

Long-Term Symptom Relief from Primary Hyperparathyroidism Following Minimally Invasive Parathyroidectomy

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Abstract

Background The affect of the surgical approach for primary hyperparathyroidism (1HPT) on long-term symptom relief has not been studied. This study compares the long-term relief of symptoms assessed by the Parathyroidectomy Assessment of Symptoms (PAS) score in patients undergoing bilateral neck exploration (BNE) and minimally invasive parathyroidectomy (MIP).

Methods In this case–control study, patients with 1HPT who had followed a protocol to assess symptoms before and after parathyroid surgery between 1999 and 2008 were contacted by letter and had blood taken to assess calcium, ionized calcium, and parathyroid hormone (PTH). The main aim was to assess symptoms at long-term follow-up using the PAS score. The incidence of persistent or recurrent 1HPT at long-term follow-up after MIP and BNE was also compared.

Results Two hundred and forty-six patients underwent parathyroid surgery and 142 responded to our correspondence, of which 64 underwent MIP and 78 BNE. Follow-up after BNE was longer than MIP (61 vs. 41 months). At

long-term follow-up, the mean PAS score fell by 125 and 175 in the MIP and BNE groups, respectively. There was no statistically significant difference in the decline of the PAS score between the MIP and BNE groups. Six patients developed persistent or recurrent 1HPT following MIP compared to three after BNE; this difference was not statistically significant.

Conclusions This study is the first to report on long-term symptom relief from 1HPT after MIP, and demonstrates that both MIP and BNE can achieve this. In order to establish whether the long-term outcomes from these procedures are equivalent, further adequately powered studies are required.

Introduction

Focused unilateral neck exploration (UNE) or minimally invasive parathyroidectomy (MIP) has been widely adopted as the procedure of choice for treating primary hyperparathyroidism (1HPT) when preoperative localization studies have identified a single enlarged or hyperfunctioning parathyroid gland [1]. Parathyroidectomy not only restores serum calcium and parathyroid hormone (PTH) to normal and improves bone mineral density, it also improves a number of significant and underestimated symptoms associated with parathyroid disease [2]. It has been demonstrated that in the short term, the improvement in symptom relief and health-related quality of life following the focused approach is comparable [3, 4] and may be superior to that of bilateral neck exploration (BNE) [5]. The advantages of MIP over BNE, such as a shorter incision, minimal tissue dissection, shorter operative time, shorter hospital stay, and less postoperative hypocalcemia [6–9], might be expected to result in a greater short-term improvement in health-related quality of life following the

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Table 1 Fall in mean serum calcium, ionized calcium, and PTH following parathyroidectomy

Mean serum	MIP		<i>t</i> Test <i>P</i> value	BNE		<i>t</i> Test <i>P</i> value
	Preoperation	Follow-up		Preoperation	Follow-up	
Calcium (mmol/l)	2.75	2.43	<0.0001	2.75	2.39	<0.0001
Ionised calcium (mmol/l)	1.39	1.24	<0.0001	1.39	1.22	<0.0001
PTH (pmol/l)	15.9	5.3	<0.0001	13.8	4.39	<0.0001

focused approach to parathyroid disease. It is important therefore to examine whether the symptom relief from the focused approach to parathyroid disease is durable in the long term. The aim of this study was to establish whether the long-term symptom relief from MIP is comparable to that following BNE.

Materials and methods

Patients who had followed a protocol to assess symptoms before and after parathyroid surgery were invited to participate in this study. Each had completed a PAS score and had serum calcium, ionized calcium, and PTH levels assessed before surgery. Eligible patients with 1HPT who had undergone surgery between 1999 and 2008 were contacted by letter. Those patients who returned their PAS scores and had blood taken for calcium, ionized calcium, and PTH were included. Patients with a family history of 1HPT or multiple endocrine neoplasia (MEN) were excluded from this study.

The surgical strategy was to offer MIP to patients who had a parathyroid gland identified by sestamibi or ultrasound scans. Colocalization of a parathyroid adenoma with sestamibi and ultrasound scan was not considered essential. A previous study by this group has shown this approach to be acceptable [10].

