Validation of a Method to Replace Frozen Section During Parathyroid Exploration by Using the Rapid Parathyroid Hormone Assay on Parathyroid Aspirates

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Hypothesis: The parathyroid hormone (PTH) content of tissue aspirates is an accurate indicator of parathyroid tissue and can replace frozen section during parathyroid surgery.

Design and Setting: Prospective data collection in a tertiary care hospital with a single surgeon.

Patients: One hundred sixty-seven consecutive patients completing limited parathyroid explorations.

Interventions: Parathyroid adenomas removed during limited parathyroid exploration were aspirated through a 22-gauge needle into 0.5-mL isotonic sodium chloride solution and the solution held on ice in a purple-top tube. Aspirates of in situ thyroid tissue were also taken for comparison. Samples were then assessed for PTH content at the same time the serial blood samples were routinely assessed to monitor the physiologic impact of the surgery.

Main Outcome Measure: The PTH content of tissue aspirates was compared with histologic identification of removed putative parathyroid tissue.

Results: Elevated tissue PTH content was associated with the identification of the tissue of origin as parathyroid in every case. Tissue aspirates from pathologically proven parathyroid tissue had a mean PTH level of at least 1691 pg/mL, with 160 of the aspirates having values exceeding the upper limit of the assay. This measure was significantly higher than values obtained from thyroid aspirates, which had a mean PTH level of 88 pg/mL (P<.01), reflective of blood levels at the time of aspiration. Using the 99% confidence interval of histologically confirmed parathyroid glands as the lower limit of a positive test result at 1610 pg/mL, tissue aspirate PTH assay has a sensitivity of 97% and a specificity of 100%.

Conclusions: Positive identification of removed tissue as parathyroid is a necessary adjunct to limited parathyroid exploration, where decreases in false-positive blood PTH levels can be a result of operative manipulation of the neck. Analysis of tissue PTH content during the same assay that is being used for assessing blood PTH concentration is an efficient and accurate method for identifying the tissue with certainty. This measure also prevents the occasional ambiguity in frozen sections of parathyroid tissue that apparently contain thyroidlike colloid material.

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In focused parathyroid surgery, accurate intraoperative recognition of parathyroid tissue is fundamental to correcting primary hyperparathyroidism. Visual identification depends heavily on the expertise of the surgeon and is more difficult where there has been prior neck surgery, irradiation, anatomical variation, or coexisting thyroid disease such as multinodular goiter or Hashimoto thyroiditis. Even in routine cases, frozen section often is used to verify the identity of the tissue. When there are other sources of doubt, as with intrathyroidal parathyroid glands or with a parathyroid gland with a microfollicular histological pattern resembling a Hurthle cell thyroid adenoma, paraffin sections are sometimes needed for definitive identification.

A rapid serum PTH assay performed intraoperatively to observe a fall in parathyroid hormone (PTH) concentrations after the excision of an adenoma demonstrates the effect of removing a hyperfunctioning gland. A greater than 50% drop in the PTH level within 10 minutes is generally agreed to be indicative of cure, although the exact timing of the samples before and after excision still is under investigation. However, this technique suffers from both false negatives and positives. In the false-positive case, unwitting manipulation of the parathyroid adenoma prior to the pre-removal blood sample could result in falsely elevated PTH levels, resulting in a greater
in the literature advocate the use of this technique, no
to run the serum assay. Although some smaller studies

tional time in the operating room beyond that required
incure minimal independent additional expense. The rapid turnaround time to run this assay in
logic processing and interpretation and might, depend-
cally eliminates some of the cost associated with patho-
is a direct way to identify parathyroid tissue and offers
rate identification of the removed tissues as parathy-
is more significant because it can lead to failure of the sur-
morbidity to the patients. However, the false-positive case
causing removal but after the preremoval blood sample might
cause a spike in PTH levels, resulting in an insufficient drop
compared with postexcision, despite removal of all patho-
logic parathyroid tissue.5,6 With a false negative, further
neck exploration is undertaken, with a slight increase in
morbidty to the patients. However, the false-positive case
is more significant because it can lead to failure of the sur-
gery could not be performed. Specimens were aspirated into
0.5-mL isotonic sodium chloride solution using a 22-gauge
needle and then held on ice in purple-top tubes. The PTH con-
centration of the aspirates was determined using the dual an-
tibody immunoassay for intact PTH (1-84), which was per-
formed at the same time as the analysis of the serum samples.
The results of the putative gland PTH values were compared
with the final pathologic diagnosis; the thyroid gland PTH val-
tues served as the negative controls.

Samples were analyzed by the hospital's chemistry labora-
atory following the manufacturer's instructions and using the
Quick Intraoperative Biointact PTH assay kit (Nichols Insti-
tute, San Clemente, Calif).

Statistical analysis was performed using Sigmaplot (SPSS Inc,
Chicago, Ill). Results are presented as means ± SE. If it was
needed, we subjected comparison groups to 1-way analysis of
variance and, when significance was found, applied the t test.

In the statistical analysis, when the PTH measurement is
greater than the limit of detection of the assay, a value of 1800
pg/mL was assumed (the highest value detected by the assay).
Given that the real but unknown values are even higher than
that, the statistical significance would be even greater and
the clinical management would remain the same.

METHODS

From November 1997 through April 2004, we entered 167 con-
secutive putative parathyroid and thyroid aspirates and their cor-
responding resected specimens into this single-arm prospective
study at Brigham and Women's Hospital (Boston, Mass). A single
surgeon performed all aspirations as well as the operations.

