Pitfalls of Intraoperative Quick Parathyroid Hormone Monitoring and Gamma Probe Localization in Surgery for Primary Hyperparathyroidism

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Hypothesis: Intraoperative quick parathyroid hormone (qPTH) monitoring and gamma probe (GP) localization greatly aid the surgeon.

Design: Prospective case series of patients undergoing parathyroidectomy (PTX) with preoperative localization studies, operative data (including intraoperative qPTH values and GP localization), and outcomes. Follow-up was complete (mean, 4.2 months).

Setting: University teaching hospital.

Patients: We studied 57 consecutive patients with primary hyperparathyroidism from December 1, 1999, through November 30, 2000. Of these, 51 underwent first-time PTX, and 6, reoperative PTX (rePTX).

Main Outcome Measures: Cure rate and morbidity after PTX or rePTX; sensitivity and accuracy of preoperative localization studies; prediction of cure from results of qPTH monitoring (comparing Nichols [≥50% fall from the highest baseline level and lower than the lowest baseline] or normal-limit [≥50% fall from first baseline level and lower than upper limit of the reference range] criteria); and value of GP localization.

Results: Patients were cured in 50 (98%) of 51 PTX and 6 (100%) of 6 rePTX for single adenomas (n=49), double adenomas (n=4), and multigland hyperplasia (n=3). Nichols criteria for qPTH monitoring correctly categorized 45 (92%) of 49 cured single adenomas 10 minutes after excision. Only 35 (71%) of these adenomas were correctly categorized as cured by means of the normal-limit criteria. In double adenomas, both sets of criteria in the 10-minute samples indicated unresected glands in only 2 of 4 cases. Preoperative sestamibi parathyroid scans correctly localized 38 (76%) of 50 single adenomas. The GP was used in 54 of 57 cases. All adenomas measured greater than 20% of background ex vivo, but 6 thyroid nodules also measured greater than 20% ex vivo. In double adenomas, the GP helped locate the second adenoma in only 2 of 4 cases. The GP was graded as crucial in 2 cases with dense scar (both rePTX), helpful in 12 (22%) of 54 cases (particularly in retroesophageal glands), confirmatory in 32 (59%), and not helpful in 8 (15%). The GP helped localize 3 (43%) of 7 glands not seen on sestamibi parathyroid scans.

Conclusions: Intraoperative qPTH monitoring confirmed cure in most cases. For single adenomas, use of the Nichols criteria for qPTH assessment allowed more accurate and faster confirmation than the normal-limit criteria. The GP was less useful but was crucial in 2 rePTX cases; it was not specific for parathyroid tissue. Both techniques have potential pitfalls that could result in surgical failure.

Arch Surg. 2002;137:659-669

Surgical treatment of primary hyperparathyroidism has a high success rate in experienced hands, with major series reporting 95% to 98% cure rates with traditional bilateral neck exploration.1,3 Because failures occur and because of a drive toward cost containment, shorter operative and recovery times, and more minimally invasive procedures, innovations have been investigated in parathyroid surgery. These have included unilateral exploration with guidance by means of a preoperative sestamibi parathyroid scan (SPS),7,9 minimally invasive radio-guided parathyroidectomy using a handheld gamma probe (GP),7,9 and intraoperative quick parathyroid hormone (qPTH) monitoring to demonstrate a rapid decrease in PTH level.10,14 Many reports have been published concerning the utility and the benefits of these various approaches, and many have included warnings of failures using these minimal approaches.15-17 At present, no consensus exists on the best way to approach parathyroidectomy for primary hyperparathyroidism.

We hypothesized that the incorporation of qPTH and GP localization into a routine academic surgical practice would
PATIENTS AND METHODS

OVERVIEW

This prospective study includes 57 consecutive patients undergoing operations for primary hyperparathyroidism at The University of Chicago Medical Center, Chicago, Ill, from December 1, 1999, through November 30, 2000. Bilateral explorations, using a small incision when possible, were performed in first-time operations; most reoperations were unilateral. All operations were performed under general anesthesia, and all patients were observed for at least 23 hours postoperatively as inpatients. All operations were performed by a single surgeon (E.L.K.) with the assistance of a surgical resident or fellow. Frozen sections of suspected abnormal parathyroid tissue were routinely obtained intraoperatively. We evaluated outcomes (alleviation of hypercalcemia, permanent laryngeal nerve injury, and permanent hypoparathyroidism) and results of preoperative localization studies, intraoperative GP localization, and intraoperative qPTH monitoring.

We used technetium Tc 99m sestamibi for preoperative dual-phase SPS of the neck and chest with planar images and, in some cases, single-photon emission computed tomography. Most patients underwent SPS at The University of Chicago, but some had the study performed at an outside hospital. We reviewed films and reports in all cases. A true-positive finding was defined as a scan that delineated the location of a single abnormal gland in a single region, with subsequent surgical confirmation and biochemical cure. In the case of multigland disease, the true-positive findings included scans that displayed all regions of overactivity found at the subsequent operation. If the scan missed 1 region, the finding was considered false negative. If the scan displayed a region of uptake that was not a hyperfunctioning parathyroid gland at surgery, the finding was considered false positive. All patients underwent preoperative high-resolution cervical real-time ultrasonography (UTS), most of them at The University of Chicago. Interpretation of UTS findings was similar to that of SPS findings. Magnetic resonance imaging and venous sampling were performed selectively in 2 of the reoperations.

