Unilateral Versus Bilateral Neck Exploration for Primary Hyperparathyroidism

A Prospective Randomized Controlled Trial

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Objective
To compare unilateral and bilateral neck exploration for primary hyperparathyroidism in a prospective randomized controlled trial.

Summary Background Data
Based on the assumption that unilateral neck exploration for a solitary parathyroid adenoma should reduce operating time and morbidity, a variety of minimally invasive procedures have challenged the idea that bilateral neck exploration is the gold standard for the surgical treatment of primary hyperparathyroidism. However, to date, no open prospective randomized trial has been published comparing unilateral and bilateral neck exploration.

Methods
Ninety-one patients with the preoperative diagnosis of primary hyperparathyroidism were randomized to unilateral or bilateral neck exploration. Preoperative scintigraphy and intraoperative parathyroid hormone measurement guided the unilateral exploration. Gross morphology and frozen section determined the extent of parathyroid tissue resection in the bilateral group. The primary end-point was the use of postoperative medication for hypocalcemic symptoms.

Results
Eighty-eight patients (97%) were cured. Histology and cure rate did not differ between the two groups. Patients in the bilateral group consumed more oral calcium, had lower serum calcium values on postoperative days 1 to 4, and had a higher incidence of early severe symptomatic hypocalcemia compared with patients in the unilateral group. In addition, for patients undergoing surgery for a solitary parathyroid adenoma, unilateral exploration was associated with a shorter operative time. The cost for the two procedures did not differ.

Conclusions
Patients undergoing a unilateral procedure had a lower incidence of biochemical and severe symptomatic hypocalcemia in the early postoperative period compared with patients undergoing bilateral exploration. Unilateral neck exploration with intraoperative parathyroid hormone assessment is a valid surgical strategy in patients with primary hyperparathyroidism with distinct advantages, especially for patients with solitary parathyroid adenoma.
sis and reduce postoperative pain. However, from a principle point of view, the main difference is still between bilateral and unilateral neck exploration.

A recent systemic review comparing unilateral with bilateral neck exploration indicated a tendency to favor the unilateral procedure. To the best of our knowledge, no open prospective randomized controlled trial has been published comparing these two surgical strategies for the treatment of pHPT. Therefore, we designed the present study. We focused on the impact of surgical strategy on early postoperative hypocalcemia.

METHODS

Study Population

Ninety-one patients (18 men, 73 women), referred to the Department of Surgery, Lund University Hospital, Lund, Sweden, for first-time surgery for pHPT between September 1996 and March 2001, were enrolled in the study after written and oral information was given. The exclusion criteria for entering the study were a family history of pHPT (MEN 1, MEN 2, hereditary pHPT), previous neck surgery, other planned operations during the surgical procedure (including thyroid surgery), pregnancy and breast-feeding, emergency operation due to hypercalcemic crisis, and inability to understand information or to comply with scheduled follow-up.

Eight eligible patients were operated on outside the study. Six patients entered a prospective trial for video-assisted surgery of pHPT due to their own preference. Two patients could not be randomized during a short time period when intraoperative PTH analysis was not available due to technical problems. Thus, the 91 randomized patients represented 92% of eligible individuals during the study period.

Informed consent was obtained in all cases. The Ethical Committee of the Medical Faculty, Lund University, approved the study. The preoperative biochemical diagnosis of pHPT was based on a serum calcium level of more than 2.60 mmol/L and a serum PTH level of more than 3.5 pmol/L, with a serum creatinine level of less than 200 μmol/L. The mean age (± SD) of the patients was 67 ± 15 years. The mean (± SD) preoperative serum level of calcium was 2.77 ± 0.15 mmol/L. The mean (± SD) serum PTH level of 10.1 ± 5.2 pmol/L. The mean preoperative serum calcium level of the eight patients operated on outside the study was 2.80 ± 0.16 mmol/L.

Preoperative symptoms and signs were recorded. Thirteen patients were considered asymptomatic.

Planned Intervention

A flow chart summarizing the study is shown in Figure 1. During the outpatient visit, eligible patients were randomized to either unilateral neck exploration (study group) or bilateral neck exploration (control group). After randomization, patients in the unilateral group underwent preoperative sestamibi subtraction scintigraphy; no localization procedure was performed in the bilateral group.
Preoperatively, all patients underwent indirect laryngoscopy. Biochemical variables reflecting calcium metabolism and renal function were assessed.

