

Minimally invasive parathyroidectomy without intraoperative parathyroid hormone monitoring in patients with primary hyperparathyroidism

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Background: Minimally invasive parathyroidectomy (MIP) is the preferred operation for patients with primary hyperparathyroidism (HPT) and positive preoperative imaging. This non-randomized case series assessed the long-term results of MIP performed without the use of intraoperative parathyroid hormone (ioPTH) monitoring.

Methods: The study involved prospective collection of demographic, biochemical and operative details on a consecutive, unselected cohort of 298 patients who underwent surgery for non-familial primary HPT during a 5-year interval. The mean preoperative serum calcium level was 3.00 mmol/l with a mean parathyroid hormone concentration of 25.8 pmol/l. ^{99m}Tc-labelled sestamibi scanning and neck ultrasonography were performed in 262 patients.

Results: Sestamibi scan showed unilateral uptake in 182 patients and a single parathyroid adenoma was confirmed on ultrasonography in 161 patients. MIP was performed in 150 patients. The mean duration of operation was 25 (range 8–65) min. Four patients needed conversion to conventional neck exploration. There was one postoperative haematoma and three cases of temporary recurrent laryngeal nerve neuropraxia. All but four patients were normocalcaemic after MIP. All the parathyroid tumours removed were adenomas, with a mean weight of 1.3 (range 0.1–17.4) g. No patient developed recurrent HPT after a median follow-up of 16 (range 3–48) months.

Conclusion: The outcome of MIP without ioPTH monitoring was comparable to that reported in series that used ioPTH monitoring.

Paper accepted 18 October 2006

Published online 2 November 2006 in Wiley InterScience (www.bjs.co.uk). DOI: 10.1002/bjs.5574

Introduction

Bilateral neck exploration was the standard operation for primary hyperparathyroidism (HPT). The goal of the procedure was to identify all four parathyroid glands and to remove all abnormal parathyroid tissue. In expert hands up to 99 per cent of patients were cured with minimal morbidity¹. Such results have, however, been reported mainly from centres with very high volume practice. A 70 per cent cure rate may possibly reflect general surgical practice more faithfully². The British Association of Endocrine Surgeons' guidelines recommend that 95 per cent of patients should be normocalcaemic after first neck exploration for HPT³.

Over 85 per cent of patients with primary HPT have single-gland disease. In these, unilateral cervical

exploration would therefore appear to be better than four-gland exploration. This was first proposed in the 1980s^{4,5}, but the unreliability of thallium–technetium subtraction scintigraphy at that time meant that few surgeons had the confidence to perform single-gland resections. Computed tomography and magnetic resonance imaging were too insensitive to allow unilateral surgery. The introduction of ^{99m}Tc-labelled sestamibi scanning has revolutionized parathyroid imaging. Multiple authors have reported that over 70 per cent of parathyroid adenomas can be localized⁶. When ultrasonography of the neck concordantly localizes a diseased parathyroid gland, the combination of the two imaging techniques offers 95–98 per cent accuracy⁷. This improvement in imaging has made the application of minimal-access approaches to primary parathyroid disease

a reality. Although videoscopically assisted parathyroidectomy and endoscopic parathyroidectomy are technically feasible^{8,9}, the technique favoured by most endocrine surgeons is minimally invasive parathyroidectomy (MIP), based on a focused lateral approach¹⁰. Surgeons who first embraced this new technique have used it in conjunction with intraoperative parathyroid hormone (ioPTH) monitoring to confirm excision of the overactive parathyroid gland. Results of several retrospective series have been published^{11–13} and confirmed in a recent randomized trial¹⁴. As a consequence, the availability of MIP has lowered the referral threshold for HPT and more patients are having surgery than previously¹⁵.

The aim of this study was to determine whether omitting ioPTH measurement in patients with two concordant preoperative localization studies affected the cure rate of HPT after MIP.

Patients and methods

From April 2001 all patients with a biochemical diagnosis of primary HPT have been considered for MIP. Patients with familial disease, a history of persistent or recurrent HPT or with a large goitre were excluded and underwent conventional neck exploration. Previous neck surgery was mistakenly not considered a contraindication in two patients at the beginning of this series; subsequently this was changed. The remaining patients underwent preoperative localization with ^{99m}Tc-labelled sestamibi imaging and ultrasonography of the neck. Patients underwent MIP when the two localization studies were concordant.

