

Persistent symptomatic improvement in the majority of patients undergoing parathyroidectomy for primary hyperparathyroidism

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Received: 29 May 2010 / Accepted: 5 July 2010 / Published online: 25 July 2010
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Abstract

Background Parathyroidectomy for primary hyperparathyroidism (PHPT) is followed by a decrease in the severity of symptoms reported on the Pasieka's parathyroid symptoms score (PPSS) and SF-36 questionnaires. Some argue that such benefits are short-lived. This study investigates the severity of symptoms at more than 12 months after parathyroidectomy.

Methods A prospective database collected clinical/operative data on consecutive patients with PHPT. PPSS was calculated as the sum of the 13 parameters self-assessed using a visual analog scale. SF-36(v2) was analyzed using commercially available software (QualityMetric Inc., Lincoln, USA).

Results Over 3-year interval, 166 patients (119 F/47 M, age 15–89 years) were operated for with PHPT (Ca 2.90 ± 0.25 mmol/L, PTH 21.64 ± 23.05 pmol/L). Their preoperative PPSS ranged 0–1,260 (median 413) and did not correlate with the severity of hypercalcemia. One hundred and seven patients responded when contacted by post at 18 ± 6 months postoperatively. Their postoperative PPSS was significantly lower (398 ± 226 to 231 ± 203 , $p < 0.001$) and in 55 of 107 patients the severity of symptoms reduced by at least 50%. Most significant improvements were for mood (36 ± 33 vs. 16 ± 23), weakness/tiredness (37 ± 32 vs. 17 ± 23), irritability (35 ± 31 vs. 17 ± 21), and thirst (37 ± 32 vs. 18 ± 25 ; $p < 0.0001$). Physical and mental component scores of SF-36 questionnaire improved in patients whose PPSS decreased postoperatively.

Conclusion Symptomatic benefits persist for at least 1 year after parathyroidectomy in the majority of patients with PHPT.

Keywords Primary hyperparathyroidism · Parathyroidectomy · Symptoms score · SF-36

Introduction

Primary hyperparathyroidism (PHPT) is a common endocrine condition generally diagnosed at the time when biochemical abnormalities are mild and patients lack the classical symptoms summarized by the mnemonic bones, stones, and groans. During the last decade, the National Institute of Health (NIH) has debated the indications for surgery in patients deemed to be asymptomatic [1]. Although there are few level I randomized clinical trials addressing the benefit of parathyroidectomy in patients with PHPT, there are supportive data to demonstrate that most patients with PHPT would benefit from operative cure [2, 3] and that parathyroidectomy is cost-effective in all patients with life expectancy in excess of 6 years [4]. Furthermore, severity of symptoms was found to be similar between patients who met the NIH criteria for parathyroidectomy and those who did not [5], and both groups appear to benefit equally from parathyroidectomy [6].

Arguably, patients with PHPT have a significant impairment in their quality of life (QoL) with the potential for significant improvement after parathyroidectomy. This was demonstrated using the Medical Outcomes Study Short-Form Health Survey (SF-36) questionnaire in randomized trials [7–10] and prospective cohort analysis [8, 11]. In contrast, other authors failed to demonstrate a benefit of surgical intervention in patients with asymptomatic PHPT in comparison with long-term medical follow-up even though at baseline all patients had significantly lower QoL and more psychological symptoms compared with age- and sex-matched healthy subjects [12]. Seven well-designed

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studies of QoL in PHPT have recently been reviewed and all reported improvement across multiple domains following surgery [13].

An important contribution to this field has been the development of a surgical outcome tool designed specifically for PHPT symptoms by Pasieka and co-workers [14–16]. In response to a set of 13 questions, patients can self-assess the severity of their symptoms on a 100-mm visual analog scale from which the Pasieka's parathyroid symptoms score (PPSS) is derived. This allows for a more specific symptomatic assessment that it is easier to implement in clinical practice. In a previous study, we have demonstrated a negative correlation between increasing PPSS and decreasing mental component scores and physical component scores of the SF-36 assessment [17]. This prospective cohort study aims to determine whether the postoperative symptomatic improvement is apparent at over 12 months after parathyroidectomy for PHPT.