Surgery was performed by three of the authors (A.B., P.L., J.W.), all experienced endocrine surgeons, each performing one third of the operations.

In both groups, surgery was performed through a short (<5 cm) standard Kocher incision. The strap muscles were dissected in the midline and not divided.

In the unilateral group, surgery was started on the side indicated by the preoperative scintigram. If no enlarged parathyroid gland was visualized on the scintigram, the left side was first explored. After finding the first enlarged parathyroid gland, blood samples were drawn for intraoperative measurement of PTH before and at 5 and 15 minutes after gland excision. Surgery was terminated if the PTH levels declined more than 50% after 5 minutes or more than 60% after 15 minutes. No attempts were made per se to visualize normal parathyroid glands.

If no enlarged parathyroid gland was found on the first explored side, or the decline of PTH was insufficient for the diagnosis of a solitary parathyroid adenoma, comprehensive bilateral exploration was performed. Frozen section was not used.

In the bilateral group, surgery was started on the left side and comprehensive bilateral exploration was performed. An attempt was made to visualize four parathyroid glands. The enlarged parathyroid glands were removed for frozen section. The decision to terminate surgery was based on the gross morphology of visualized and excised parathyroid glands in combination with frozen section. Normal parathyroid glands were not routinely biopsied.

Evaluation

Follow-up was done on postoperative days 1 to 4 and 6 weeks after surgery with biochemistry and with a patient questionnaire focusing on the incidence, frequency, and severity of hypocalcemic symptoms. After the first postoperative day, the patients were kept in the patient hotel of the hospital and made individual visits on postoperative days 2 to 4. Patients were given thorough information regarding the specific items on the questionnaire by a registered nurse. The patients were similarly informed by the nurse about hypocalcemic symptoms and were instructed to medicate with oral calcium (T. Kalcitena 250 mg; ACO, Stockholm, Sweden) up to a maximum of 3 g/24 hours when symptomatic. No patient was placed on oral calcium by the surgeon immediately postoperatively. Calcium ingestion and complications were recorded in the study protocol. Indirect laryngoscopy was done before discharge if possible; otherwise, it was performed within 3 weeks postoperatively.

The primary outcome measure was postoperative medication for hypocalcemia during the first 4 postoperative days. The secondary outcome measures were symptomatic hypocalcemia, serum levels of calcium (severe hypocalcemia defined as serum calcium < 2.00 mmol/L), persistent hyperparathyroidism, complications, operative time, and cost.

Sample Size

We previously showed that bilaterally explored patients with pHPT due to a solitary parathyroid adenoma have an increased risk for symptomatic hypocalcemia compared to unilaterally explored patients. They also had lower calcium levels during the first 4 postoperative days. In a pilot study we found that unilaterally explored patients differed in the ingestion of oral calcium during the first 4 postoperative days. Thus, with a type 1 error of 0.05 (two-tailed) and a power of 0.80, it was determined that 44 patients in each arm would be sufficient to detect a difference in 1.0 g oral calcium ingestion in the unilateral group versus 1.75 g calcium in the bilateral group. The difference in calcium medication was considered important since it reflects the severity of early postoperative hypocalcemia.

Statistics

Analysis of outcome for the unilateral and bilateral group was done on an intention-to-treat basis. For numeric data, differences between groups were analyzed with an unpaired t test, except for data with skewed distribution of numbers, when the Mann-Whitney test was used. For categorical data, statistical significance was analyzed using the chi-squared test and the Fisher exact test when expected frequencies were less than 5. A probability level of a random difference of P < .05 was considered significant. Results for continuous variables are reported as mean ± SD if not stated otherwise. For categorical data, absolute numbers in addition to percentage are given.

To estimate early biochemical hypocalcemia, the area under the curve (AUC) for serum calcium concentrations during the first 4 postoperative days was used according to the equation: AUC = T × [(0.5f₀ + f₁ + f₂ + ... + fₙ₋₁ + 0.5fₙ)]/(0.5f₁ + 0.5f₂ + ... + 0.5fₙ), where T equals the days between sampling and f the calcium concentration of the consecutive samples.

