Novel Criteria for Parathyroid Hormone Levels in Parathyroid Hormone–Guided Parathyroid Surgery

Robert de Vos tot Nederveen Cappel, MD; Nicole Bouvy, MD, PhD; Wouter de Herder, MD, PhD; Yolanda de Rijke, PhD; Hans van Toor; Jaap Bonjer, MD, PhD

Parathyroidectomy is the only cure for hyperparathyroidism. The traditional surgical approach involves a bilateral neck exploration to identify all parathyroid glands and remove grossly enlarged ones. Using this approach allows experienced endocrine surgeons to cure 97% to 99% of patients undergoing their first parathyroidectomy.1

Primary hyperparathyroidism is generally caused by a solitary adenoma, although 15% of patients have multiple gland disease.2

Using localizing methods such as technetium-99m sestamibi and ultrasonography, minimally invasive surgery can be performed in the case of a single hyperfunctioning adenoma.3–6 Bilateral surgery is required when multiple gland disease is present in primary hyperparathyroidism and inevitable in cases of secondary or tertiary hyperparathyroidism or multiple endocrine neoplasia (MEN) I/IIa syndromes. Most of these disorders are caused by 4 hyperplastic glands, but variations of 2 to 8 glands have been reported.7 Preoperative and perioperative discrimination between uniglandular disease and multiglandular disease remains the key problem in parathyroid surgery.

Measuring parathyroid hormone (PTH) levels perioperatively (quick PTH [qPTH]) was introduced in the early 1990s as a tool to determine whether resection of parathyroid tissue was sufficient.5,9 A 50% reduction of qPTH value 5 minutes after removal of all hyperfunctioning parathyroid tissue is generally assumed to indicate complete parathyroidectomy. Hence, further exploration of the neck would be unnecessary. However, various authors have reported postoperative hypercalcemia in spite of an apparent sufficient drop of qPTH levels during surgery of the neck.10–12

The purpose of this consecutive study was to determine whether novel criteria for decrease of perioperative qPTH levels can improve the accuracy of perioperative qPTH-guided parathyroidectomy.

PATIENTS AND METHODS

From February 2000 to February 2003, all consecutive patients eligible for parathyroidectomy for hyperparathyroidism at our institution were included in this prospective study. Patients with primary hyperparathyroidism, as well as patients with secondary or tertiary hyperparathyroidism or MEN I/IIa disease, were entitled to qPTH measurement during surgery.

Sequential sestamibi scintigraphy was done routinely. Planar images were collected at 15, 90, and 150 minutes after intravenous administration of 370 MBq sestamibi. Single photon emission computed tomogram images were documented at 30 minutes after injection of the radiofarmacon. Ultrasonography was only performed in some patients undergoing first explorations of the neck. In patients with either persistent or recurrent hyper-
Results of 110 quick parathyroid hormone (qPTH)–guided surgical interventions for hyperparathyroidism on 100 patients. PHP indicates primary hyperparathyroidism; SHP, secondary hyperparathyroidism; THP, tertiary hyperparathyroidism; and MEN, multiple endocrine neoplasia.

RESULTS
A total of 100 patients underwent 110 parathyroid surgeries with qPTH monitoring. Of these 100 patients, 72 had primary hyperparathyroidism and 28 had secondary or tertiary hyperparathyroidism or MEN I/IIa disease. The average age of all patients was 53 years (range, 10–91 years), and 70 (70%) were female. The Figure presents the results of surgical interventions performed in both groups.

Primary Hyperparathyroidism (n = 72)
Sixty-three patients did not have a history of neck surgery. Fifty-eight (92%) of them were cured after the first surgical intervention, most (46/58) by unilateral exploration. Furthermore, 10-minute samples were taken until the criteria of decline were reached. If peripheral blood samples could not be obtained, samples were collected from the internal jugular vein via the operative field.

The qPTH assessment was carried out with use of a solid-phase, 2-site, quick chemiluminescent enzyme immunometric assay (IMMULITE 1, DPC-Biermann, Los Angeles, Calif) and results were available in the operating room within 20 to 30 minutes. The reference range of qPTH measurement with this assay was 12 to 72 ng/mL.

In conventional bilateral neck surgery, performed in secondary and tertiary hyperparathyroidism and MEN I/IIa disease, an attempt was made to visualize all 4 glands and subsequently perform subtotal parathyroidectomy, leaving a remnant of 100 mg at a site accessible for reexploration in case of recurrent disease.

