁹⁻¹² However, this technique has not been used for intraoperative confirmation before the availability of quick PTH assay because of the long turnover time required for the standard PTH assay. On the other hand, frozen section examination is widely used to identify tissue type during parathyroid exploration in patients with pHPT. It is used to confirm that excised tissue is parathyroid in origin as well as to determine if it is abnormal hypercellular tissue.^{6,7} Frozen section examination is a highly reliable means of identifying tissue type during parathyroid exploration.⁶ Intraoperative frozen section confirmation is routinely performed during parathyroid exploration, although a more selective biopsy has been recommended to decrease the risk of postoperative hypoparathyroidism. This biopsy is performed for the suspected abnormal gland instead of performing a routine biopsy of all normal glands.⁵

The availability of intraoperative quick PTH assay has revolutionized the operative strategies adopted during parathyroid exploration. Aside from confirming surgical success and identifying the presence of functioning parathyroid tissue, the potential application of the quick PTH assay during parathyroidectomy has been extended. Quick PTH assay has been used to predict postoperative hypocalcemia during thyroid¹³ and reoperative parathyroid surgery.¹⁴

The need for routine frozen section confirmation has also been challenged with the availability of quick PTH assay. A significant decline in PTH level after excision of a suspected parathyroid adenoma may be confirmatory of operative success and provides the operating surgeons indirect evidence of removal of all hyperfunctioning parathyroid tissue.¹⁻³ Frozen section examination of the excised specimens may no longer be required. However, it is not uncommon for the operating surgeons to send the parathyroid tissue to the pathologist for histological confirmation by frozen section examination despite the use of quick PTH assay because they are concerned about false-positive results and want tissue confirmation. For radioguided parathyroidectomy, the gamma probe can be used to confirm the identity of the excised parathyroid tissue. It has been shown that ratio of ex vivo count to background count of greater than 20% can be used to confirm the identity of parathyroid tissue and no frozen section examination is required.¹⁵

Perrier et al¹⁶ has shown that aspirate for quick PTH assay can be used as a biochemical frozen section to confirm the identity of parathyroid tissue. Frozen section examination was routinely performed even though aspirations successfully identified either parathyroid or nonparathyroid tissue. In our study, we evaluated the accuracy as well as the feasibility in the application of this technique to confirm tissue identity during parathyroidectomy for pHPT. In addition to the use of quick PTH assay in blood samples to confirm surgical success during parathyroid exploration, aspirate from excised parathyroid tissues for quick PTH assay can be performed expeditiously. This technique is highly accurate in confirming that excised tissue is abnormal parathyroid tissue and distinguishing parathyroid from nonparathyroid tissue. If a cut-off quick PTH aspirate level of 500 pg/mL was used, the sensitivity, specificity, positive and negative predictive values in identifying abnormal parathyroid glands were 100%. However, quick PTH assay of aspirate from a nonparathyroid tissue might be exceptionally high in the presence of a grossly elevated serum PTH level. Such false-positive results can lead to diagnostic difficulty and potential pitfalls in interpreting the results without performing the quick PTH serum assay. In addition, it might be technically difficult to aspirate enough content from a small adenoma, but our results showed that adenomas as small as 70 mg were successfully confirmed by this assay method. Because of similarities to parathyroid adenoma identification, application of this technique to hyperplastic parathyroid glands is feasible. For a normal parathyroid gland, this technique is not reliable and is not recommended because of the technical difficulty involved in performing the aspiration.

Parathyroid tissue confirmation can reassure the operating surgeon of the high probability of operative success and eliminate the need for frozen section confirmation. The results are readily available, sooner than the results from the delayed quick PTH blood sample at the end of the procedure. It provides an alternative tool as a biochemical frozen section and does not add additional cost if quick PTH assay is adopted for minimally inva-

sive parathyroidectomy because the assay can be accomplished by the same measurement kit. In fact, in our institution, savings of \$180 were made by eliminating the need of a frozen section histological examination.

Similar to other operative strategies during thyroid and parathyroid surgery,¹⁷ routine frozen section examination is not necessary during parathyroid explorations for pHPT. When quick PTH assay is adopted for parathyroid explorations, tissue aspiration for quick PTH assay will be used as a biochemical frozen section tool. This technique is an alternative to the traditional frozen section examination, which can be employed in a more selective manner.

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