Technetium Tc 99m sestamibi (20 mCi [740 MBq]) was given 1 to 2 hours before surgery in preparation for intraoperative GP scanning. Data on GP localization was collected on 54 of the 57 patients. Intraoperative GP localization was performed using a parathyroid probe (Navigator; US Surgical Corp, Norwalk, Conn). Probe measurements were recorded at the skin level, below the strap muscles, and in a directed fashion in areas of increased counts in deeper levels of the neck or where indicated by preoperative scans. Ex vivo measurements were recorded of excised specimens, as well as background levels in the resection bed. Ratios were calculated in all cases, as described by Murphy and Norman,14 using the following equation:

\[
\text{(Ex Vivo Counts/Background Counts)} \times 100
\]

The utility of GP localization was scored at the completion of each procedure on a 4-point, subjective scale in which 1 indicates crucial; 2, helpful/directive; 3, confirmatory; and 4, not helpful.

INTRAOPERATIVE qPTH MONITORING METHODS

The rapid PTH immunochemiluminometric assay was performed according to the protocol provided by the Nichols Laboratory (Nichols Institute Diagnostics, San Juan Capistrano, Calif), with the equipment and technician inside or just outside the operating room. Intraoperative qPTH data were collected for all 57 patients. Peripheral blood samples were collected via an antecubital intravenous line at the following times: after the induction of anesthesia but before the incision (baseline 1); after the incision but before resection of the gland (baseline 2); at excision; and at approximately 5 and 10 minutes after the excision. Additional samples were collected when necessary, particularly when multiple excisions were performed or when qPTH levels did not fall as expected. If peripheral blood samples could not be obtained, samples were drawn using the internal jugular vein via the operative field.

Because of the multiple published criteria for interpretation of qPTH results,9,10,12,13,14,15,16,17,20-24 the exact criteria by which to gauge qPTH results were unclear. We decided to prospectively compare 2 sets of criteria, one more rigid than the other, formulated from previously published recommendations. The criteria included the Nichols criteria, in which there is a greater than 30% fall from the highest preexcision baseline qPTH level and an absolute value lower than the lowest baseline level at a given time point,14,20 and normal-limit criteria, in which there is a greater than 50% fall from the initial baseline level and an absolute value lower than the upper limit of the reference range (hereafter referred to as the normal limit) for the qPTH assay (<65 pg/mL).12 Data were analyzed according to these criteria at 5 and 10 minutes after gland excision.

POSTOPERATIVE FOLLOW-UP

All patients underwent at least 2 determinations of serum calcium levels postoperatively, and at least 1 determination of PTH and calcium levels 1 week to 1 month postoperatively. Normalization of calcium level (reference range, 8.4-10.2 mg/dL [2.1-2.6 mmol/L]) was defined as a cure. Recurrent laryngeal nerve status was determined clinically. Follow-up was available in all cases.

The average age of the patients was 57 years (range, 16-81 years), and 43 (75%) were women. Mean preoperative serum calcium level was 11.0 pg/mL (2.8 mmol/L; range, 9.4-13.3 pg/mL [2.4-3.3 mmol/L]); mean preoperative intact PTH (iPTH) level, 137 pg/mL (range, 47-1694 pg/mL). Forty-nine patients (86%) had single adenomas resected at operation; 4 (7%), double adenomas; 3 (5%), multigland hyperplasia; and 1 (2%) was not cured, in whom the etiology of the hyperparathyroidism remains unclear. Six patients had previously undergone operations...
for hyperparathyroidism, all at outside institutions. Eight patients had previously undergone thyroid surgery of varying extent. Ten patients underwent concomitant thyroid surgery at the time of the current parathyroid exploration. Mean gland weight at excision was 1321 mg (range, 38-9000 mg); median weight was 1000 mg.

Of the 57 patients, 56 were cured (98%). All 6 patients undergoing reoperation were cured after resection of a single adenoma. One patient with previous thyroid surgery was not cured, despite bilateral neck exploration with completion thyroidectomy and biopsies of 2 normal-appearing parathyroid glands. That patient remains hypercalcemic and with elevated postoperative iPTH levels. For the purposes of calculating test sensitivity/accuracy, that case is assumed to be a single missed adenoma. Follow-up ranged from 1 week to 19 months (mean, 4.2 months). No permanent hypoparathyroidism or recurrent nerve injuries occurred in this series.

PREOPERATIVE LOCALIZATION STUDIES

All patients underwent preoperative SPS (Table 1). In patients with single adenomas, SPS correctly identified only the abnormal gland in 38 (76%) of 50 cases. In 7 cases (14%), no hyperfunctioning gland was identified on SPS images. In 4 cases (8%), more than 1 lesion was seen on delayed SPS images. In each of these 4 cases, 1 of these lesions was the actual abnormal parathyroid gland.