At operation an enlarged gland was removed and a sensible but limited effort was made to identify the remaining gland through the same minimally invasive incision. This was an expedient and easy option that did not involve extending the incision, nor did it prolong the procedure by more than several minutes. It is important to stress that this operation is a minimally invasive approach using modern technology and different from the well-reported unilateral approach. Surgical technique involved marking the skin over the gland when visible with on-table ultrasound. When the enlarged gland was seen with sestamibi alone, an assessment of its position was made to plan the incision. No attempt was made to limit the incision length, which varied between 2 and 4 cm depending on patient size and ease of access. Most cases had a medial approach with elevation of the strap muscles from the thyroid gland to gain access to the parathyroid glands. A

few patients had a lateral approach for teaching purposes. The former made it easier to look for the noninvolved gland.

Bilateral neck exploration was undertaken if no enlarged parathyroid was found by ultrasound and sestamibi. If at operation a parathyroid adenoma was not found at the site indicated by localization studies or two enlarged parathyroid glands were seen on the same side of the neck, then MIP was converted to BNE. If localization studies identified adenomas on the same side of the neck but in different locations, then this side of the neck was still explored through a minimally invasive incision with the intention of identifying both parathyroid glands. Results were not analyzed on an intent-to-treat basis, i.e., if a MIP was converted to BNE, the results were analyzed in the BNE group.

Results

Two hundred and forty-six patients who underwent parathyroid surgery and were eligible for inclusion in the study were contacted by letter; 142 responded to our correspondence of whom 64 underwent MIP and 78 BNE. The mean ages of patients in both groups were similar (64.0 years for MIP and 63.2 years for BNE). Mean follow-up was significantly longer in the BNE group (60.8 vs. 41.4 months, $P < 0.0001$) and the mean number of glands removed at BNE was greater than at MIP (1.44 vs. 1.1, $P = 0.0046$). Mean serum calcium, ionized calcium, and PTH decreased at long-term follow-up after both MIP and BNE (Table 1).

At long-term follow-up, the mean PAS score fell by 125 ± 27 after MIP ($P = 0.0024$, *t* test) and by 175 ± 26 after BNE ($P < 0.0001$, *t* test), although the difference in the mean decline in the PAS score after these two procedures was not statistically significant ($P = 0.18$, *t* test, 95% confidence interval = -126 to 23) (Figs. 1, 2).

At long-term follow-up after MIP, 11 of the 13 symptoms that the PAS score comprises improved, of which five improved significantly ($P < 0.05$, Mann–Whitney) (Fig. 3), whereas 12 of the 13 PAS symptoms improved following BNE, of which 11 improved significantly ($P < 0.05$, Mann–Whitney) (Fig. 4).

Although 12 of the PAS symptoms improved more at long-term follow-up after BNE than MIP, the difference in the mean decline between the two groups in each of the 13

