Minimally invasive surgery for primary hyperparathyroidism with or without intraoperative parathyroid hormone monitoring

Kiminori Sugino, Koichi Ito, Mitsuji Nagahama, Wataru Kitagawa, Hiroshi Shibuya, Keiko Ohkuwa, Yukiko Yano and Kunihiko Ito

Surgical Branch, Ito Hospital, Tokyo 150-8308, Japan

Abstract. We analyzed the utility of intraoperative parathyroid hormone (IOPTH) monitoring in minimally invasive surgery for primary hyperparathyroidism (pHPT). The subjects were the 167 consecutive patients with pHPT performed initial operation with or without IOPTH between January 2000 and December 2006. Patients were divided into 2 groups. A group who underwent surgery without IOPTH monitoring (Group 1; n=87), and a group who underwent surgery with IOPTH monitoring (Group 2; n=80), in which IOPTH was measured at 5, 10, 15 minutes after excision of the abnormal parathyroid gland. Criterion for evaluation as a cure was a drop in intact PTH level of 50% or more from the preoperative baseline value. The overall cure rate in Group 1 was 93.1%. An enlarged parathyroid gland that was consistent with the results of a preoperative imaging study was found in 84 patients (96.6%). The overall cure rate in Group 2 was 97.5%. In 7 of the patients, there was no drop of 50% or more at any of the 3 points in time measured. Two of these patients were found to have had double adenomas, one on each side, during the initial surgery. Three others were eucalcemic and had normal intact PTH values after surgery, and the remaining 2 patients had persistent disease. Although preoperative localization studies are accurate and essential, IOPTH monitoring improves the cure rate of minimally invasive parathyroidectomy. IOPTH monitoring is a valuable adjunct to achieve adequate intraoperative decision-making, recognizing and resecting additional image-negative hyperfunctioning lesions.

Key words: Primary hyperparathyroidism, Minimally invasive surgery, Intraoperative parathyroid hormone assay

BILATERAL NECK EXPLORATION, the identification of all parathyroid glands and removal of all abnormal glands, has traditionally been regarded as the standard surgical strategy for the treatment of primary hyperparathyroidism (pHPT) [1-4]. However, in recent years, several investigators have questioned the routine performance of bilateral neck exploration because the cause of pHPT in most patients is a single parathyroid adenoma and preoperative imaging tests, such as Technetium-99m sestamibi scans and ultrasound examination have enabled precise localization of the affected parathyroid gland with high sensitivity [5-7]. Use of intraoperative PTH (IOPTH) measurement or the gamma probe with perioperative sestamibi injection has also contributed to improving results of surgery. For all of these reasons, a focused, image-guided operation by a direct approach with limited exploration termed minimally invasive parathyroidectomy appears to be replacing conventional bilateral neck exploration in most patients with pHPT.

Minimally invasive parathyroidectomy was introduced at our hospital in January, 2000, and IOPTH monitoring was introduced in September, 2004. In this paper we report the surgical outcome of minimally invasive surgery in patients with pHPT and the utility of IOPTH monitoring.

Subjects and Methods

Patients

Between January, 2000 and December, 2006, 265 patients with pHPT (confirmed by biochemical evaluation, including elevated serum calcium and plasma intact PTH measurement) were surgically treated at Ito Hospital. The criteria for inclusion in this
study were: at least one positive parathyroid localization study that showed evidence of parathyroid swelling (Technetium-99m sestamibi scan, ultrasound examination of the neck or computed tomography), no previous neck surgery, absence of concurrent thyroid disease requiring surgery, and no family history of pHPT. The 167 patients who remained after excluding those who did not meet these criteria were the subjects of this study. There were 135 females and 32 males, and their mean age was 56.4 years old (range: 13-86 years). The subjects were divided to 2 groups, i.e., the initial series of 87 patients operated on between January 2000 and August 2004 underwent parathyroidectomy without IOPTH monitoring (Group 1) and the 80 patients between September 2004 and December 2006 who underwent parathyroidectomy with IOPTH monitoring (Group 2).