Methods

Patients

With the approval of the Local Research Ethics Committee, consecutive unselected patients with biochemical diagnosis of primary hyperparathyroidism were recruited in the study. Demographic, biochemical, radiological, operative, and histological details were recorded in a prospective database. All patients underwent parathyroid imaging with Tc^{99m}-sestamibi scan and neck ultrasound. According to a protocol described previously [18], patients with concordant imaging were offered minimally invasive parathyroidectomy without PTH monitoring and those with negative or nonconcordant imaging underwent bilateral cervical exploration.

Quality of life assessment

Patients were assessed at the preoperative outpatient clinic visit, at the first follow-up outpatient visit (6–12 weeks postoperatively) and subsequently contacted by post at over 12 months postoperatively.

PPSS was derived from the answers to the standardized questionnaire. The 13 items explored included: bone pain, feeling tired easily, mood swings, feeling “blue” or depressed, pain in the abdomen, feeling weak, feeling irritable, pain in the joints, being forgetful, difficulty getting out of a chair or car, headaches, itchy skin, and being thirsty. Each item was scored according to the response on a 100-mm visual analog scale, and PAS was calculated as the sum of all 13 answers, with a maximum PAS possible of 1,300.

The SF-36(v2) questionnaire was made available to all patients at each assessment. The responses were analyzed using the commercially available SF Health Outcomes™ Scoring Software (QualityMetric Inc., Lincoln, USA).

Statistical analysis

Nonskewed data are presented as means \pm standard deviation (range) and descriptive statistics using parametric comparisons (*t* test) were calculated. Skewed data were analyzed using nonparametric test (Mann–Whitney *U* test and Wilcoxon) and presented as median values.

Results

Demographic and biochemical data

Between November 2005 and January 2009, 166 patients (119 F/47 M, age 15–89 years) were diagnosed with PHPT based on hypercalcemia (Ca 2.90 ± 0.25 mmol/L, normal range 2.05–2.65 mmol/L) in the presence of inappropriate PTH levels (21.64 ± 23.05 pmol/L, normal range 0.2–7.5 pmol/L). Preoperative PPSS ranged 0–1,260 (median 413) and did not correlate with the severity of hypercalcemia (Fig. 1). Patients with mild hypercalcemia (Ca < 2.8 mmol/L) had similar scores as those with more severe hypercalcemia: 428 ± 300 vs. 437 ± 269 ($p = \text{NS}$). Using a threshold of 3 mmol/L, the symptoms appeared more severe in those with lower calcium levels (421 ± 212 vs. 344 ± 250 , $p = \text{NS}$).

A total of 107 patients replied to the request to complete a follow-up assessment at over 12 months postoperatively, and these patients were included in the final analysis. There were 29 men and 78 women, aged 15–89 years (mean $60 \pm$

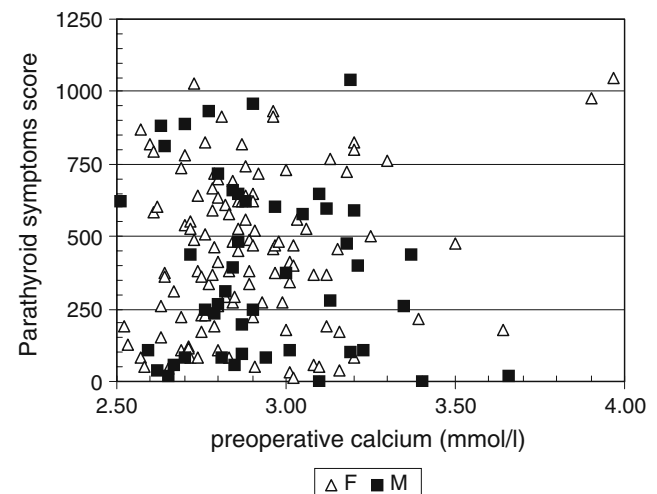


Fig. 1 Plasma calcium levels and Pasieka's parathyroid symptoms score in individual patients with primary hyperparathyroidism

14 years, median 63 years). Their biochemical parameters were similar to the entire cohort (Ca 2.89 ± 0.2 mmol/L, range 2.53–3.64 mmol/L; PTH 21.0 ± 15.1 nmol/L, range 3.3–78.2 nmol/L). Minimally invasive parathyroidectomy was performed in 57 patients and 50 patients underwent bilateral cervical exploration. All patients were found to have a parathyroid adenoma, weighing 100–12,000 mg (mean $1,680 \pm 3,187$ mg, median 1,000 mg). During follow-up, all patients were normocalcemic at 1-year postoperatively.