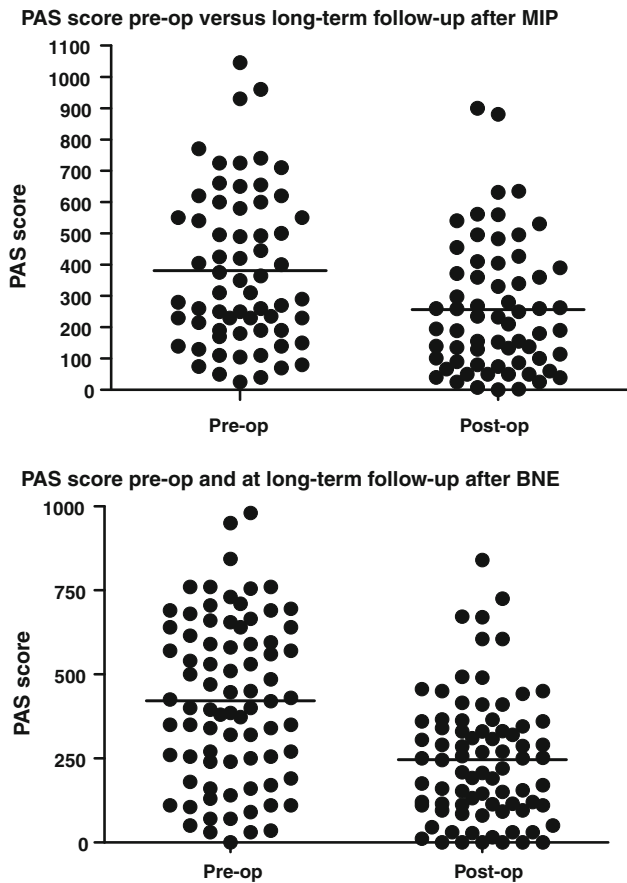


Fig. 1 PAS score preop versus long-term follow-up after MIP and BNE

symptoms in the PAS score was not statistically significant ($P > 0.05$, t test) (Fig. 5).

Two of the three patients who underwent BNE and who developed persistent or recurrent disease were subsequently found to have mediastinal parathyroid glands. The third patient had a 713-mg parathyroid adenoma excised at the first operation. Postoperatively, serum calcium and PTH fell to within the normal range but at 10 months' follow-up there was biochemical evidence of recurrent disease. No further surgery has been performed at this stage.

Three patients had persistent 1HPT following MIP. The parathyroid adenoma was missed at operation in one case; since the histopathology from the excised tissue showed a normal parathyroid gland in a fat pad, no further surgery was performed. Persistent 1HPT was due to failure to identify multigland disease (MGD) in two cases who subsequently had successful reoperative surgery with normalization of serum biochemistry.

Three patients developed recurrent 1HPT at long-term follow-up after MIP. One had a very large parathyroid adenoma (12.3 g) excised at the first operation, after which the serum calcium fell to within the normal range, but

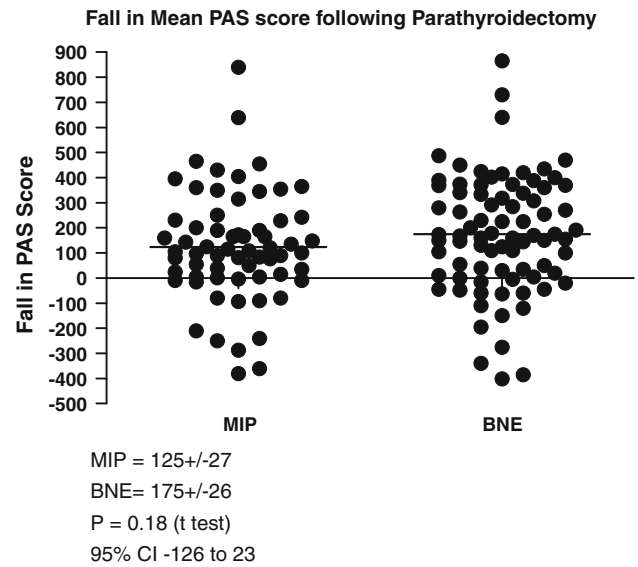


Fig. 2 Fall in mean PAS score at long-term follow-up following MIP and BNE

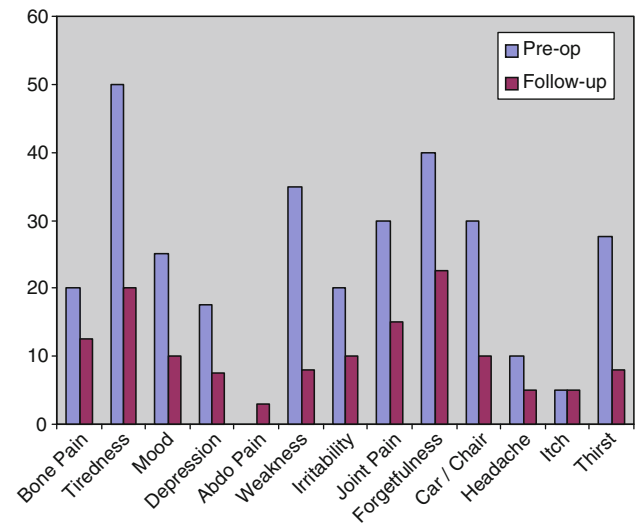


Fig. 3 Fall in median PAS score at long-term follow-up after MIP

biochemical evidence of recurrent disease was present at 13 months' follow-up. The remaining two patients had adenomas (420 and 390 mg) excised initially, after which serum calcium and PTH fell to within the normal range, but both developed recurrent pHPT at long-term follow-up (60 and 57 months). None of these three patients have undergone further surgery yet.