Parathyroidism, ultrasonography was done routinely. Computed tomography of the chest was performed to identify ectopic parathyroid tumors in patients with persistent or recurrent hyperparathyroidism.

In cases of primary hyperparathyroidism, unilateral explorations were attempted in patients with a single positive spot of increased uptake on the sestamibi scan. Surgery was performed through a 5-cm standard Kocher incision 4 cm cranially to the jugular notch or by a lateral endoscopic approach, as described by Henry et al. Patients with negative preoperative imaging had a standard open approach. The right side of the neck was routinely explored first.

Intraoperative blood samples for qPTH measurements were drawn from a peripheral vein. A preoperative sample was taken after induction of anesthesia and before manipulation of the enlarged parathyroid gland(s), subsequently followed by sampling 5 (t = 5) and 10 (t = 10) minutes after resection of parathyroid tissue (t = 10). Furthermore, 10-minute samples were taken until the criteria of decline were reached. If peripheral blood samples could not be obtained, samples were collected from the internal jugular vein via the operative field.

The qPTH assessment was carried out with use of a solid-phase, 2-site, quick chemiluminescent enzyme immunometric assay (IMMULITE 1, DPC-Biermann, Los Angeles, Calif) and results were available in the operating room within 20 to 30 minutes. The reference range of qPTH measurement with this assay was 12 to 72 ng/mL.

Preoperative and postoperative laryngoscopy was performed to evaluate injury of the recurrent laryngeal nerve. Patients were considered cured when normocalcemic blood samples were obtained at least 6 months postoperatively.

In conventional bilateral neck surgery, performed in secondary and tertiary hyperparathyroidism and MEN I/IIa disease, an attempt was made to visualize all 4 glands and subsequently perform subtotal parathyroidectomy, leaving a remnant of 100 mg at a site accessible for reexploration in case of recurrent disease.

Primary Hyperparathyroidism (n = 72)
Sixty-three patients did not have a history of neck surgery. Fifty-eight (92%) of them were cured after the first surgical intervention, most (46/58) by unilateral exploration. Furthermore, 12 of 58 patients were cured by 1 surgical procedure but needed bilateral exploration. Reasons for bilateral surgery in these 12 patients were misdirection or lack of detection by preoperative imaging techniques (n = 5); concomitant contralateral thyroid enlargement, thyroid nodules, or thyroiditis (n = 4); double adenoma bilaterally (n = 1); absence of preoperative imaging (n = 1); or intrathyroidal parathyroid location (n = 1).

Five (8%) of the 63 primary explorations were unsuccessful due to undetected multiple gland disease, and
these patients were cured by second intervention (n = 2) or are still being followed.

Nine patients (of 72, 13%) previously underwent surgery for primary hyperparathyroidism at another hospital. Seven of them (78%) were subsequently cured by 1 unilateral exploration, and 2 patients needed 2 and 3 procedures, respectively, to achieve normocalcemia at our institution.

Table 1 shows the results of preoperative imaging techniques for patients with uniglandular and multiglandular disease. Seventy-four preoperative sestamibi scans revealed a single positive lesion suggesting parathyroid hyperactivity in 61 patients (82%). Ultrasonography was less distinctive with 9 positive localizations (26%) of 35 studies.

Measurement of qPTH based on criteria of solely greater than 50% decrease of PTH showed 69 true-positive assay declines in primary hyperparathyroidism patients (Table 2). Multiple gland disease was found in 8 patients (13%). In these 8 patients, 4 neck explorations were completed after a drop of greater than 50% of qPTH. However, hypercalcemia persisted in these patients who should have been cured according to conventional criteria. These 4 procedures with false-positive results were performed in 3 patients (Table 2, patients 1–3). Subsequent successful reexploration (with true-positive qPTH results) took place in 2 of them, and 1 patient will be operated on in the near future. In 4 patients (6%) there was a decrease of less than 50% (at t 5'/t 10') of the qPTH level after removal of 1 enlarged parathyroid (patients 4–7). However, the exploration was ended because the surgical team considered the resection of hyperparathyroid tissue to be sufficient. These patients were subsequently found to have another hyperfunctioning gland and were considered to have true-negative results. If surgical strategy had been based on the results of qPTH measurement, further exploration in the same procedure had been performed with good reason. Measurement of qPTH in 1 patient with multiple gland disease (cured by 1 bilateral exploration) was performed after resection of the second (and last) adenoma, and results were interpreted as true positive.

