Minimally Invasive Surgery

Fewer adverse events after reoperative parathyroidectomy associated with initial minimally invasive parathyroidectomy

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Primary hyperparathyroidism; Reoperative parathyroidectomy; Persistent or recurrent hyperparathyroidism; Minimally invasive parathyroidectomy; Standard cervical exploration

Abstract
BACKGROUND: This study compared reoperative complication rates after initial minimally invasive parathyroidectomy and standard cervical exploration.

METHODS: Records from patients who underwent 1 reoperative parathyroidectomy at a single institution (1998 to 2012) were retrospectively reviewed.

RESULTS: Seventy-seven patients were included; 74% underwent initial standard cervical exploration. Preoperative and operative characteristics were similar between groups; 74% underwent focused, unilateral reoperation. A significantly higher rate of postoperative complications occurred in the initial standard cervical exploration group (42% vs 15%, \( P = .03 \)) that could not be explained by differences in the rates of symptomatic hypocalcemia (\( P = .5 \)). The type of prior parathyroidectomy was significantly associated with postoperative complications (odds ratio 4.1, 95% confidence interval 1.1 to 15.7, \( P = .04 \)). In a multivariable logistic regression model that included body mass index, type of operation (for initial and reoperation), and initial operation performed prereferral as covariates, type of prior parathyroidectomy remained a significant predictor of postoperative complications.

CONCLUSION: Higher rates of postoperative sequelae after initial standard cervical exploration should be considered before performing routine 4-gland exploration.

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While cure rates for initial parathyroidectomy for primary hyperparathyroidism approach 98% in high-volume centers, the failure rate can be as high as 15% in low-volume centers. 1–5 Minimally invasive parathyroidectomy—a focused, unilateral operation in selected patients with positive, concordant preoperative localization studies and an appropriate intraoperative parathyroid hormone drop after excision of a single adenoma—has become
the standard initial operation for appropriate patients with primary hyperparathyroidism. Standard cervical (bilateral) exploration is used predominantly by 2 groups of surgeons: high-volume parathyroid surgeons who feel that standard cervical exploration is more efficacious than minimally invasive parathyroidectomy and lower volume surgeons who are not trained in or do not have access to image-guided techniques. Higher complication rates have been reported for standard cervical exploration compared with minimally invasive parathyroidectomy, including higher rates of hypocalcemia, presumably because of a more involved operation and bilateral dissection.

After failure of initial parathyroidectomy, reoperation can be technically challenging because of scarring, distorted anatomy, and loss of normal tissue planes from the prior dissection. Reoperations for primary hyperparathyroidism are associated with increased morbidity. Because of the unilateral, focused nature of minimally invasive parathyroidectomy, we hypothesized that reoperation after initial minimally invasive parathyroidectomy would be more straightforward than after initial standard cervical exploration, leading to fewer perioperative events. This research question is important to any surgeon who performs parathyroid operations—those who preferentially perform standard cervical exploration and those who perform minimally invasive parathyroidectomy in appropriate circumstances. To determine how the extent of initial operation might impact reoperation, we compared complication rates for patients requiring reoperation after initial minimally invasive parathyroidectomy and reoperation after initial standard cervical exploration.

**Methods**

Records from patients with sporadic primary hyperparathyroidism who underwent reoperative parathyroidectomy at MD Anderson Cancer Center by one of 4 surgical endocrinologists between November 1998 and September 2012 were retrospectively reviewed. Exclusion criteria were familial hyperparathyroidism; secondary or tertiary hyperparathyroidism; having undergone >1 prior parathyroidectomy or a previous thyroid operation; or required a simultaneous, unrelated thyroid procedure at the time of remedial parathyroidectomy. Prior operative and pathology reports were reviewed to determine the extent of initial parathyroidectomy. Initial minimally invasive parathyroidectomy was defined as a focused, unilateral operation guided by preoperative imaging. Initial standard cervical exploration involved the surgeon describing a bilateral neck exploration in the operative report. Reoperation was undertaken on the basis of 2 positive, concordant preoperative localization studies in patients with a biochemical diagnosis of primary hyperparathyroidism who met 2009 consensus criteria for parathyroidectomy. Intraoperative parathyroid hormone monitoring was used in each case, measured preincision and 5 and 10 minutes postexcision of the abnormal gland(s). A 10-minute intraoperative parathyroid hormone monitoring drop of ≥50% from the preincision value was considered to be predictive of operative cure. A true positive intraoperative parathyroid hormone monitoring result occurred when the value fell by ≥50% and the patient was cured. A false-positive result occurred when the intraoperative parathyroid hormone monitoring value fell by ≥50% and the patient had hyperfunctioning parathyroid tissue remaining (persistent hyperparathyroidism).