Pain during the first 4 postoperative days, as reported by the patients on a visual analog scale, was also calculated as the AUC.

Stopping Rules

No particular stopping rules were applied, since previous retrospective comparative studies have not shown the cure rate to differ between unilaterally and bilaterally explored patients.

Assignment

Patients were randomized in blocks of 10 with a sealed envelope to either unilateral or bilateral neck exploration
during the outpatient visit at the Department of Surgery, Lund University Hospital.

**Histopathology**

The diagnosis of a parathyroid adenoma and hyperplasia was established by conventional histologic criteria, aided by gross morphology in the bilateral group and in the unilateral group by the perioperative decrease in the serum level of intact PTH.

**Sestamibi Scintigraphy**

Sestamibi subtraction scintigraphy was performed with 30 MBq $^{99m}$Tc and 500 MBq $^{99m}$Tc sestamibi. A result was classified as true positive only if it clearly corresponded to an enlarged parathyroid gland found at the same location at neck exploration.

**Renal Function**

Glomerular filtration rate was measured using a method for the calculation of plasma clearance of the contrast agent iohexol. The reference values are 20 to 50 years, 80 to 125 mL/min; 51 to 65 years, 60 to 110 mL/min; and 66 to 80 years, 50 to 90 mL/min.

**Biochemical Variables**

Preoperative blood samples were drawn after an overnight fast the day before surgery. Serum levels of PTH were measured with the intact PTH assay (Incstar, Stillwater, MN). The sensitivity of this assay is 0.13 pmol/L. The interassay coefficient of variation (CV) is less than 11% and the intraassay variation less than 6%. The method has a CV of 2.2% at a value of 5 pmol/L. The reference range is 1.0 to 5.0 pmol/L. To shorten the time for intraoperative analysis, the assay was modified as previously described. The within-assay variation between 0.8 and 10 pmol/L is less than 8% for the rapid method. The correlation between the two methods is 0.99.

High-performance liquid chromatography was used for assessment of 25-hydroxycholecalciferol (25 (OH) D$_3$) and 1,25-dihydroxycholecalciferol (1,25(OH)$_2$ D$_3$) with a radioreceptor assay (Incstar). Serum levels of calcium, alkaline phosphatase, phosphate, and creatinine were analyzed with a routine autoanalyzer (Kodak Ektachem, 700xR-C, Eastman Kodak Co., Rochester, NY).

**Costs**

The costs for the operative procedure for the two groups of patients were calculated from official in-hospital charges for services performed by different departments. The cost for sestamibi scintigraphy (in U.S. dollars) was $134, intraoperative PTH $126, frozen section $155, and time for anesthesia $12/min.

**RESULTS**

Forty-seven patients were randomized to the unilateral group and 44 patients to the bilateral group. The preoperative clinical and biochemical data as well as renal function were well balanced and did not differ between the two groups (Table 1). There was no difference in clinical signs and symptoms between the two groups (data not shown). Six patients in the unilateral group and seven patients in the bilateral group were considered asymptomatic ($P_{/\text{H11005}}<0.05$). The eight patients operated on outside the study all had a solitary parathyroid adenoma. They were normocalcemic at the 6-week follow-up.

**Analysis of the Whole Group of Patients**

At surgery, 40 patients in the bilateral group had a solitary adenoma and 4 patients multiglandular disease. In the unilat-
eral group, 41 patients had a solitary adenoma and 5 patients multiglandular disease ($P > .99$). The mean ($\pm SD$) weight of the parathyroid adenoma in the unilateral group was $1.24 \pm 1.12$ g; in the bilateral group it was $1.04 \pm 1.29$ g ($P = .48$).

In 21 patients, the adenoma weighed less than 500 mg. In one patient in the unilateral group (explored bilaterally, see below), no enlarged parathyroid gland was found at neck exploration. Three patients had persistent hyperparathyroidism at 6 weeks after surgery, two in the unilateral group and one in the bilateral group. Clinical and biochemical data on these patients are shown in Table 2. Thus, the overall cure rate was 97%. There was no difference between the mean ($\pm SD$) time for operation in the unilateral group compared with the bilateral group ($72 \pm 42$ minutes vs. $82 \pm 37$ minutes, $P = .22$). The costs for the surgical procedure were slightly but not significantly higher in the unilateral group ($\$2,258 \pm 509$ vs. $\$2,097 \pm 505$, $P = .13$).