Additional abnormalities on SPS included the following: (1) unknown, since unilateral exploration in the reoperative setting was curative after excision of the most suspicious SPS lesion; (2) thyroid nodule, which measured greater than 20% of background ex vivo; (3) unknown, because of cure after resection of 1 lesion, with no abnormal tissue found at second site; and (4) unknown, with 3 abnormalities on SPS, cured after resection of 1 area, and no abnormalities found at other sites. In the failed operation, SPS showed an area of increased uptake on the right side, but no parathyroid gland could be found at operation. A completion right-sided thyroidectomy was performed, and colloid nodular disease was found. A postoperative SPS no longer shows increased uptake on the right side, so this is thought to represent a false-positive initial SPS finding.

In the 4 patients with double adenomas, preoperative SPS showed both adenomas in only 1 case. In 2 cases, a suspicious area was seen that was 1 of the adenomas, but the second adenoma was not seen. In the fourth patient, no abnormalities were seen on SPS.

In the 3 patients with multigland hyperplasia, various SPS results occurred. In the first case, an abnormal parathyroid and a colloid nodule of the thyroid were seen. The other abnormal parathyroid glands were not seen. In the second case, no abnormalities were seen on SPS. In the final case, multiple glands were seen on SPS, although the largest (which was cystic) was not detected.

All patients underwent preoperative UTS (Table 1). In patients with single adenomas, UTS findings were true positive in 32 (64%) of 50 cases. In 2 cases (4%), UTS showed 2 lesions, one an adenoma and the other not. Two other UTS findings were false positive, and 13 (27%) of 49 were false negative. The UTS findings were positive in 3 of 7 single adenoma cases with false-negative SPS findings. In the failed operation, UTS showed a possible left-sided gland; none was found despite extensive exploration. In the 4 patients with double adenomas, UTS revealed both parathyroid adenomas in 1 case, 1 of 2 parathyroid adenomas in 1 case, and no enlarged glands in 2 cases. In the 3 patients with multigland hyperplasia, UTS findings were normal in 2 cases. In the third, UTS revealed a cystically enlarged parathyroid gland, but no other glands.

**qPTH MONITORING**

Data from intraoperative qPTH monitoring were recorded in all cases. Data were analyzed at 5 and 10 minutes after gland excision.

For the 49 patients with single adenomas who were classified as cured, the Nichols criteria correctly categorized 40 (82%) as cured at 5 minutes and 45 (92%) as cured at 10 minutes after excision (Figure 1 and Table 2). Of the 4 patients not categorized as cured at 10 minutes, 3 had 5-minute qPTH levels higher than the highest baseline level (29%-164% higher). These dropped at 10 minutes, but not below 50% of the highest baseline level. All 3 had levels of less than 50% of the highest baseline level documented before leaving the operating room at 20 minutes or longer. The fourth patient had a delayed decrease

<table>
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<th>True Negative</th>
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<th>Accuracy, %</th>
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* A failed case was included as a single adenoma (assumed).*
in qPTH level and, although not below 50% of the highest baseline level at the end of the operation, the patient was cured postoperatively as documented by means of a calcium level of 10.2 mg/dL (2.6 mmol/L) and an iPTH of 14 pg/mL on postoperative day 7. In contrast, only 35 (71%) of the patients were correctly categorized as cured using the stricter normal-limit criteria at 10 minutes postexcision (Figure 2 and Table 2). Of 14 patients not meeting the criteria at 10 minutes, 10 had qPTH levels that did not fall below 50% of the initial baseline level, and 12 did not have levels below 65 pg/mL (Figure 2B). No false-positive values occurred in the single-adenoma group. In the failed exploration, the qPTH level remained elevated above the preincision baseline level for the duration of the case (Figure 3). This finding is categorized as true negative under both sets of criteria, correctly reflecting unresected abnormal parathyroid tissue. The sensitivity and accuracy of the Nichols criteria in patients with single adenomas were 92% and 92%, respectively, whereas those of the normal-limit criteria at 10 minutes were 71% and 72%, respectively.

The results of qPTH monitoring in patients with multigland disease were mixed. In the 3 patients with multigland hyperplasia, the results of qPTH monitoring at 10 minutes after excision of the first abnormal gland under both sets of criteria were true negative in all cases. Figure 4A shows the results using the Nichols criteria. All 3 cases of multigland hyperplasia remained above the 50% mark at 10 minutes, reflecting the true-negative status. For double adenomas, the results of qPTH monitoring were less clear and need to be addressed on a case-by-case basis. Overall, at 10 minutes after the first excision, both sets of criteria showed false-positive results for 2 cases of double adenoma and true-negative results for 2 (Figure 4B and Table 2). This represents a 50% accuracy rate in double adenomas at 10 minutes after the first excision. Of the 2 false-positive findings in cases in which the qPTH value was misleading at 10 minutes, one (case A; Figure 5A) involved a marked decrease of 95% of the highest baseline level at 10 minutes after resection of a 3100-mg parathyroid adenoma. In the course of further exploration of the contralateral neck, a second enlarged parathyroid gland was encountered. It was removed, and pathological examination revealed a 1.1-cm parathyroid adenoma with rim tissue (no weight obtained). Although no other qPTH values were obtained during the case, the iPTH level 8 days postoperatively was 8 pg/mL, and the calcium level was 9.3 mg/dL (2.3 mmol/L). In the other case with a false-negative finding (case B, Figure 5B), a decrease of 69% of the highest qPTH baseline level at 10 minutes after resection of a 100-mg parathyroid adenoma was measured. Further samples were obtained while a thyroidectomy was performed. At 34 minutes after the first excision, the qPTH level rose. A second enlarged parathyroid gland was then found in the contralateral neck. Excision of this 160-mg parathyroid adenoma led to a decrease of 74% of the highest baseline level at 10 minutes, reflecting the true-negative status.