**Surgical procedure**

Image-guided, focused cervical exploration was performed in every patient. An approximately 4cm long, collar incision was made one fingerbreadth above the sternal notch in every patient, and no change was made in this length of the incision even when a lesion is suspected in a superior gland. In Group 1, the operation was terminated when an enlarged parathyroid gland was excised. In Group 2, an abnormal parathyroid gland was removed and the incision was closed, and the operation was terminated after the intraoperative PTH level was confirmed to be decreased. No intraoperative frozen-section performed in any of the cases.

**Intraoperative PTH assay**

IOPTH monitoring was routinely performed on all patients in Group 2. An Elecsys intact-PTH assay (ECLIA: electrochemiluminescence immunoassay, Roche Diagnostic GmbH, Penzberg, Germany) was used to make the intraoperative quantitative determination of intact PTH. A preoperative (before tracheal intubation) baseline peripheral venous blood sample was collected, and intraoperative samples were collected 5 min, 10 min, and 15 min after excision of an abnormal parathyroid gland. The criterion for evaluation as a cure was 50% or more drop in intact PTH between the preoperative baseline level and the level in one of the 3 intraoperative peripheral blood specimens. There are several criteria for evaluating the fall in IOPTH level after parathyroidectomy and this is the first attempt of IOPTH in our institution. Thus, we employed 3 points evaluation.

**Evaluation of surgical outcome**

All patients were followed up in our outpatients department at 1, 3, and 6 months postoperatively and every 12 months thereafter. A biochemical examination that included serum calcium, albumin, and intact PTH determination was performed at every follow-up examination. If recurrent or persistent disease was suspected, neck ultrasonography and Technetium-99m sestamibi scans are performed and reoperation was recommended if they revealed evidence of a lesion. Parathyroidectomy was judged to have been successful when a patient was eucalcemic for at least 6 months postoperatively. The definition of persistent disease (operative failure) was hypercalcemia and an elevated intact PTH level within 6 months after surgery, and recurrent disease was defined as hypercalcemia and an elevated intact PTH level 6 months or more after successful surgery.

**Results**

**Patient characteristics**

There are no significant differences between the 2 groups in age, gender, preoperative Ca level, preoperative intact PTH level or preoperative localization procedures (Table 1). More patients in Group 2 underwent Technetium-99m sestamibi scans, but, the difference between the groups was not significant. If a preoperative ultrasound examination showed an obviously enlarged parathyroid gland, a sestamibi scan was not always performed. At least one preoperative imaging study was positive in every case. A total of 96 patients were examined by a sestamibi scan. In three patients the scan was negative and in other 93 patients (97%) it was positive and the localization found to have been correct at surgery. Mean operation time of Group 1 (30.4 min) was significantly shorter than that of Group 2 (48.2 min) (Student’s t test, p<0.05).

**Group 1**

The overall cure rate of 87 patients in Group 1 was 93.1% (Fig. 1). The pathological diagnosis was adenoma in 76 cases, hyperplasia in 5 cases, and carcinoma in 2 cases. The postoperative pathological examination of the tissue from 4 patients showed that the tissue suspected of being an enlarged parathyroid...
gland was not parathyroid gland tissue. They were all lymph nodes. Six patients had persistent disease, and they consisted of the 4 patients mentioned above, one patient with adenoma, and one patient with hyperplasia. Localization studies were performed again in these patients, and 5 patients underwent reoperation and were cured. The other patient had hyperplasia and was followed up because of mild hypercalcemia.

Of the 4 patients with no evidence of an enlarged parathyroid during the initial surgery, 1 was found to have a solitary adenoma at the same site as in the initial localization study, and the others had at the opposite sites. One patient with persistent disease who was found to have a parathyroid adenoma during the initial surgery, was found to have a second enlarged parathyroid on the opposite site within the thyroid gland (double adenoma).

An enlarged parathyroid gland was found intraoperatively at the same site as indicated by the preoperative imaging study in 84 of the patients (96.6%) in Group 1.