The average weight of the removed parathyroid of all 77 procedures was 2656 mg (range, 23–27000 mg) with a median weight of 870 mg. No permanent laryngeal nerve injury occurred.

Secondary and Tertiary Hyperparathyroidism and MEN I/IIa Disease

Thirty-two neck explorations with simultaneous qPTH measurement were performed in 28 patients. Five patients had undergone previous neck surgery for hyperparathyroidism. Three of those 5 patients had positive preoperative imaging results, so a reexploration could be performed unilaterally. All but those 3 patients in this group underwent bilateral neck surgery.

Nine sestamibi scans were performed in 7 patients, and all but 1 of them showed locations (varying from 1 [n = 8] to 2 [n = 1]) of hyperactive parathyroid (89%). Only 4 patients had preoperative ultrasound imaging, which revealed enlarged parathyroid glands in 3 of them (75%). The average weight of the removed parathyroids was 1042 mg (range, 30–12850 mg), with a median value of 398 mg. Measurement of qPTH in this multiglandular disease group (based solely on the criterion of greater than 50% decrease of PTH) showed 25 true-positive declines (Table 2). Four patients had false-positive qPTH results at t 10' (patients 8–11). All these patients had additional hyperactive glands to be excised. In 1 of these 4 patients, there were 3 procedures with true-negative results besides the procedure with false-positive results (patient 9). After 3 procedures this patient still has persistence of disease. True-positive results in both patients with primary hy-

---

**Table 1. Results of Sestamibi Scanning and Ultrasonography in Primary Hyperparathyroidism Patients**

<table>
<thead>
<tr>
<th></th>
<th>No. of Explorations</th>
<th>No. of Unilateral Explorations</th>
<th>Positive Sestamibi Scanning, No./Total (%)</th>
<th>Positive Ultrasonography, No./Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uniglandular disease (n = 64)</td>
<td>64</td>
<td>52</td>
<td>53/62 (85)</td>
<td>8/27 (30)</td>
</tr>
<tr>
<td>Multiglandular disease (n = 8)</td>
<td>13</td>
<td>0</td>
<td>8/12 (67)</td>
<td>1/8 (13)</td>
</tr>
<tr>
<td>Total (n = 72)</td>
<td>77</td>
<td>52</td>
<td>61/74 (82)</td>
<td>9/35 (26)</td>
</tr>
</tbody>
</table>

**Table 2. False-Positive and True-Negative Results Based on Greater Than 50% Fall of Quick Parathyroid Hormone (qPTH) Measurement in 77 Primary Hyperparathyroidism Procedures**

<table>
<thead>
<tr>
<th>Procedures by criterion</th>
<th>Patients</th>
<th>Preop</th>
<th>t 5'</th>
<th>t 10'</th>
<th>% Fall</th>
<th>t 5'</th>
<th>t 10'</th>
<th>Cured</th>
</tr>
</thead>
<tbody>
<tr>
<td>False-positive procedures</td>
<td>1</td>
<td>74.6</td>
<td>24.5</td>
<td>NA</td>
<td>67</td>
<td>NA</td>
<td>37</td>
<td>No</td>
</tr>
<tr>
<td>&gt;50% (n = 4)</td>
<td>2</td>
<td>370</td>
<td>338</td>
<td>162</td>
<td>9</td>
<td>56</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>355</td>
<td>111</td>
<td>6</td>
<td>NA</td>
<td>69</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>True-negative procedures</td>
<td>4</td>
<td>347</td>
<td>244</td>
<td>218</td>
<td>9</td>
<td>32</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>&gt;50% (n = 4)</td>
<td>5</td>
<td>359</td>
<td>193</td>
<td>123</td>
<td>9</td>
<td>42</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>388</td>
<td>303</td>
<td>330</td>
<td>22</td>
<td>15</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>335.4† (92–1719)</td>
<td>79.2† (7.1–417)</td>
<td>41.2† (0.5–190)</td>
<td>72.1†</td>
<td>86.6†</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

* 5' and 10' indicate 5 and 10 minutes; NA, not available.
† Average results of 69 procedures.
periparathyroidism and patients with secondary or tertiary hyperparathyroidism or MEN I/IIa disease are less than 100 ng/L at t 5' and t 10' in primary hyperparathyroidism patients and at t 10' in patients with secondary or tertiary hyperparathyroidism or MEN I/IIa disease. High postexcision PTH levels (t 5' and t 10') occur in patients with remaining hyperactive parathyroid tissue.