In the unilateral group, 29 of 47 patients were unilaterally explored (62%). Sestamibi subtraction scintigraphy visualized one enlarged parathyroid gland in 35 of 47 patients (74%); in 12 patients (26%) the scan was negative. In comparison, had the same surgical strategy been used in the bilateral group (remove large gland, check PTH, no frozen section) and the left side first explored, 19 of 44 patients (44%) could have had a unilateral dissection.

The median weight of nonlocalized glands was 0.43 g (range 0.20–2.55 g) versus 0.87 g (range 0.20–5.85 g) for localized glands ($P < .05$, Mann-Whitney U test). Of the patients with negative scans, 1 patient had asymmetric hyperplasia with three enlarged glands and 10 patients had a solitary parathyroid adenoma; in 1 patient with four normal parathyroid glands identified during surgery, no enlarged gland was found. Of the 35 positive scans, a solitary parathyroid adenoma at the suggested location was confirmed in 29 patients. Thus, the sensitivity to localize a solitary parathyroid adenoma in the unilateral group was 71% (29 of 41 parathyroid adenomas) and the positive predictive value for an adenoma was 83%. In the six patients with incorrect scans, two patients with solitary parathyroid adenoma were not correctly lateralized and four patients had asymmetric hyperplasia with two enlarged glands each. Thus, in no patient was multiglandular disease predicted by the scan.

The mean ($\pm SD$) decline of PTH after excision of the first enlarged parathyroid gland was $54 \pm 25\%$ after 5 minutes ($n = 44$, three tests missing due to technical problems) and $69 \pm 25\%$ after 15 minutes. Fifteen minutes after excision of the enlarged parathyroid gland, 35 patients (74%) declined by more than 60%. These patients were cured by surgery (solitary parathyroid adenoma). Twelve patients (36%) declined by less than 60%. Five of these patients were found to have multiglandular disease during neck exploration, and they were cured. In one patient, a 3.5-gland resection was performed due to suspicion of diffuse hyperplasia macroscopically as well as on frozen section (protocol violation). However, histology showed normal parathyroid glands. The patient has persistent hyperparathyroidism, and therefore a solitary parathyroid adenoma in a fifth gland is suspected (see Table 2, patient 49). One patient declined by more than 50% at 5 minutes after surgery, and thus the operation was terminated. However, this patient has persistent HPT as predicted by the PTH level 15 minutes after gland excision (see Table 2, patient 38).

In three patients, no other enlarged gland was found despite comprehensive bilateral exploration. These patients are cured (serum calcium 2.21, 2.46, and 2.48 mmol/L at 1 year after surgery, with normal levels of intact PTH).

Thus, the sensitivity for a solitary parathyroid adenoma at 15 minutes was 92%, the specificity 100%, the positive predictive value 100%, and the negative predictive value 75%

During the first 4 postoperative days, patients in the unilateral group consumed significantly less oral calcium

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**Table 2. PATIENTS WITH PERSISTENT HYPERPARATHYROIDISM AFTER NECK SURGERY**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Randomized to</th>
<th>Preoperative serum-calcium 2.63 mmol/L, serum-PTH 9.0 pmol/L. Four glands identified at neck exploration. Right upper gland removed. Histology showed parathyroid adenoma (weight 0.57 g). At 1 year after surgery, serum-calcium 2.74 mmol/L, serum-PTH 14 pmol/L. GFR 35 mL/min. Urinary-calcium 1.2 mmol/L.</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Bilateral</td>
<td>Preoperative serum-calcium 2.74 mmol/L, serum-PTH 5.5 pmol/L. Negative sestamibi scintigraphy. Bilateral explored. Three glands identified (right lower missing). Right upper removed. The decline of PTH was 55% after 5 min and 54% after 15 min. Histology showed parathyroid adenoma. At 1 year after surgery, serum-calcium 2.97 mmol/L, serum-PTH 7.1 pmol/L. GFR 66 mL/min. Urinary-calcium 4.9 mmol/L.</td>
<td></td>
</tr>
<tr>
<td>38</td>
<td>Unilateral</td>
<td>Preoperative serum-calcium 2.80 mmol/L, serum-PTH 13 pmol/L. Sestamibi scintigraphy negative. Bilateral exploration. Four glands identified during surgery. On gross morphology and frozen section (protocol violation), suspected diffuse hyperplasia. Subtotal parathyroidectomy was performed. The decline of PTH was 0% 15 min after excision of first gland and 16% after excision of second gland. Histology showed normal parathyroid glands (weight 0.70 g, 0.70 g, 0.37 g, 0.10 g). At 1 year after surgery, serum-calcium 2.84 mmol/L, serum-PTH 10.0 pmol/L. GFR 107 mL/min. Urinary-calcium 3.2 mmol/L.</td>
<td></td>
</tr>
</tbody>
</table>
(0.78 ± 1.07 g) compared to patients in the bilateral group (1.94 ± 2.69 g, \( P < .01 \)).