**Group 2**

The overall cure rate of the 80 patients in Group 2 was 97.5% (Fig. 2). The pathological diagnosis was adenoma in 77 cases, and hyperplasia in 3 cases. A drop in IOPTH of 50% or more compared to the preoperative level was observed at 5 min, 10 min, and 15 min after removal of enlarged parathyroid gland were observed in 58 patients (72.5%), 69 patients (86.3%), and 73 (91.3%) patients, respectively.

Eleven patients had less than a 50% drop in IOPTH level at 10 min, but 4 of these 11 patients had more than a 50% drop at 15 min. The other 7 patients did not have a more than 50% drop at any of the times measured intraoperatively. Exploration was performed at other sites in all 7 patients. In 2 of the 7 patients double adenomas were found on the opposite site during the initial surgery. No other enlarged parathyroid glands could be found during the initial surgery in any of the other 5 patients, and 3 of them were eucalcemic and had a normal intact PTH level after surgery. The IOPTH levels of these 3 patients were higher than the postoperative level at all 3 points measured, which decreased in normal range on the next day. The other 2 patients had persistent disease. A localization study was performed again after the initial surgery, and reoperation resulted in a cure. The pathological diagnosis was adenoma (double). Both patients had exploration for other sites during operation but we did not find pathological parathyroid glands. One patient had intrathyroidal parathyroid adenoma, and the other patients had small parathyroid adenoma (170 mg) on the opposite site. The latter patient was an 88 year-old woman and underwent the initial operation under local anesthesia. It is thought that insufficient exploration was performed at the initial operation. All patients in Group 2 had enlarged parathyroid gland that was seen on the preoperative imaging study, however, 4 patients with double adenoma had been diagnosed with a single lesion based on the preoperative imaging study.

**Surgical complications**

There were no operative deaths in either group. One patient had transient recurrent nerve palsy and had recovered by 6 months after surgery. Two patients had postoperative bleeding that required reoperation.

**Discussion**

Bilateral neck exploration with the objective of visualizing all of the parathyroid glands used to be the standard surgical procedure for pHPT with excellent outcomes of more than 95% cure rate [1-4]. Recently, preoperative localization imaging studies including by sestamibi scintigraphy and ultrasonography, have enabled accurate localization of enlarged parathyroid glands [5-7], and the surgical approach to the treatment of pHPT has changed to image-guided, focused, targeted parathyroidectomy through smaller incisions, with fewer complications and a shorter operating time [8-11]. However, the success of this minimally invasive surgery depends not only on the accuracy of localization studies, but on the methods of ruling out multiglandular disease and determining that a cure has been achieved. IOPTH monitoring and the use of a gamma probe after perioperative sestamibi injection have been widely recognized as the tool of intraoperative determination. However, because most pHPT is induced by a single adenoma, focused parathyroidectomy without these intraoperative adjuncts has been reported to result in an excellent surgical outcome [12-15]. Thus, whether these techniques actually contribute to a successful surgical outcome, remains unclear.

Focused parathyroidectomy has been used as the standard surgical procedure in our institution for suspected single parathyroid adenomas, and the overall cure rate without IOPTH monitoring was more than
### Table 1 Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=87)</th>
<th>Group 2 (n=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong>*</td>
<td>56.8</td>
<td>55.8</td>
</tr>
<tr>
<td><strong>Gender: Female</strong></td>
<td>73 (84%)</td>
<td>62 (78%)</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>14 (16%)</td>
<td>18 (22%)</td>
</tr>
<tr>
<td><strong>Resected weight (mg)</strong>*</td>
<td>1068</td>
<td>1074</td>
</tr>
<tr>
<td><strong>Preoperative Ca (mg/dL)</strong>*</td>
<td>11.5</td>
<td>11.6</td>
</tr>
<tr>
<td><strong>Preoperative i-PTH (pg/mL)</strong>*</td>
<td>183</td>
<td>211</td>
</tr>
<tr>
<td><strong>Localization test (US/CT/sestamibi %)</strong></td>
<td>100/80/48</td>
<td>100/85/70</td>
</tr>
</tbody>
</table>

*: mean

---

**Fig. 1** Surgical outcome in Group 1. After the initial surgery 93% of the patients had been cured. Five of the 6 patients with persistent pHPT were reoperated and cured.