Table 2. Results of Intraoperative qPTH Monitoring at 10 Minutes After Excision*

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<tr>
<th>Findings</th>
<th>Total</th>
<th>True Positive</th>
<th>False Negative</th>
<th>False Positive</th>
<th>True Negative</th>
<th>Sensitivity, %</th>
<th>Accuracy, %</th>
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<tr>
<td>Total</td>
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*qPTH indicates quick parathyroid hormone.
†Failed case was included as a single adenoma (assumed).
In 1 case (case C, Figure 5C), a 5-minute sample was below 50% of the highest baseline level, but the qPTH level rose at 10 and 15 minutes after resection of a 1300-mg parathyroid adenoma. Further exploration revealed a second enlarged gland in the contralateral neck, which was a 69-mg parathyroid adenoma on pathological examination. The qPTH level fell substantially after the second excision.

In 18 (37%) of the 49 single adenoma cases, the second baseline qPTH level (from samples drawn after manipulation of the neck and possibly of the parathyroid adenoma) was substantially higher than the first baseline level. To further investigate this phenomenon, qPTH data were gathered before incision in a separate patient (not part of this consecutive series) after external massage of the area of the neck with suspicious SPS findings. As seen in Figure 6, the qPTH level nearly doubled after external massage, then fell to a level below the first baseline level and below 50% of the peak level after 15 minutes. During resection to remove the adenoma, the level rose again to equal the postmassage level. After excision, the levels fell dramatically, meeting both sets of criteria.

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Subjective scoring of GP usefulness demonstrated 2 cases (4%) in which the GP proved to be crucial to the success of the operation, 12 (22%) in which it was helpful, 32 (59%) in which it confirmed operative findings, and 8 (15%) in which it was not helpful. The 2 cases scored as crucial were both reoperations for hyperparathyroidism, with dense scar and extremely obscured anatomy. In both of these cases, the GP was used extensively to direct the dissection of the adenoma. Several patterns can be seen in the analysis of the 12 helpful cases. Five of these cases were also in a reoperative setting, 1 after a previous parathyroid exploration and 4 after previous thyroid surgery. By using a lateral approach, the GP helped guide the dissection. In 7 of the helpful cases, the ad-
enoma was in an ectopic position, including 4 retroesophageal glands, 1 intrathymic gland, 1 gland deep in the tracheoesophageal groove, and 1 gland (in a double adenoma case) nearly anterior to the trachea. Three of the helpful cases were in situations in which no parathyroid adenoma was seen on the preoperative SPS. All 3 of these glands were in ectopic locations and were not significantly different in size than most glands detected by SPS.

In most cases (32 [59%]), the GP merely confirmed an easily discovered/dissected parathyroid adenoma. In 3 of the double adenoma cases, the probe confirmed 1 abnormal gland, but was not helpful in identifying the second gland. In the fourth case, the probe helped in localizing the second gland after a rebound in the qPTH level. The GP was not helpful in any of the 3 cases of multigland hyperplasia, and it did not provide any directive guidance in 5 other single-adenoma cases (including the failed operation). The GP helped localize 3 (43%) of 7 glands not seen on SPS.

Figure 4. A, Percentage of change of quick parathyroid hormone (qPTH) level from the highest baseline level in multigland hyperplasia cases (n=3). At 10 minutes after excision, qPTH levels correctly reflected persistent disease in all 3 cases. B, Percentage of change of qPTH level from the highest baseline level in double-adenoma cases (n=4, all cured). At 10 minutes after excision, qPTH levels in 2 cases correctly reflected persistent disease. In 2 cases, qPTH levels below 50% of the highest baseline level falsely indicated a cure.