On the first postoperative day, 19 of 39 patients in the bilateral group (49%) and 12 of 43 patients (28%) in the unilateral group reported mild hypocalcemic symptoms (tingling in the lips, fingers, and toes) (\( P = .052 \)). Furthermore, 4 of 39 patients (10%) in the bilateral group versus zero of 43 patients in the bilateral group reported severe symptoms (i.e., muscle cramps) (\( P < .05 \)). No difference was found in the frequency of self-reported hypocalcemic symptoms on postoperative days 2 to 4. There was no significant difference between the two groups in terms of postoperative pain recorded by the patients (Fig. 2).

The serum calcium levels during the first 4 postoperative days for the patients in the unilateral and the bilateral group are shown in Figure 3. On the second postoperative day, the serum calcium concentration was significantly lower in the bilateral group compared with the unilateral group (2.15 ± 0.14 mmol/L vs. 2.26 ± 0.17 mmol/L, \( P < .01 \)). Furthermore, the AUC for serum calcium during the first 4 postoperative days was smaller in the bilateral group (6.53 ± 0.42 vs. 6.71 ± 0.44, \( P < .05 \)). During the first 6 weeks after surgery (excluding the first 4 postoperative days), patients in the bilateral group consumed more oral calcium (4.20 ± 6.67 g) than patients in the unilateral group (1.92 ± 3.86 g, \( P < .05 \)), although self-reported hypocalcemic symptoms did not differ between the two groups. There was no difference in the biochemical variables measured at 6 weeks after surgery (Table 3).

Three patients had vocal cord palsy on indirect laryngoscopy after surgery, two in the unilateral and one in the bilateral group (\( P = .99 \)); all were temporary.

Two patients with a solitary parathyroid adenoma and one patient with multiglandular disease experienced postoperative hypoparathyroidism with vitamin D substitution therapy, all in the bilateral group (\( P = .11 \)). In two of these cases (one patient with adenoma and one patient with multiglandular disease), the medication was temporary, whereas one patient with adenoma still requires vitamin D substitution 1 year after surgery. Three other significant complications were recorded, all in the bilateral group (Table 4). Thus, 5 of 44 patients (11%) in the bilateral group and 2 of 47 patients (4%) in the unilateral group had a significant complication (\( P = .27 \); Fisher’s exact test).

## Analysis of Patients With Solitary Parathyroid Adenoma

The mean (± SD) operative time was significantly shorter in the unilateral group compared to the bilateral group (62 ± 29 minutes vs. 84 ± 38 minutes, \( P < .01 \)). During the first 4 postoperative days, patients in the unilateral group consumed significantly less oral calcium (0.66 ± 0.89 g) compared to patients in the bilateral group (1.85 ± 2.77 g, \( P = .01 \)). On the first postoperative day, 4 of 35 patients in the bilateral group (11%) and zero of 38 patients

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### Table 3. BIOCHEMICAL DATA AT 6 WEEKS FOLLOW-UP