**Fig. 2** Surgical outcome in Group 2. The overall cure rate was 97%. More than a 50% drop at 10 min was observed in 86% of the patients. Four patients had more than a 50% drop at 15 min. Re-exploration in 7 patients revealed other adenomas in 2 patients, but no other enlarged parathyroid glands were found in the other 5 patients.
Surgery for primary hyperparathyroidism

93%. After the introduction of IOPTH monitoring, the overall cure rate improved to 97%. Although in most cases primary hyperparathyroidism is caused by a single parathyroid adenoma [16-18], a few patients have parathyroid hyperplasia or multiple adenomas. An excellent success rate can be achieved by focused parathyroidectomy with IOPTH monitoring. Our results showed a 4% improvement in the success rate after the introduction of IOPTH monitoring.

The Miami criterion, i.e., a drop in intact PTH level of 50% or more from the preoperative baseline or the pre-excision level, whichever is higher, 10 min after excision is often used to determine whether a cure has been achieved [19, 20]. Since this was our first attempt to perform focused parathyroidectomy with IOPTH monitoring, we measured intact PTH at 3 points, i.e. 5 min, 10 min and 15 min after excision. A 50% or more drop from the preoperative baseline level was observed in 58 patients (72.5%) after 5 min, after 10 min in 69 (86.3%), and after 15 min in 73 (91.3%). These percentages are not as high as previously reported because we used only preoperative PTH levels as the baseline values. We should have used whichever level was higher, the preoperative PTH level or the pre-excision PTH level, as the baseline value. Three patients with less than a 50% drop in the IOPTH level at 15 min had a higher IOPTH level at all 3 points than their preoperative level. This hypersecretion of PTH was induced by manipulation of an enlarged parathyroid gland, and the PTH value just before excision or ligation of drainage vein is thought to be the proper baseline value. However, since there were no increases in PTH values after excision of the lesion in any of the patients in whom the enlarged parathyroid gland had been carefully handled during the operation, we have used the preoperative PTH level as the baseline value.

Localization studies are essential before minimally invasive parathyroidectomy. We usually perform a sestamibi scan and ultrasound examination as localization studies. A sestamibi scan is usually used as the standard localization imaging study and the lesions were accurately localized by sestamibi scans in 97% of our patients. Some reported IOPTH is not always necessary for minimally invasive because these localization studies accurately diagnosed [12-15]. However, we think IOPTH monitoring is necessary during minimally invasive surgery because some patients have double adenomas and hyperplasia although they are less common. In our study there was one case of double adenoma in Group 1 and 2 cases in Group 2 that could not be diagnosed preoperatively. IOPTH monitoring would be a great help in such patients.

Some patients have been reported to have an increased intact PTH level despite normocalcemia after curative parathyroidectomy. We measured the serum calcium and intact PTH levels of every patient in Group 2 during follow up in the outpatient department. High PTH values with normocalcemia were recorded after surgery in 33 (42%) of the 78 patients evaluated as cured in our study, and these findings continued for 6-24 months after surgery. An elevated PTH level with normocalcemia is considered a physiological response to an overall calcium deficit and low preoperative vitamin D3 level [21-24]. It has been reported that most such patients respond to exogenous calcium and vitamin D3 supplementation and that their PTH levels decrease within 3-6 months but their normocalcemia continues.

In conclusion, although preoperative localization studies are accurate and essential, IOPTH monitoring improves the cure rate of minimally invasive parathyroidectomy. IOPTH monitoring is valuable adjunct to achieving adequate decision-making during surgery and to recognizing and resecting additional imaging-negative hyperfunctioning lesions.

References