Figure 5. A, Case A met cured criteria after excision of a 3100-mg adenoma. Contralateral exploration showed a second enlarged gland, but no further quick parathyroid hormone (qPTH) monitoring data were collected. B, Case B met cured criteria at 10 minutes after the first excision (100-mg parathyroid adenoma [PTA]). However, a later qPTH level checked during contralateral thyroidectomy showed a rise and a second (160-mg) PTA was found. The qPTH levels then dropped. C, Despite a drop in qPTH levels at 5 minutes after excision of a 1300-mg adenoma, samples at 10 and 15 minutes indicated persistent disease in case C. Excision of a second gland (69-mg PTA) resulted in a drop that met criteria for cure. D, The qPTH measurements after excision of a 600-mg parathyroid adenoma did not meet criteria for cure at 10 minutes in case D. Additional dissection (using the gamma probe) localized the abnormal gland (100-mg PTA), excision of which led to cure.
Ex vivo counts were recorded on nearly all parathyroid specimens removed and on some other excised tissues. Ratios of ex vivo tissues to background were calculated. All adenomas measured greater than 20% of background ex vivo. Cases with single adenomas had a mean ex vivo ratio of 99% (range, 29%-235%). Adenomas in the double-adenoma cases had a mean ex vivo ratio of 71.5% (range, 26%-168%). Not enough data were recorded to make a statement about the cases with multigland hyperplasia. Other tissues also measured greater than 20% of background. Of 7 thyroid nodules counted ex vivo, 6 measured greater than 20% of background (mean, 56%; range, 24%-143%), and 1 measured 18% of background. These encompassed a variety of thyroid abnormalities, including 4 colloid nodules of greater than 20%, 1 follicular adenoma of 39%, and 1 medullary cancer of 39%.

An interesting case, not part of this consecutive series, illustrates the problem of false-positive findings. An 83-year-old woman with primary hyperparathyroidism underwent preoperative imaging studies. The SPS was read as strongly suspicious on the right side for a parathyroid adenoma (Figure 7A). A UTS finding similarly was read as suspicious on the right side for a parathyroid adenoma immediately adjacent to the thyroid gland (Figure 7B). At surgery, through a 2-cm incision, a nodule was detected with a hot GP finding, and this was removed. The qPTH level did not fall. Results of frozen-section analysis showed hyperplastic thyroid nodule with Hurthle cell features. At bilateral neck dissection, a 200-mg parathyroid adenoma was found and removed from the left side of the neck (not detected by means of SPS or GP). After this, the qPTH level dropped to 20 pg/mL, a decrease of 74% of the highest baseline level, signifying a cure.

The purpose of this study was to evaluate the utility of new technical innovations in parathyroid surgery in the hands of an experienced endocrine surgeon. How would these approaches fit into practice, particularly if a unilateral minimally invasive radio-guided parathyroidectomy approach, as described by Norman and Chheda9 and others8,9 was not planned? Does the reliability of these techniques ensure that a unilateral approach is warranted?

In evaluating the usefulness of the GP, one must consider the following potential advantages: (1) Localizing the parathyroid adenoma, (2) decreasing the number of frozen sections (and thereby the cost), (3) decreasing operative and recovery times (and thereby the cost), and (4) ensuring cure.6,9,25 The second issue was not specifically addressed in this study. In cases of single adenomas, the GP localization was most often confirmatory, with the probe revealing high counts over a gland that was easily found. In general, the GP was more likely to be of value in harder cases. In 2 reoperative parathyroidectomies in which there was dense scar, the probe was crucial in directing the dissection of the gland. In 5 other reoperations (1 previous parathyroidectomy and 4 previous thyroid operations), the GP also helped. Others have reported similar results in the reoperative setting.26-28 The GP also proved helpful in dissection of 7 ectopic glands, deep in the neck (retroesophageal and tracheoesophageal groove) and in the thyms.

The GP helped in several cases in which the preoperative SPS showed no abnormalities (3/7), demonstrating that the intraoperative GP use may be helpful in cases that do not localize on preoperative SPS. The GP was not helpful in 3 of 4 cases of double adenoma, although it did help locate the second adenoma in 1 case.

Proposed advantages of intraoperative qPTH levels include assurance of cure by documenting the appropriate fall of qPTH levels, preventing failures by identifying cases in which qPTH levels do not fall appropriately, and assisting in localization of hard-to-find glands by drawing bilateral internal jugular vein samples to establish laterality intraoperatively.19,20 The large number of criteria for evaluation of change in qPTH levels pre-
sent a problem, as previously reported. Table 3 summarizes a number of published reports on qPTH monitoring. Critical evaluation reveals variations in the number and timing of baseline values (preincision, postincision, after strap muscles split, and after the thyroid is mobilized), the number and timing of postexcision values (5, 7, 10, 15, and 20 minutes), and the degree of change required for a confirmation of cure (50% decrease from the first baseline level, 50% decrease from the highest baseline level, below the upper normal limit, and 65% decrease from the baseline level).8,9,11-13,19,22-24 A kinetic model has been formulated also.21 The numerous criteria available led us to decide to formulate 2 sets of criteria for prospective evaluation, one more rigid than the other, by which to evaluate the results. The Nichols criteria were based on the recommendations of the kit provider (Betsy Siekierski, oral communication, January 2000) and the published reports of Irvin et al11,20 and Garner and Leight,14 among others. This set of criteria recognizes that there can be significant changes in qPTH level with manipulation of the neck (Figure 6), which can result in immediate postexcision levels that are higher than the preincision baseline levels. When we used the Nichols criteria, overall sensitivity was 92% and accuracy was 89% at samples taken 10 minutes after gland excision (Table 2). Sensitivity and accuracy at 5 minutes after excision were poorer. The failures to correctly predict cures at 10 minutes occurred in several settings. In cured patients with single adenomas, 4 cases were categorized as not cured at 10 minutes after excision; 3 had postmanipulation rises in qPTH levels that took longer than 10 minutes to fall to less than 50% of the highest