**Novel Criteria**

Postexcision qPTH levels higher than 100 ng/L combined with a greater decline of qPTH than the conventional 50% decrease diminish the number of false-positive results in our series of 110 procedures by using the following criteria (Table 4).

When postexcision qPTH levels of between 100 and 200 ng/L were combined with a fall of more than 70%, no false-positive results occurred. Furthermore, no false-positive results occurred when postexcision qPTH levels of more than 200 ng/L were combined with a serum qPTH decline of more than 80%. Table 5 shows results of false-positive, true-negative, and true-positive qPTH measurement by conventional (>50%) criteria versus our novel criteria.

**COMMENT**

Perioperative qPTH measurement was introduced by Irvin and colleagues. This technique is used to determine whether multiple parathyroid tumors are present. An inappropriate fall of qPTH requires further exploration to identify and remove hyperactive parathyroid tissue. Rapid PTH assessment has been accepted by many as a useful tool during parathyroid surgery. Due to the use of this technique, surgeons have become increasingly tempted to perform limited neck explorations when a qPTH fall of more than 50% is established. However, false-positive results have been reported, and therefore the specificity of this technique demands improvement. Another disadvantage is that results of blood testing are reported to the surgeon 20 to 30 minutes after sampling, which is an expensive way of passing time. A mobile qPTH system inside the operating room can reduce these delays but is not available in most hospitals. It is still unclear whether major benefits such as reduction of operating time and diminution of postoperative events of hypoparathyroidism and recurrent laryngeal nerve injuries can be accomplished by performing PTH-guided parathyroidectomy.

In this study 7 patients with primary hyperparathyroidism had unsuspected multiple gland disease. Four of them could have been cured by further exploration during the same session when we would have complied with the qPTH outcome. However, in 4 procedures (3 patients), qPTH measurement revealed a fall of more than 50% at t 10', suggesting no further need for exploration based on conventional criteria. In these patients, hyperparathyroidism persisted, and therefore qPTH results should be considered as false-positive.

False-positive and true-negative qPTH results have been reported with use of different criteria and can be due to various factors. Using other criteria as suggested by Carneiro et al may reduce false-positive events, but the rate of false-negative predictions would increase. Manipulation of parathyroid glands can increase PTH levels, causing "spikes," which gives a false-negative result and a prolonged surgical time. Therefore, baseline levels should be achieved at skin incision time (before mobilization).
ization of suspected glands). In our study, sampling at the time of manipulation was not performed routinely. Nonetheless, we did not find any false-negative results.

Another cause of a false-positive qPTH test is suppression of an enlarged parathyroid gland in multiple gland disease. Although questioned previously, experience with qPTH assay has provided evidence for parathyroid suppression.

In order to increase the specificity of this procedure, we tried to find a solution for diminishing false-positive results. In this report we introduced new criteria for adequately interpreting the perioperative fall of qPTH (Table 4) measured by the Immulite assay, especially for patients with primary hyperparathyroidism. These criteria may not apply to other assays that do not measure the 7-84 PTH fragment.

In our series, false-positive qPTH outcome was associated with postexcision levels of at least 100 ng/L in 3 of 4 procedures in patients with primary hyperparathyroidism as well as in 3 of 4 procedures in patients with secondary or tertiary hyperparathyroidism or MEN 1/IIa disease. We believe that this is suggestive for remnance of hyperactive parathyroid tissue. For revealing true-positive results we propose t 10’ qPTH levels between 100 and 200 ng/L combined with a decline of more than 70% and t 10’ levels of more than 200 ng/L combined with a drop of 80% of qPTH to be interpreted as a measure for adequate surgery. Preexcision PTH levels of all 72 primary hyperparathyroidism patients may seem quite high (329 ng/L on average [mean, 239 ng/L]). A clear explanation for these high concentrations cannot be given, other than the fact that our institution is a tertiary referral center with possibly worst cases and many reoperations.

Criteria based on blood samples at exact postexcision timings (5 minutes and 10 minutes after removal of the gland) can be of influence in perioperative decision making. Thus, criteria founded on the short half-life time of qPTH in order to detect residual hyperactive parathyroid tissue.

By adhering to the novel criteria and thereby correcting for high postexcision levels, reexploration of the neck could have been prevented in 29% of patients with primary hyperparathyroidism due to multiple gland disease (from 4/7 [57%] to 6/7 [86%]), as shown in Table 5. These novel criteria demand future evaluation to establish their value.

References