Permanent hypoparathyroidism was defined as parathyroid hormone <10 pg/mL and continued need for daily calcium and/or calcitriol supplementation at ≥6 months after parathyroidectomy. Cure was assessed in patients followed for at least 6 months as a serum calcium in the normal range (<10.2 mg/dL).

Patient demographic and clinical characteristics were summarized using frequencies, percents, medians, and minimum and maximum values. Fisher’s exact test was used to investigate associations between 2 categorical variables, and the Wilcoxon rank-sum test was used to test for associations between categorical and continuous variables. A logistic regression model was run to estimate the odds of having postoperative complications by the type of initial surgical procedure while adjusting for other potential independent predictors of postoperative complications. A final model was chosen through a backward selection procedure. All P values were 2-tailed and considered significant at alpha < .05. Analyses were conducted using SAS for Windows (release 9.2; SAS Institute, Cary, NC).

**Results**

A total of 96 consecutive patients underwent reoperative parathyroidectomy during the study period. After 19 patients were excluded (see Methods), the 77 patients who had undergone only 1 previous parathyroidectomy comprised our main study group. These patients were subdivided into initial treatment groups: 20 patients (26%) underwent initial minimally invasive parathyroidectomy and 57 patients (74%) underwent initial standard cervical exploration. A significantly higher number of patients who had their initial operation performed at MD Anderson underwent initial minimally invasive parathyroidectomy (45%, 10/22 compared with 18%, 10/55 who had minimally invasive parathyroidectomy performed prereferral, P = .02) (Fig. 1).

The indication for reoperation was persistent primary hyperparathyroidism in three fourths of patients, while one fourth had recurrent disease after at least 6 months of normocalcemia. There were no differences in age at operation, body mass index, American Society of Anesthesiologists physical status classification system (ASA score), or preoperative parathyroid hormone, creatinine, or 25-hydroxy vitamin D levels between initial treatment groups. The preoperative calcium level was significantly higher in the initial standard cervical exploration group (11 vs 10.5 mg/dL, P = .01).
Reoperation was performed at a median of 15.7 months after initial surgery (range .5 to 234 months). Fifteen patients (19.5%) underwent reoperation less than 6 months following the first parathyroidectomy. There was no significant difference in the time interval between first and second operation between the 2 operative groups ($P = .31$).

In a univariate logistic regression model, the time interval between operations was not significantly associated with postoperative complications.

Most patients (74%) underwent a targeted, focused reoperation. There was no difference in operating room time, dissection time, length of stay, or extent of second operation (minimally invasive parathyroidectomy versus standard cervical exploration) between groups (Table 1). There was 1 intraoperative complication in this series: 1 patient in the initial standard cervical exploration group experienced a pneumothorax. There were no documented temporary or permanent recurrent laryngeal nerve injuries or hematomas requiring reoperation. Among 20 patients in the initial minimally invasive parathyroidectomy group, 10 underwent reoperative minimally invasive parathyroidectomy on the contralateral side, 3 underwent reoperative minimally invasive parathyroidectomy on the ipsilateral side, and 7 underwent reoperative standard cervical exploration. There was no significant difference in postoperative complications by whether the reoperation was ipsilateral or contralateral. There was no difference in the postoperative complication rate based on the extent of the reoperative procedure (reoperative minimally invasive parathyroidectomy 37% and reoperative standard cervical exploration 25%, $P = .41$).

Clinically significant postoperative sequelae (within 30 days of parathyroidectomy) included symptomatic hypocalcemia, surgical site infection or collection, other infection, deep vein thrombosis, chest pain requiring cardiology consultation, new arrhythmia, and any issue that required emergency department evaluation or hospital admission. The initial standard cervical exploration group had a higher number ($P = .01$) and higher rate of postoperative sequelae (42% vs 15%, $P = .03$) compared with the number and rate in the initial minimally invasive parathyroidectomy group. While there was a lower rate of symptomatic hypocalcemia in patients who had undergone initial minimally invasive parathyroidectomy (15% vs 25%, $P = .5$), this could not entirely account for the difference in complication rates between groups (Table 2). When all 96 patients were evaluated, there was a nonsignificant trend toward having a higher rate of complications among patients who had >1 prior parathyroidectomy (58%) versus the rate of complications among those who had only 1 prior parathyroidectomy (35%) ($P = .11$).

Cure rates at 6 months following reoperation were nonsignificantly lower in the initial minimally invasive parathyroidectomy group (73% vs 94%, $P = .06$). Of the 5 patients with persistent hyperparathyroidism after their second parathyroid exploration, 3 patients had a false-positive intraoperative parathyroid hormone drop (87%, 68%, and 64%) at 10 minutes after excision of the abnormal parathyroid gland or glands. Two of the 3 patients had a total of 3 parathyroid glands removed, while the third patient had a total of 2 parathyroid glands removed. The remaining 2 patients had no adenoma identified on re-exploration. For patients who were cured of hyperparathyroidism at reoperation, the median intraoperative parathyroid hormone drop at 10 minutes postexcision was 86%.