Sestamibi scans were performed using the single-agent washout technique. Patients were given 600 MBq ^{99m}Tc-labelled sestamibi. Single frontal planar images were obtained at 10 min and 2 h after isotope administration. Single-photon emission tomography images were obtained at 2 h. Patients were imaged using a Sophix[®] DST-XL γ camera (General Electric; Paris, France) with a low-energy, high-resolution parallel collimator and pictures were obtained with a 256 \times 256 matrix. Ultrasonography was performed by a single experienced operator using a small-footprint high-resolution 15-MHz linear array probe (Sequoia[®]; Accuson, Mountain View, California, USA).

Laryngeal mask general anaesthesia with propofol and a superficial cervical block on the side of the localized adenoma were employed. Frail patients considered at risk for general anaesthesia had surgery under local anaesthesia.

An intravenous infusion of 5 mg/kg methylene blue in 500 ml normal saline was started 1 h before surgery to aid

intraoperative localization of the parathyroid glands. A 20-mm transverse incision was made in a skin crease directly over the localized parathyroid gland, along the medial border of the sternomastoid muscle¹⁶. The sternomastoid muscle was mobilized laterally and the strap muscles medially to reveal the lateral margin of the thyroid gland. The parathyroid adenoma was then identified and dissected out; ioPTH measurements or frozen-section analysis were not performed.

All patients were considered for discharge on the day of surgery, or the following morning if surgery was performed in the afternoon. Calcium tablets were provided to be taken when needed and patients were given instructions on how to identify the symptoms of hypocalcaemia.

The duration of operation (skin-to-skin time) was recorded prospectively along with the length of hospital stay, complications and conversion rates. All patients were seen in the outpatient clinic 4–6 weeks after surgery, and assessed for symptoms and complications along with a review of the histological findings. A further follow-up appointment was organized at 6–12 months. Patients treated earlier in this series were contacted once more and had a repeat calcium and PTH measurement.

Statistical comparison of biochemical variables between subgroups of patients was done using an unpaired Student's *t* test. Proportions were compared using the χ^2 test. For all tests $P < 0.050$ was considered significant.

Results

Between June 2001 and January 2006, 298 patients underwent surgical treatment for non-familial primary HPT. The mean (s.d.) preoperative serum calcium level was 3.00 (0.36) mmol/l with a parathyroid hormone concentration of 25.8 (22.2) pmol/l. Thirty-six patients had no imaging studies, either because they had surgery as an emergency or for administrative reasons. Localization investigations were performed in 262 patients. There were 72 negative imaging studies. Eight patients had bilateral sestamibi uptake and ultrasonography suggesting the possibility of bilateral adenomas. The sestamibi scan indicated unilateral uptake in 182 patients and a single parathyroid adenoma was seen on ultrasonography in 161 of these (*Fig. 1*). MIP was not performed if patients had additional procedures during the same anaesthetic (three patients), very large tumours (over 5 cm in diameter as suggested by ultrasonography; three) or adenomas localized behind the clavicle or in the thymus (five).

MIP was performed in 150 patients. Their demographic and biochemical data were similar to those in patients undergoing formal neck exploration (*Table 1*). Surgery