Discussion

Parathyroid disease is associated with many and often quite severe unrecognized symptoms. Parathyroidectomy, in

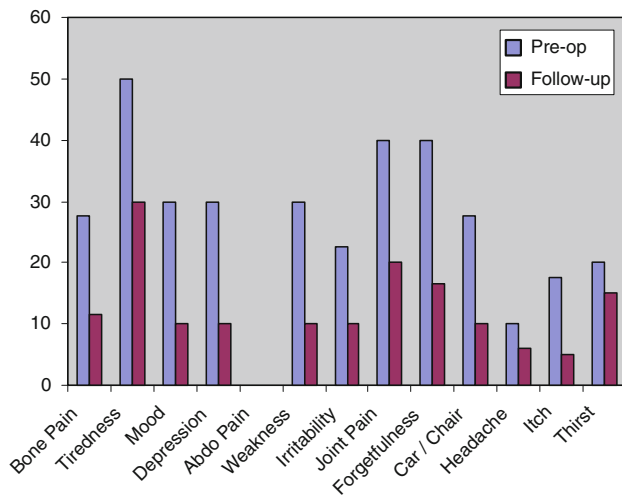


Fig. 4 Fall in median PAS score at long-term follow-up after BNE

addition to restoring the serum calcium and PTH to normal, has been shown to improve these symptoms and health-related quality of life. The most widely used measure of health-related quality of life is the Medical Outcomes Short Form (SF-36) health status questionnaire: this assesses nine domains of health status and function to arrive at a global score [11]. However the SF-36 has limited clinical utility in assessing health-related quality of life following parathyroidectomy because it is cumbersome, generic, and contains several domains that are unresponsive to the changes that occur after parathyroid surgery [4].

The Parathyroid Assessment of Symptoms (PAS) score, developed by Janice Pasioka, was designed as a disease-specific outcome tool to assess symptom relief following parathyroid surgery based on 13 symptoms most commonly seen in hyperparathyroidism. Each symptom is graded using a visual analog score from 0 (no symptoms) to 100 (extreme symptoms). The PAS score is calculated from the sum of each symptom score [12]. The PAS score has been shown to correlate with health-related quality of life measured by the SF-36 following parathyroid surgery [4]. It has been validated in primary, secondary, and tertiary hyperparathyroidism and in a multicenter trial across Canada, US, and Australia, the Australian arm of this trial being our institution [13]. In addition, a recent study from this group has confirmed that symptom relief following parathyroidectomy, measured by the PAS score, persists in the long term [14].

The short-term improvement in quality of life following MIP might be expected to be equivalent to or greater than that after BNE, provided both procedures achieve similar biochemical cure rates, as the focused approach involves a shorter wound, less tissue dissection, a shorter hospital stay, quicker recovery, and less postoperative hypocalcemia [6–9]. The published evidence supports this hypothesis, as