Patients were included in the study when they were re-
ferred with signs, symptoms, and laboratory findings consist-
tent with primary hyperparathyroidism. All patients under-
went preoperative imaging with ultrasound or nuclear imaging.
They were then excluded from the study if they were thought
to have multiglandular disease or if limited parathyroid sur-
gery could not be performed. Specimens were aspirated into
0.5-mL isotonic sodium chloride solution using a 22-gauge
needle and then held on ice in purple-top tubes. The PTH con-
centration of the aspirates was determined using the dual an-
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The results of the putative gland PTH values were compared
with the final pathologic diagnosis; the thyroid gland PTH val-
tues served as the negative controls.

Samples were analyzed by the hospital's chemistry labora-

Data were collected on 167 patients during the study pe-
period. Thirty-six (21%) were men, and the mean ± SD age was
58.1 ± 9 years. The average PTH measures before and af-
ter excision were 271.31 ± 59 pg/mL and 43.57 ± 4.3 pg/mL,
respectively. The mean decrease in the PTH level of 227.73
pg/mL (72.58%) was consistent with removal of parathy-
roid adenomas.

Aspirates from the putative parathyroid gland, later con-
frmed histologically, had a mean PTH level of 1691.83
pg/mL, which is significantly higher than thyroid aspir-
ates with a mean PTH level of 87.90 pg/mL (P < .01)
(Figure). One hundred sixty parathyroid aspirates, in fact,
had values above the upper limit of the assay. Using the
99% confidence interval of known parathyroids as the lower
limit of a positive test result (or 1610 pg/mL), tissue aspi-
rate PTH assay has a sensitivity of 97% and a specificity
of 100% (Table 1). Two thyroid aspirates exhibited high
PTH values, likely from aspirating too far into adjacent
structures containing parathyroid secretions. In those cases,
the tests were voided and frozen sections were obtained.

Five histologically confirmed parathyroid adenomas
were found to have low PTH values (false negatives), likely

Table 1. Summary of Aspirate Data Compared
With Pathologic Diagnosis*

<table>
<thead>
<tr>
<th></th>
<th>Parathyroid</th>
<th>Nonparathyroid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive test, No.</td>
<td>160</td>
<td>0</td>
</tr>
<tr>
<td>Negative test, No.</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

*Tissue aspirates have a sensitivity of 97% and a specificity of 100%.

Figure. Graphical representation of parathyroid hormone (PTH) content in
aspirates of nonparathyroid, parathyroid, and thyroid tissues. Mean PTH
level of parathyroid (bar) is significantly higher than that of other tissue
(P < .01). The large black circle at 1800 pg/mL represents values above the
upper limit of the assay. The statistics assume that the greater than
1800-pg/mL value is 1800 pg/mL. Given that the real but unknown values
are even higher than that, the statistical significance would be even greater
and the clinical management would remain the same.
Correctly identifying the parathyroid gland is important in a successful parathyroid exploration, especially considering the increasing proportion of minimally invasive explorations. Even with the use of decreasing intraoperative venous PTH concentrations as an indicator for cure of hyperparathyroidism, there is still a need for positive tissue identification. A false-negative fall in PTH levels can result in the added morbidity of a failed operation and the need to surgically reexplore the neck at a later date. Identifying glands as parathyroid tissue currently relies on frozen section, which can be misleading when the parathyroid adenoma has a follicular architecture. Here we have shown that tissue PTH content can be an alternative indicator in frozen section identification.

Currently, we advocate tissue aspirates as an alternative or additional indicator to confirm after removal that a putative enlarged parathyroid gland is indeed of parathyroid origin. Although such a technique might also allow for in situ identification of a parathyroid adenoma prior to resection, we have been reluctant to apply it to normal parathyroid tissue in situ. This technique samples a volume of tissue for PTH content. Although the total PTH content of an adenoma is clearly elevated, there are no generally accepted data that its PTH concentration per volume sampled differs from that of a normal gland. Second, the aspiration samples vary, depending on tissue turgor and length of needle insertion, making it difficult to sample constant volumes of tissue. Finally, the bevel of the 22-gauge needle often is larger than the thickness of a suppressed parathyroid gland, and the technique might irreversibly damage the normal glands in situ, either from barotraumas due to aspiration or from hemorrhage into the glands. For all these reasons, we did not attempt to distinguish normal parathyroid tissue from adenoma using tissue aspirates.

The parallel testing of serum PTH levels and tissue aspirates eliminates the routine need for a pathologist but still provides the information necessary to perform an operation. The successful removal of a parathyroid adenoma would be reflected in a greater than 50% decrease in serum PTH levels together with a high parathyroid aspirate and a low thyroid aspirate. If the thyroid aspirate is high, the parathyroid aspirate cannot be interpreted correctly and a frozen section should be done to identify the excised tissue. A scheme for interpreting these data is outlined in Table 2. The combination of serum PTH level, aspirate of tissue and thyroid, and clinical judgment must be used to determine whether the surgery performed was adequate.

We conclude that tissue PTH content is a highly accurate measure for identifying a neck mass as parathyroid tissue.

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**Previous Presentation:** This study was presented at the 85th Annual Meeting of the New England Surgical Society; October 1, 2004; Montreal, Quebec; and is published after peer review and revision.

<table>
<thead>
<tr>
<th>Venous PTH</th>
<th>Tissue Aspirate</th>
<th>Thyroid Aspirate</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease</td>
<td>High</td>
<td>Low</td>
<td>Success</td>
</tr>
<tr>
<td>Decrease</td>
<td>Low</td>
<td>High</td>
<td>Frozen section on tissue</td>
</tr>
<tr>
<td>Decrease</td>
<td>Low</td>
<td>Low</td>
<td>Frozen section on tissue; consider continuing exploration</td>
</tr>
<tr>
<td>No change</td>
<td>Not applicable</td>
<td>Not applicable</td>
<td>Continue exploration</td>
</tr>
</tbody>
</table>

Abbreviation: PTH, parathyroid hormone.

**REFERENCES**