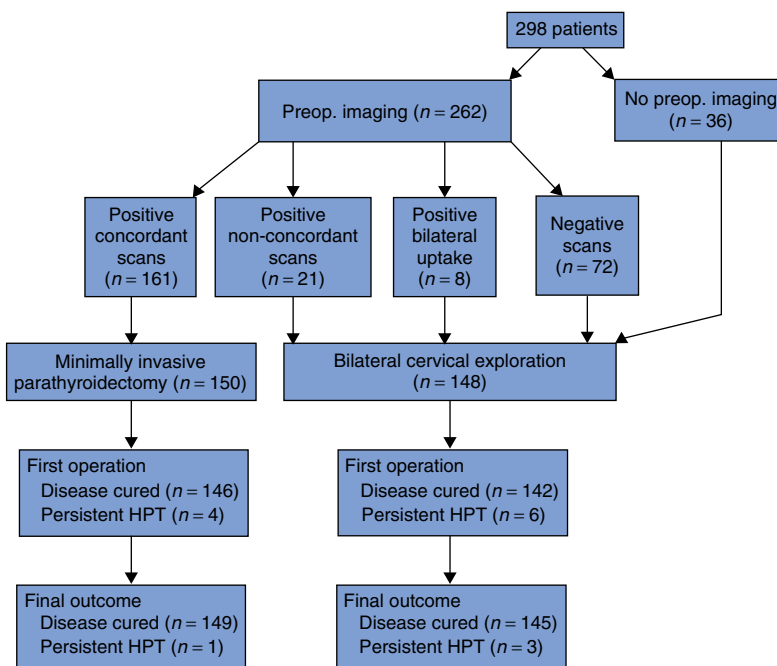


Fig. 1 Flow chart describing the selection of patients undergoing minimally invasive parathyroidectomy in a cohort of 298 consecutive patients with primary hyperparathyroidism (HPT)

Table 1 Preoperative demographic and biochemical data for 298 patients with primary hyperparathyroidism who underwent minimally invasive parathyroidectomy or formal bilateral or unilateral neck exploration

	MIP (n = 150)	Non-MIP (n = 148)
Sex ratio (M:F)	46:104	40:108
Age (years)*	60(16) (17–89)	63(14) (18–90)
Preoperative calcium (mmol/l)*	2.95(0.33) (2.67–3.86)	2.97(0.26) (2.71–3.97)
PTH (pmol/l)*	25.3(25.0) (4.5–137.0)	18.8(17.6) (3.9–117.0)

*Values are mean(s.d.) (range). Normal ranges for calcium and parathyroid hormone (PTH) are 2.12–2.65 mmol/l and 0.8–8.5 pmol/l respectively. MIP, minimally invasive parathyroidectomy.

was performed under general anaesthesia in 146 patients and under local anaesthetic in four. The mean(s.d.) duration of operation was 25(12) (median 20, range 8–65) min. Conversion to a conventional neck exploration was required in four patients. One frail elderly patient unsuitable for a general anaesthetic had MIP under local anaesthesia, but the procedure was abandoned because of discomfort.

A parathyroid adenoma was identified and excised in 146 patients. All parathyroid tumours removed by MIP were histologically adenomas with a mean(s.d.) weight of 1.3(0.9) (median 1.0, range 0.1–17.4) g. There was no significant

difference in the weight of adenomas removed by MIP or conventional dissection. All but four patients became normocalcaemic after surgery. In two, thyroid nodules were excised instead, in one no adenoma was found, and in the fourth an adenoma was too close to the recurrent laryngeal nerve. Three patients underwent subsequent bilateral neck exploration and were cured, and the fourth died 3 months later with persistent hypercalcaemia.

Seventy-four patients were discharged home the same day and 70 patients the following day (within 23 h). Six patients were admitted for 2–4 days owing to social circumstances. There was one postoperative local haematoma that was treated conservatively. Three patients had recurrent laryngeal nerve neuropraxia with voice changes that lasted 2 months. Subsequent voice recovery was complete.

All patients who underwent successful MIP were normocalcaemic (mean(s.d.) calcium level 2.34(0.11) mmol/l) when first reviewed in outpatients 4–6 weeks following surgery. Most patients reported an improvement in symptoms, in particular tiredness and lethargy.

Follow-up for more than 3 months was possible in 139 patients who underwent MIP. Four patients died during follow-up (at 18, 26, 26 and 3 months). Five patients were lost to follow-up because they lived outside the region and two patients failed to attend their

appointments. Mean(s.d.) follow-up was 15(10) (median 16, range 3–48) months and 103 patients had follow-up for longer than 1 year. All but one had normal serum calcium levels and no patient developed recurrent HPT.

Discussion

Minimal-access parathyroidectomy using a focused lateral approach is the current method of choice for 92 per cent of members of the International Association of Endocrine Surgeons and several large series have already been published^{11–14}.