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of Baseline Levels</th>
<th>When Baseline Level(s) Drawn</th>
<th>Determination of Cure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irvin et al11,20</td>
<td>2</td>
<td>Preincision and during dissection</td>
<td>Decrease of ≥50% at 5 and/or 10 min after excision compared with highest baseline level</td>
</tr>
<tr>
<td>Chen et al13</td>
<td>1</td>
<td>Unclear when drawn</td>
<td>Decrease of ≥50% at 5 min after excision</td>
</tr>
<tr>
<td>Carty et al12</td>
<td>1</td>
<td>From internal jugular after division of median raphae</td>
<td>Decrease of ≥50% and below upper limit of normal at 15 min after excision</td>
</tr>
<tr>
<td>Thompson et al22</td>
<td>1</td>
<td>Unclear when drawn</td>
<td>Decrease of ≥50% at 20 min after excision</td>
</tr>
<tr>
<td>Starr et al12</td>
<td>2</td>
<td>Preincision and after thyroid exposure</td>
<td>Decrease of ≥65% or below upper limit of normal at 5 and/or 10 min after excision</td>
</tr>
<tr>
<td>Libutti et al21</td>
<td>1</td>
<td>Unclear when drawn</td>
<td>Kinetic analysis on results from 5 and 10 min postexcision samples</td>
</tr>
<tr>
<td>Patel et al24</td>
<td>1</td>
<td>At induction</td>
<td>Decrease of ≥50% at 7 min after excision</td>
</tr>
<tr>
<td>Gordon et al19</td>
<td>1</td>
<td>Before skin incision</td>
<td>Decrease of ≥50% at 10 min after excision</td>
</tr>
<tr>
<td>Garner and Leight14; Flynn et al8</td>
<td>2</td>
<td>Preincision and preexcision</td>
<td>Decrease of ≥50% at 10 min compared with highest baseline level</td>
</tr>
</tbody>
</table>

qPTH indicates quick parathyroid hormone.

Figure 7. A, Sestamibi parathyroid scan (SPS) in a patient with a parathyroid adenoma. The SPS finding was read as positive on the right side, and gamma probe findings confirmed high counts, but exploration revealed a colloid nodule with Hürthle cell changes. A parathyroid adenoma was excised from the left side of the neck. B, Cervical ultrasonography in the same patient. The scan was read as suspicious for parathyroid adenoma adjacent to right lobe of thyroid. Trans indicates transverse.
baseline level; and 1 case demonstrated an extremely slow rate of fall. Other failures of qPTH measurement included 2 false-positive findings in double adenomas, in which the 10-minute samples incorrectly predicted cure. Only through additional dissection, which led to identification of a gland in one case and to a rebound rise of qPTH level in another, were these second adenomas discovered. No false-positive findings occurred in patients with multigland hyperplasia in this study.

When we used the normal-limit criteria, overall sensitivity and accuracy at 10 minutes postexcision were lower, at 71% and 72%, respectively (Table 2). This set of criteria was certainly more rigorous, requiring a fall to 50% of the initial (often lower) of the 2 baseline levels and requiring a fall below the upper normal limit. These strict criteria incorrectly categorized many cured cases at 10 minutes as failures in both areas. At completion of this study, the Nichols criteria appear to be quite effective, although not perfect, in identifying both cures and persistent disease.

The importance of the double-adenoma cases in this series is unclear. Although histological data indicate that double adenomas were present in all 4 cases, whether these were indeed all functioning adenomas is unknown. In case A, the second adenoma was found during contralateral thyroidectomy. No functional data exist because no additional qPTH levels were measured after the first excision resulted in a profound fall compared with the preoperative level. In case B, a rise in qPTH level was detected when the level was checked during contralateral thyroidectomy. Manipulation of the gland might have led to that rise, but whether the gland was hyperfunctioning at rest cannot be known. Histological examination showed the second lesion excised to be a parathyroid adenoma. Cases C and D are more convincing, as the 10-minute levels did not indicate cure, and the levels dropped after an additional abnormal parathyroid gland was sought and found.

What, then, are the pitfalls? For intraoperative qPTH monitoring, they include a risk for false-negative findings in patients with simple adenomas and a risk for false-positive findings in patients with double adenomas. Our approach when levels fail to fall below 50% of the highest baseline level at 10 minutes, in first-time operations, has been to continue to identify other glands and to draw a subsequent sample to look for an appropriate fall. Persistence of an elevated qPTH level requires a full, bilateral exploration, using preoperative and intraoperative localization studies if possible. For surgeons using a minimally invasive approach under local anesthesia in patients with abnormal preoperative SPS findings, the implications of a false-negative finding are much greater in the setting of a planned bilateral exploration. Surgeons using a minimally invasive radio-guided parathyroidectomy approach with qPTH monitoring need to have a predetermined algorithm for how to proceed in the face of a qPTH level that does not meet criteria for a cure. This might include rechecking another qPTH level at a later time, converting to a general anesthetic and a bilateral exploration, or closing the neck and observing postoperative laboratory findings, with the patient warned preoperatively of the possible need for further surgery in the future.