Table 1: Operative variables in 77 patients who underwent reoperative parathyroidectomy, divided by the type of initial operation—minimally invasive parathyroidectomy or standard cervical exploration

<table>
<thead>
<tr>
<th>Operative variable (median) (minimum, maximum)</th>
<th>Initial MIP</th>
<th>Initial SCE</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operating room time (min)</td>
<td>121 (62, 344)</td>
<td>143 (64, 307)</td>
<td>.22</td>
</tr>
<tr>
<td>Dissection time (min)</td>
<td>74 (21, 286)</td>
<td>84 (18, 255)</td>
<td>.55</td>
</tr>
<tr>
<td>Days hospitalized</td>
<td>1 (0, 3)</td>
<td>1 (0, 8)</td>
<td>.08</td>
</tr>
<tr>
<td>Focused reoperation (MIP)</td>
<td>13 (65%)</td>
<td>44 (77%)</td>
<td>.37</td>
</tr>
</tbody>
</table>

MIP = minimally invasive parathyroidectomy; SCE = standard cervical exploration.
group (P = .53). Permanent hypoparathyroidism occurred in 4 of these patients (11%) in the initial standard cervical exploration group and none in the initial minimally invasive parathyroidectomy group (P = .56). For those who did and did not develop postoperative symptomatic hypocalcemia, the median largest intraoperative parathyroid hormone drop was not different between groups (85% each). No one with an intraoperative parathyroid hormone drop less than 81% at 10 minutes postexcision developed permanent hypoparathyroidism.

The type of prior parathyroidectomy was significantly associated with postoperative complications (odds ratio 4.1, 95% confidence interval 1.1 to 15.7, P = .04). In a multivariable logistic regression model that included body mass index, reoperation type, initial operation type, and initial operation prerereferral as covariates, the type of prior parathyroidectomy remained a significant predictor of postoperative complications.

### Comments

In this retrospective study of first reoperative parathyroidectomy performed at a high-volume endocrine surgery center, initial standard cervical exploration was associated with a 4 times higher likelihood of experiencing a postoperative complication compared with initial minimally invasive parathyroidectomy, regardless of the extent of the reoperation. While rates of symptomatic hypocalcemia were higher in the initial standard cervical exploration group, this could not entirely explain the higher rate of postoperative sequelae in this group. Interestingly, there was only 1 intraoperative complication in this reoperative series, indicating that the extent of initial dissection did not impact the ability of experienced endocrine surgeons to perform a safe operation.

This patient population is unique in that all patients had at least 1 previous parathyroid operation and all had a diagnosis of sporadic primary hyperparathyroidism. Most other large series of reoperative parathyroidectomy include patients who underwent previous nonparathyroid neck operations and patients with known familial disease. Therefore, patients in our initial standard cervical exploration group either underwent initial standard cervical exploration because of nonlocalizing preoperative imaging studies or surgeon preference.

Patients in the initial standard cervical exploration group had significantly higher calcium levels compared with those in the initial minimally invasive parathyroidectomy group, potentially indicating selection bias. It is possible that patients who had undergone initial minimally invasive parathyroidectomy were taken for reoperation more readily, reflected by their milder biochemical profile. In addition, half of the reoperations from our own institution were initially minimally invasive parathyroidectomy, so surgeons may have been more eager to reoperate on their own patients with persistent disease. Preoperative ASA scores were nearly identical between groups, suggesting that the occurrence of adverse events was not related to a difference between groups in pre-existing comorbid conditions.

There are several reasons a surgeon may choose to perform standard cervical exploration instead of minimally invasive parathyroidectomy as an initial operation for treatment of primary hyperparathyroidism. First, patient factors such as failure of localization on preoperative imaging or concern for familial disease would direct a surgeon to performing standard cervical exploration. We excluded patients with familial disease from our study. Second, surgeon expertise may play a role in operative approach. Patients who undergo initial standard cervical exploration solely because of surgeon preference are being treated by one of the 2 groups of surgeons: (1) lower volume parathyroid surgeons who are not trained in minimally invasive parathyroidectomy techniques or do not have the available image-guided localization studies or intraoperative parathyroid hormone monitoring at their disposal or (2) a select group of expert parathyroid surgeons who prefer the standard cervical exploration approach. These results should be important to all surgeons who perform parathyroidectomy.