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unilateral Group (n = 47)</th>
<th>Bilateral Group (n = 44)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum-Calcium (mmol/L)</td>
<td>2.37 ± 0.12</td>
<td>2.35 ± 0.12</td>
<td>.40</td>
</tr>
<tr>
<td>Serum-PTH (pmol/L)</td>
<td>5.7 ± 3.0</td>
<td>6.0 ± 3.3</td>
<td>.60</td>
</tr>
<tr>
<td>Serum-Phosphate (mmol/L)</td>
<td>1.03 ± 0.19</td>
<td>1.05 ± 0.16</td>
<td>.56</td>
</tr>
<tr>
<td>25 (OH) vitamin D₃ (nmol/L)</td>
<td>54 ± 21</td>
<td>59 ± 24</td>
<td>.32</td>
</tr>
<tr>
<td>1,25 (OH)₂ vitamin D₃ (pmol/L)</td>
<td>69 ± 33</td>
<td>68 ± 21</td>
<td>.90</td>
</tr>
</tbody>
</table>
DISCUSSION

During the past decade, new surgical procedures have evolved for the treatment of pHPT. From a principle point of view, the main difference is still between bilateral and unilateral neck exploration. The latter could be performed using a variety of forms of general and local anesthesia. The main claim of the proponents of unilateral neck exploration is that compared with bilateral exploration, the unilateral approach carries a decreased risk for temporary and permanent hypocalcemia,\textsuperscript{10–13,40} without an increased risk for persistent or recurrent pHPT.\textsuperscript{13} To the best of our knowledge, the present trial is the first prospective randomized study analyzed on an intention-to-treat basis between unilateral and bilateral neck exploration.

The results from the present study are quite clear. Although only 29 of 47 patients (62\%) in the unilateral group ultimately underwent focused adenoma excision, the unilateral approach offered some distinct benefits. Patients operated on using a unilateral approach consumed less oral calcium during the first 4 postoperative days. They also had less incidence and severity of symptomatic and biochemical hypocalcemia. Patients with a solitary parathyroid adenoma, we also found that the operative time was shorter in the unilateral group. Furthermore, there was no difference in cure rate between the two patient groups. The complications were found mainly in the bilaterally explored patients (see Table 4).

Our trial raises a number of possible questions. Although the costs for the operative procedures did not differ between the two groups, the moderate sensitivity for a solitary parathyroid adenoma by the sestamibi scintigraphy, in this study 71\%, is a cause of concern. A high sensitivity of the preoperative localization procedure is of great importance for a successful focused neck exploration. Furthermore, in agreement with previous investigations, we confirmed that preoperative sestamibi scintigraphy does not reliably predict multiglandular disease.\textsuperscript{38,41} We have previously reported a high sensitivity for solitary parathyroid adenoma,\textsuperscript{38} but the results were not reproduced in the present trial. Since gland weight has been shown to be one of the chief determinants of sestamibi sensitivity,\textsuperscript{42} one reason could be the relatively high incidence of small adenomas. In the present study the adenoma weight was less than 500 mg in 21 patients, and the mean weight for nonlocalized glands was lower than the weight for glands in the unilateral group reported severe hypocalcemic symptoms (i.e., muscle cramps) ($P < .05$). Self-reported hypocalcemic symptoms did not differ day 2 to 4. Patients with a solitary parathyroid adenoma in the bilateral group had lower serum levels of calcium on the second postoperative day compared to patients in the unilateral group (2.15 ± 0.14 mmol/L vs. 2.25 ± 0.15 mmol/L, $P < .01$). Furthermore, the nadir of serum calcium during the first 4 postoperative days was lower in the bilateral group (2.09 ± 0.15 mmol/L) compared with the unilateral group (2.15 ± 0.12, $P < .05$). In 10 of 40 patients in the bilateral group (25\%) and 3 of 41 patients (7\%) in the unilateral group, severe biochemical hypocalcemia (<2.00 mmol/L) was recorded during the first 4 postoperative days ($P = .04$).

The AUC for serum calcium levels during the first 4 postoperative days was significantly smaller for patients in the bilateral group compared to the unilateral group (6.5 ± 0.42 vs. 6.7 ± 0.39, $P < .05$). At the 6-week follow-up, there was no difference in the biochemical variables measured or in self-reported hypocalcemic symptoms and oral calcium medication.