MIP has been restricted to patients with concordant positive sestamibi and ultrasonographic scans, and as a consequence MIP was offered to just over half of the patients who had localization studies (150 of 262 patients, 57.3 per cent). This figure compares favourably with published data. When similar criteria were applied to a group of 149 consecutive patients, unilateral cervical exploration was considered feasible in only 30 per cent¹⁷. In contrast, clinicians who use sestamibi imaging as their only selection criteria offer MIP to over 80 per cent of patients. Applying the criteria of concordant imaging studies leads to fewer patients being selected for MIP. This was compensated by a lower rate of conversion to bilateral cervical exploration in the present series (four of 150 procedures, 2.7 per cent) compared with reported conversion rates of 7 per cent¹¹ and 8.8 per cent¹⁸.

MIP was performed in a mean of 25 min, while respecting established principles of conventional parathyroid surgery: avoiding parathyroid capsular breach and identification of the recurrent laryngeal nerve (although the position of some glands has sometimes made this unnecessary).

Four patients remained hypercalcaemic after MIP. In two a thyroid nodule was removed instead and arguably these would have been identified if ioPTH monitoring had been used. Three of the four patients with persistent HPT underwent a total of four bilateral cervical explorations to identify their single parathyroid adenomas and were subsequently cured. The rates of persistent HPT were similar after MIP (four of 150 patients) and bilateral cervical exploration (six of 148 patients) (*Fig. 1*).

No patient developed recurrent HPT after a median follow-up of 16 months. These findings counteract previously expressed concerns that MIP could underestimate multigland disease and might increase the risk of persistent or recurrent hypercalcaemia¹⁹. These reassuring findings are possibly a result of the strict selection of patients offered MIP. A major contribution to the ongoing

debate was a randomized trial demonstrating that scan-directed unilateral cervical exploration for primary HPT did not significantly increase the incidence of persistent hypercalcaemia²⁰.

In previous studies, the use of ioPTH measurement has been encouraged to confirm the success of parathyroidectomy at the time of minimal-access surgery given that not all four parathyroid glands are visualized. A decrease of greater than 50 per cent in PTH concentration within 10–15 min of removal of the hyperfunctioning parathyroid is believed to correspond to cure. The argument in favour of ioPTH monitoring is that multigland disease is present in up to 10 per cent of patients with HPT and such patients can be identified and cured only if all four parathyroid glands are visualized during the operation^{21–23}. This view was reinforced by the findings of a recent prospective study of 350 patients from the Cleveland Clinic; unilateral exploration based on concordant preoperative sestamibi and ultrasonographic localization identified single-gland disease in 79 per cent of patients but additional abnormal parathyroid glands were found on complete exploration in 15 per cent, even in patients with concordant imaging studies and an appropriate fall in PTH²³. Similar findings were reported in a large cohort of 345 patients; when ioPTH measurement was used all 188 patients were cured of disease at first operation, whereas in the group of 157 patients who did not have ioPTH monitoring there was a 10 per cent incidence of persistent disease owing to additional unidentified overactive parathyroid glands²⁴.

However, ioPTH measurement may also fail to identify multigland disease²⁵. In a study of 69 patients who underwent conventional bilateral cervical exploration with ioPTH monitoring, multiple-gland disease was missed in 75 per cent of patients²⁶. In addition, ioPTH results did not identify multiglandular disease in 11 of 423 patients undergoing focused parathyroidectomy²⁷.

Another recent analysis of MIP with ioPTH measurement failed to support its use²⁸. Several studies have reported that MIP without ioPTH monitoring achieved normocalcaemia in 44 of 47 patients²⁹, in 41 of 45 patients³⁰ and in 44 of 49 patients³¹. The Mayo Clinic reported that patients with primary HPT and an unequivocally positive preoperative sestamibi scan can successfully be managed by focused unilateral cervical exploration without ioPTH monitoring³².

Omitting ioPTH monitoring in a selected group of patients offers financial advantages related to the cost of the equipment and PTH assays. Furthermore, the operation is finished as soon as the adenoma is excised without having to wait for the blood samples to be drawn 10 and 30 min after

excision of the parathyroid adenoma. This can increase the throughput of patients during one operating session.

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