For intraoperative GP localization, the pitfalls are several. We found that false-positive results occur, principally because thyroid nodules and parathyroid adenomas can retain sestamibi late. Furthermore, the 20% rule was not specific for parathyroid adenomas in our hands, with several thyroid nodules measuring above 20%. The GP failed to help locate the second adenoma in 3 (75%) of the 4 double-adenoma cases.

**CONCLUSIONS**

Intraoperative qPTH level confirmed cure in most cases and identified unresected tissue in others. The routine use of qPTH monitoring gave the surgeon an elevated confidence of cure at completion of the operation. The Nichols criteria at 10 minutes postexcision allowed for more accurate and faster confirmation than did normal-limit criteria, but both required late sampling for reliability in some cases and both were misleading in 50% of double adenomas. The problems of variability of the baseline findings and a potential false-negative cure after manipulation of the adenoma (Figure 6) must also be understood by the operator. The GP localization was less helpful in most cases, but proved crucial in several cases of reoperation and was helpful in other reoperations and in some cases with ectopic glands. The GP localization was not specific for parathyroid adenomas, as thyroid nodules caused confusion. Both techniques have potential pitfalls that could lead to surgical failure in primary hyperparathyroidism if these issues are not understood. They do not offer a panacea for the inexperienced surgeon, and they do not replace the judgment of an experienced endocrine surgeon.

This study was supported in part by the Nathan and Frances Goldblatt Society for Cancer Research, Chicago.

This paper was presented at the 109th Scientific Session of the Western Surgical Association, San Antonio, Tex, November 12, 2001.

We thank Victoria Staszak, RN, MS, MBA, for her assistance in the care of these patients.

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**REFERENCES**

9. Goldstein RE, Blevins L, Delbeka D, Martin WH. Effect of minimally invasive
Risk of double adenomas

Richard A. Prinz, MD, Chicago, Ill: The treatment of hyperparathyroidism used to be simple and straightforward. Find an experienced parathyroid surgeon, and a 98% chance of cure was guaranteed. Despite this near-perfect record, parathyroidectomy has been a fertile area for a number of innovative techniques. Technology can be addictive and it is always expensive. Because of this, we have to be certain it is providing real benefit when we incorporate it in our care of patients. I use both intraoperative sestamibi scanning and intraoperative qPTH monitoring. Both have pitfalls, either in their performance, or more commonly, in their interpretation, so experience is needed if the best results are to be had.

I limit the use of intraoperative sestamibi scanning to the reoperative setting, where I take any and all help I can get. I do not find its expense justifies its use in primary operations, especially if preoperative ultrasound and/or sestamibi scanning have already shown where the enlarged gland is located. I use intraoperative qPTH in all patients and have found it extremely helpful in confirming single-gland disease and identifying double adenomas and multiple-gland disease. I was never very good at math, so the formulas used to interpret these tests are difficult for me, especially in the operating room. My goal is to have the intraoperative PTH level back in the normal range and preferably in the low-normal range before I am satisfied that the patient is cured. I will get delayed samples beyond 10 minutes after removal, if need be, to achieve this. The wait can be tedious, but it is usually less than the time it took to get the manuscript to me. I use qPTH in conjunction with preoperative localization to perform a focused minimally invasive parathyroidectomy. The benefits are better cosmesis, less operative trauma, and earlier discharge. The added cost is counterbalanced by eliminating the need for frozen sections.

Now that I have explained what I do, I would like to know if and how your operative approach to patients with hyperparathyroidism has changed after evaluating these techniques. Are you still going to do bilateral explorations and routine frozen section evaluations? If so, I see little need or value for the intraoperative techniques. Can you share your results with parathyroidectomy before using these technologies and if they have been improved in any way since you have been evaluating them? I believe you have increased the cost of the operation and probably the time with no appreciable improvement in outcome. Dr George Irvin, who has championed intraoperative qPTH, claims that there are enlarged but not functioning parathyroid glands. Do you agree with this hypothesis? I think it is pertinent in at least one of your failed double adenomas.

Finally, you have used postoperative normalization of serum calcium levels as your measure of the success of your operation, which is standard. However, you also measured postoperative PTH levels, which you did not share with us. As many as 30% of my patients will still have an elevated PTH value 1 month after operation. Is this your experience and, if so, how do you explain it?

Theodore X. O’Connell, MD, Los Angeles, Calif: I have a question similar to Dr Prinz’s, and that is, what is the clinical value added of the qPTH? It is relatively expensive, it is time consuming, and in this report, it can be misleading. So the only advantage would be that it tells you something that you don’t already know. If you’re 98% accurate with your operation, to tell you that you’re accurate, this gives you a pat on the back, but doesn’t really help you or the patient.

How many times after you took out an adenoma and you thought it was only a single adenoma was the qPTH abnormal, which you explore additionally, and you found additional adenomas?

Steven A. Dejong, MD, Maywood, Ill: I have 2 questions. The authors report on patients with positive localizing studies. Is there a role for using intraoperative PTH levels in patients with negative preoperative localizing studies and, if so, how should it be used?