**Table 4. COMPLICATIONS**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Randomized Operated</th>
<th>Histology</th>
<th>Complication and Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>Bilateral</td>
<td>Bilateral</td>
<td>Adenoma</td>
</tr>
<tr>
<td>22</td>
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<td>Bilateral</td>
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</tr>
<tr>
<td>26</td>
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<tr>
<td>90</td>
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</tr>
<tr>
<td>95</td>
<td>Bilateral</td>
<td>Bilateral</td>
<td>Hyperplasia</td>
</tr>
</tbody>
</table>

Vitamin D substitution therapy at 1 year after surgery
Patient with rheumatic arthritis
1. Postoperative acute tracheal edema with no response to conservative treatment. Emergency operation with tracheostomy.
2. Temporary paresis of the recurrent laryngeal nerve
3. Temporary vitamin D substitution therapy due to hypocalcemia
Refused surgery for large goiter. On first postoperative day, tracheal edema. Emergency operation with total thyroidectomy.
Temporary paresis of the recurrent laryngeal nerve. Scintigraphy neg.
Temporary paresis of the recurrent laryngeal nerve. Scintigraphy true positive.
Operated due to rebleeding
Temporary vitamin D substitution therapy due to hypocalcemia

\textsuperscript{1} Postoperative acute tracheal edema with no response to conservative treatment. Emergency operation with tracheostomy.
localized by sestamibi scintigraphy. Another possibility is that the previous study was confounded by a referral bias; that is, patients tend to be referred for surgery more often if sestamibi scintigraphy is positive.

To optimize the cost-effectiveness of the unilateral method, the accuracy of sestamibi scintigraphy clearly needs to be improved. By adding delayed sestamibi scans based on differential washout kinetics and single photon emission computed tomography (SPECT) or oblique views with a higher-dose 99mTc sestamibi, an increased sensitivity might be possible. However, this remains to be proven in prospective controlled trials.

The incidence of multiglandular disease has previously been estimated to be about 15% of patients being operated on due to pHPT. However, the incidence of multiglandular disease in a patient cohort in which intraoperative PTH guided the extent of tissue resection was recently found to be as low as 5%. In this study, histologically proven multiglandular disease was found in 5 of 47 patients in the unilateral group and in 4 of 44 patients in the bilateral group. One patient in each group had persistent hyperparathyroidism despite one enlarged gland being excised. Thus, the true incidence of multiglandular disease was 13% in the unilateral group and 11% in the bilateral group. The data therefore strongly suggest that the incidence of multiglandular disease was not underestimated in the unilateral group.

One patient in whom the PTH level declined by more than 50% 5 minutes after excision of an enlarged parathyroid gland was not cured. This finding is in agreement with previous investigations suggesting that a 50% decrease in PTH level is not an entirely reliable predictor for postoperative normocalcemia.

To enhance the accuracy of the intraoperative PTH measurement, we have developed a rigid protocol. First, blood samples are always drawn in a peripheral vein. Second, the baseline sample should be obtained when the first enlarged parathyroid gland is visualized, since we have shown that after general anesthesia the levels of ionized calcium decrease and the levels of PTH increase. Third, the dissection of the enlarged parathyroid gland must be extremely precise, without pressure on the gland and with clipping of the vascular pedicle as the last measure. Fourth, we have previously shown that a decline of PTH by more than 60% at 15 minutes after excision of an enlarged parathyroid gland is highly specific in predicting cure of patients with pHPT. In agreement, in the present investigation a decline by more than 60% at 15 minutes after gland excision predicted cure in all patients.

In the present investigation, the cure rate was 97%. Three patients, two in the unilateral group (both bilaterally explored according to the study protocol) and one in the bilateral group, had persistent hyperparathyroidism. In agreement, retrospective comparative studies have not shown an increased incidence of persistent or recurrent pHPT for patients explored with a unilateral approach.

In summary, in this prospective randomized trial, patients operated on according to a unilateral approach consumed less oral calcium and had a lower incidence of biochemical and early severe symptomatic hypocalcemia compared with patients explored bilaterally, with no difference in cure rate. Whether endoscopic or video-assisted surgery or other minimally invasive techniques could provide additional benefits in terms of early ambulation and less local discomfort and pain compared to the classical “open” unilateral method needs to be answered in future randomized trials.

References