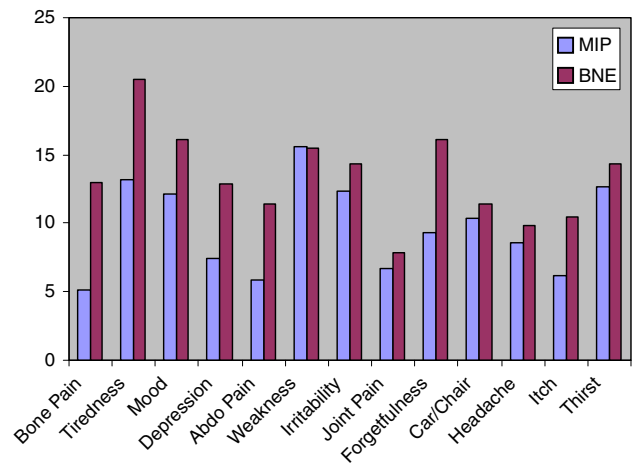


Fig. 5 Mean fall in PAS symptom scores at long-term follow-up after MIP and BNE

two studies comparing the short-term improvement in quality of life following the focused approach with BNE have reported equivalent outcomes assessed by the SF-36 [3, 4] and PAS [4] scores and one Australian study has reported a greater short-term improvement in quality of life after MIP than BNE [5]. At long-term follow-up, the short-term advantages of the focused approach outlined above have disappeared, and so the long-term improvement in quality of life can be attributed solely to normalization of hypercalcemia. Whereas several studies have established that MIP provides long-term biochemical cure equivalent to BNE [15–17], none have addressed whether the long-term symptom relief following MIP is comparable to BNE.

This study has demonstrated that both MIP and BNE can achieve long-term symptom relief from 1HPT, although whether the long-term results of the two approaches are comparable is less clear. No significant difference in the decrease in the PAS score or failure (persistence or recurrence) rate was observed at long-term follow-up between the two procedures, and the width of the 95% confidence interval for the difference in the mean fall in the PAS score suggests that there were adequate numbers of cases to be able to demonstrate a difference in symptom relief between the two groups. However, it was noted that the fall in the PAS score was less after MIP (125) than after BNE (175) and the failure rate was higher after MIP (6/64 or 10%) than after BNE (3/78 or 4%). Three of the six failures after MIP had persistent disease, two of whom subsequently had successful reoperative surgery, the third electing not to undergo this. Therefore, true long-term recurrence occurred in 3/64 or 5% of patients after MIP, which is comparable to other published long-term outcomes from focused UNE/MIP [15–17]. Persistence or recurrence rates following MIP were not the primary end point of this study as they have previously been

investigated elsewhere, but it is necessary to report them in conjunction with PAS scores because the two may be interdependent.

It is probable that the current study is insufficiently powered to determine whether there is a true difference in outcome between the two procedures and it is noted that a power calculation was not performed. One possible interpretation of these data is that MIP is not as durable a procedure as BNE because of the occurrence of a higher percentage of patients with persistent or recurrent hypercalcemia following MIP, resulting in a lower drop in PAS score at long-term follow-up. It is probable, however, that there are insufficient case numbers to support this interpretation or the null hypothesis, i.e., there is no difference in long-term outcome.

The study period included the “learning curve” for MIP at our institution, but the possibility that this affected the surgical outcome has been discounted as the six cases with persistent or recurrent disease following MIP had surgery later in the study period.

The limitations of this study are that it is retrospective and nonrandomized. There was a relatively low response (58%) to the postal correspondence. Results were not analyzed on an intent-to-treat basis, i.e., when MIP was converted to BNE, outcome was analyzed in the BNE group. Follow-up was significantly longer for the BNE group. In addition, as patients undergoing MIP are a group selected on the basis of suspected SGD, it could be argued that they are dissimilar to patients undergoing BNE, who would be expected to have more severe disease and a higher incidence of MGD, and therefore it is not justified to compare the outcome of MIP with that of BNE.

Conclusions

Focused UNE or MIP has now superseded BNE as the procedure of choice for the surgical treatment of 1HPT, when preoperative studies have identified and localized SGD. BNE has been proven to be a safe and effective operation [18]. However, the advantages of focused UNE or MIP include shorter operating time, quicker recovery, improved cosmesis, less postoperative hypocalcemia, and less postoperative scarring in the neck, allowing for safer reoperation. This study is the first to report long-term symptom relief from 1HPT after MIP, and it demonstrates that both MIP and BNE can achieve this. In order to establish whether the long-term outcomes from these procedures are equivalent, further adequately powered studies are required.

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