While traditionally reoperative parathyroidectomy has been associated with cure rates of 80%, some contemporary reports from expert centers demonstrate cure rates equivalent to that of initial parathyroidectomy. Our overall cure rate in the reoperative setting was 89%. In comparison, our cure rate for initial minimally invasive parathyroidectomy

### Table 2

<table>
<thead>
<tr>
<th>Postoperative variable</th>
<th>Total</th>
<th>Initial MIP</th>
<th>Initial SCE</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any postoperative event</td>
<td>27 (35%)</td>
<td>3 (15%)</td>
<td>24 (42%)</td>
<td>.03</td>
</tr>
<tr>
<td>Symptomatic hypocalcemia</td>
<td>17 (22%)</td>
<td>3 (15%)</td>
<td>14 (25%)</td>
<td>.53</td>
</tr>
<tr>
<td>Emergency department visit</td>
<td>5 (6.4%)</td>
<td>0</td>
<td>5 (9%)</td>
<td>.32</td>
</tr>
<tr>
<td>Readmission</td>
<td>2 (2.6%)</td>
<td>1 (5%)</td>
<td>1 (2%)</td>
<td>.45</td>
</tr>
<tr>
<td>Cured at 6 months*</td>
<td>44 (88%)</td>
<td>11 (73%)</td>
<td>33 (94%)</td>
<td>.06</td>
</tr>
<tr>
<td>Permanent hypoparathyroidism*</td>
<td>4 (8%)</td>
<td>0</td>
<td>4 (11%)</td>
<td>.30</td>
</tr>
</tbody>
</table>

MIP = minimally invasive parathyroidectomy; SCE = standard cervical exploration.

*Fifty patients were followed for ≥6 months postoperatively. There was no significant difference by prior procedure group (MIP versus SCE) in percentage of patients followed for at least 6 months.
between 1998 and 2010 was 96.6% (538/557). Of the 5 patients with reoperative failure, 3 were related to concluding the operation after a false-positive intraoperative parathyroid hormone drop at 10 minutes postexcision (64%, 68%, and 87%) and after multiple glands were excised (total of 3 glands in 2 cases and 2 glands in 1 case). Our other 2 reoperative failures occurred when no abnormal parathyroid tissue was identified.

Temporary and permanent hypoparathyroidism are more common sequelae of reoperative than initial parathyroidectomy. While the difference in complication rates between groups in this study could not be accounted for entirely by different rates of symptomatic hypocalcemia, 15% of patients in the initial minimally invasive parathyroidectomy group and 25% in initial standard cervical exploration group experienced this complication. These findings support our practice of keeping all reoperative parathyroidectomy patients for an overnight observation period. Permanent hypoparathyroidism, one of the most severe long-term sequelae of reoperative parathyroidectomy, occurred in 11% of patients in the initial standard cervical exploration group, and none in the initial minimally invasive parathyroidectomy group. Permanent hypoparathyroidism did not occur in any patient whose intraoperative parathyroid hormone dropped by less than 81% at 10 minutes after excision of all involved parathyroid tissue.

Based on our results and a review of the literature, in the reoperative setting, the intraoperative parathyroid hormone drop anticipated to ensure cure of hypoparathyroidism is the same as that which places patients at risk for hypoparathyroidism. Studies have found an average intraoperative parathyroid hormone drop of 85% as both an average threshold for cure after reoperative parathyroidectomy and for increased incidence of hypocalcemia requiring supplementation.4,17,18 We may have avoided permanent hypoparathyroidism by sacrificing long-term cure in 2 patients.

There is no clear explanation for why patients in the initial standard cervical exploration group experienced more postoperative complications, independent of hypoparathyroidism, than their initial minimally invasive parathyroidectomy counterparts. Despite our review of all prior operative reports, we were unable to determine precisely how many patients in the initial standard cervical exploration group had a planned minimally invasive parathyroidectomy converted to standard cervical exploration because of difficult clinical situations (eg, misleading preoperative imaging or failure of intraoperative parathyroid hormone to fall appropriately after excision of a suspected adenoma). Including the initial minimally invasive parathyroidectomy converted to standard cervical exploration in the same group as the planned initial standard cervical exploration patients may have added some selection bias in that converted standard cervical exploration patients may have had a more complicated clinical situation. However, patients who had undergone more than 1 initial parathyroidectomy also had a higher rate of postoperative complications than the patients undergoing their first reoperation. Taken together, these 2 findings seem to indicate that the extent of initial operation in patients who have a failed parathyroidectomy has long-term consequences.

Conclusion

Only 70% of patients have an uneventful postoperative course after reoperative parathyroidectomy. The probability of morbidity and rate of permanent hypoparathyroidism was higher in patients who had undergone an initial standard cervical exploration. Performing the appropriate initial operation in this series yielded a 98% cure rate for initial operations performed at our institution. In patients with primary hyperparathyroidism undergoing initial parathyroidectomy, for whom a targeted approach (minimally invasive parathyroidectomy) is possible, these data should be considered before performing routine initial standard cervical exploration.

References