Second, would your results and opinions of these described pitfalls change if the arbitrary threshold of a 50% drop in PTH levels were changed to a 70% or 75% decrease?
incidence of double adenomas in this series seems a little low. In our series at University of California–Davis, we have an incidence of about 12% to 13%, and this brings to rise other questions about whether all of the normal parathyroids were visualized in your bilateral explorations. Then, although you call your operations cures 98% of the time, what was the rate of recurrent hyperparathyroidism at some point down the road?

Finally, there is no question that intraoperative GP and PTH analysis are of value in reoperative parathyroid surgery, but I would like to know from the authors their final conclusions about their use at initial operations. Are we really helping our patients by doing this at a routine initial operation?

Eberhard A. Mack, MD, Madison, Wis: I also would like to echo what Dr Prinz has indicated. In most situations, the cost-benefit ratio may be questionable. However, in reoperative neck cases, and especially for intrathoracic adenomas, we find these additional studies are very helpful to make sure that the adenoma has been excised completely.

Dr Kaplan: Thank you very much for all of the discussions. I especially thank Dr Prinz for his comments. In the early 1990s, we published the results of 300 cases of primary hyperparathyroidism with a bilateral approach. At that time we achieved a 98.3% cure rate with a mean follow-up of about 4 or 5 years, if I remember correctly. In the early 1980s, we published another 100 operations with a 97.5% success rate. So the cure rates in our hands before using these new techniques had been very high. While the hypothesis stated in this paper was that we expected our hands before using these new techniques had been very high. But I would like to know from the authors their final conclusions about their use at initial operations. Are we really helping our patients by doing this at a routine initial operation?

I agree with Dr Prinz that the GP is not the panacea that some authors have described it to be. In many routine cases, it seemed to be confirmatory rather than essential in localization. If one is not schooled in parathyroid surgery, I don't think that this technique will change things considerably. It may in fact lead to more failed operations in this setting. However, we have found this helpful in reoperations, and the probe definitely has a place in these cases. In fact, I think that for the very experienced parathyroid surgeon, the harder the case (fibrosis, etc), the more useful the GP is. I definitely will continue to use this technique in neck reoperations.

How useful is intraoperative PTH determination? It certainly gives a great deal of assurance to the surgeon that a cure has been attained, but, as we stated, 10-minute sampling is not long enough in 8% of patients. It definitely was critical in 2 of 4 double adenoma cases, which means that it greatly aided in curing at least 4% to 5% of patients and probably more. Concerning the costs, we try to do 2 or 3 parathyroid operations on the same day using one “kit,” which diminishes the expenses.

Is this technique necessary in routine cases? Probably not, but it certainly adds to one’s confidence that a cure has been attained. In double adenomas, when the intraoperative PTH falls to low levels after removal of 1 lesion, is it possible that the second gland is functional? Our studies suggest that this may not be the case, for when we followed one such patient, after an initial drop of greater than 50% at 10 minutes, there was a rise to high levels again at a later time. This suggests to me that the second gland may have been temporarily suppressed but then functioned very well over time.

Finally, I would like to stress 2 points. First of all, many thyroid nodules can take up sestamibi more so than do parathyroid adenomas in the same cases. This is a real problem for those who use the GP and do not do frozen-section analyses. Lastly, I am concerned that manipulation of an enlarged parathyroid gland may cause a rise in PTH that can fall to normal baseline values or below without removal of a parathyroid lesion. This may also be the cause of some failed operations.

ARCHIVES OF INTERNAL MEDICINE

Women’s Interest in Chemoprevention for Breast Cancer

Lori A. Bastian, MD, MPH; Isaac M. Lipkus, PhD; Maggie N. Kachibhatia, PhD; Haoling Holly Weng, MHS; Susan Halabi, PhD; Paula D. Ryan, MD, PhD; Celette Sugg Skinner, PhD; Barbara K. Rimer, DrPH

Background: Chemoprevention is the use of pharmacologic or natural agents to inhibit the development of cancer. Tamoxifen citrate is the only approved chemopreventive agent for breast cancer. We sought to determine whether women are interested in taking a drug to prevent breast cancer and to assess the relationship between objective and subjective breast cancer risk and interest in chemoprevention.

Methods: We conducted telephone interviews (November 3, 1997, to May 6, 1998) among a community sample of women aged 40 to 55 years enrolled in a randomized controlled trial to evaluate the efficacy of a tailored mammography decision aid. Objective breast cancer risk was measured using the 5-year Gail score. Subjective breast cancer risk was measured using perceptions of absolute risk, perceptions of comparative risk, and worry about getting breast cancer. At 12-month follow-up (November 2, 1998, to July 20, 1999), we measured interest in taking a drug to prevent breast cancer.

Results: Among the 1273 women surveyed, 23% were interested in taking a drug to prevent breast cancer; 8% were potentially eligible for tamoxifen therapy (5-year Gail score ≥1.66%). Eligibility for chemoprevention, based on the 5-year Gail score, was not associated with interest in taking a drug to prevent breast cancer. Women who were worried about breast cancer were 3 times more likely to be interested in taking a drug to prevent breast cancer than those who were not worried.

Conclusion: Women’s interest in chemoprevention might arise more from worries about getting breast cancer than from their objective risk factors. (2001;161:1639-1644)

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