Preoperative assessment

In the group of 107 patients, preoperative PPSS ranged from 0 to 1,040. Only 29 patients had scores lower than 200, a cutoff considered nonspecific according to historical controls. There was no correlation between PPSS and age of the patients or severity of hypercalcemia.

Some of the SF-36(v2) data sets were incomplete, so further analysis was possible on 76 out of the 107 patients. The median preoperative scores of the SF-36(v2) questionnaire were lower than the 50% percentile in three domains: vitality ($36.9 \pm 23.7\%$), emotional role ($12.9 \pm 10.9\%$), and physical role ($9.9 \pm 10.4\%$).

Postoperative improvement in symptoms and quality of life

The group of 107 patients completed the final assessment at 18 ± 6 months (range 12–32 months, median 15 months). PPSS decreased from 398 ± 226 to 231 ± 203 ($p < 0.001$; Fig. 2). A significant improvement was observed in all but one parameter of the Pasieka's questionnaire (ability to move out of a chair; Fig. 3). Symptoms' scores decreased by over 50% for mood (36 ± 33 vs. 16 ± 23), feeling weak (37 ± 32 vs. 17 ± 23), irritability (35 ± 31 vs. 17 ± 21), feeling thirsty (37 ± 32 vs. 18 ± 25), and headache (19 ± 27 vs. 8 ± 16). There was no difference in the scores recorded by patients who underwent minimally invasive parathyroidectomy or bilateral cervical exploration.

A subgroup analysis aimed to identify the proportion of patients who experienced symptomatic benefits. Percentage change from preoperative PPSS was used to determine if symptoms improved or not. Using a threshold ranging 10–50%, the number in each group varied accordingly (Table 1). It was found that in half of the patients (55/107), the severity of symptoms improved by 50% or more. For more modest response of 25%, some two thirds of patients (66/107) showed an improvement in symptoms. In 24 patients, the postoperative scores were higher than preoperative scores (377 ± 229 vs. 260 ± 191) and seven of them declared that postoperatively they were diagnosed/treated for osteoarthritis and fibromyalgia.

Using Kruskal–Wallis nonparametric analysis, no difference in preoperative parameters (age, calcemia, PTH,

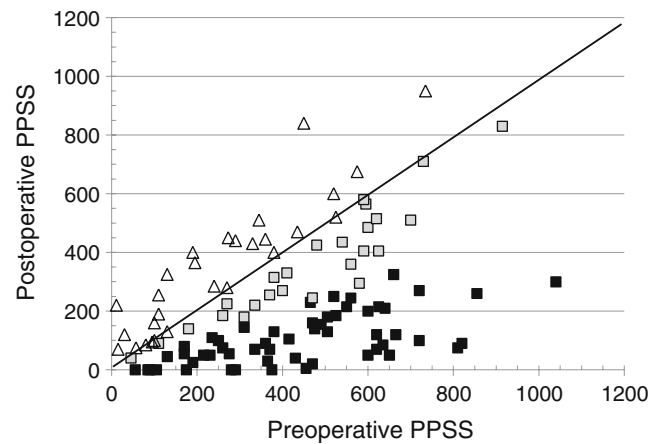


Fig. 2 Pre- and postoperative Pasieka's parathyroid symptoms scores in 107 patients with primary hyperparathyroidism. PPSS from patients whose symptoms scores reduced by more than 50% (filled squares) or less than 50% (shaded squares), and those whose symptoms worsened (open triangles) are presented individually

preoperative PPSS) was found between patients whose PPSS improved or those who worsened (Table 2).

A significant improvement in five components of the SF-36(v2) questionnaire was demonstrated at 1 year in the entire population ($n=76$): bodily pain, general health, vitality, social functioning, and mental health ($p < 0.01$, Mann–Whitney U test). In the subgroup of patients whose PPSS decreased by at least 25%, the improvement of

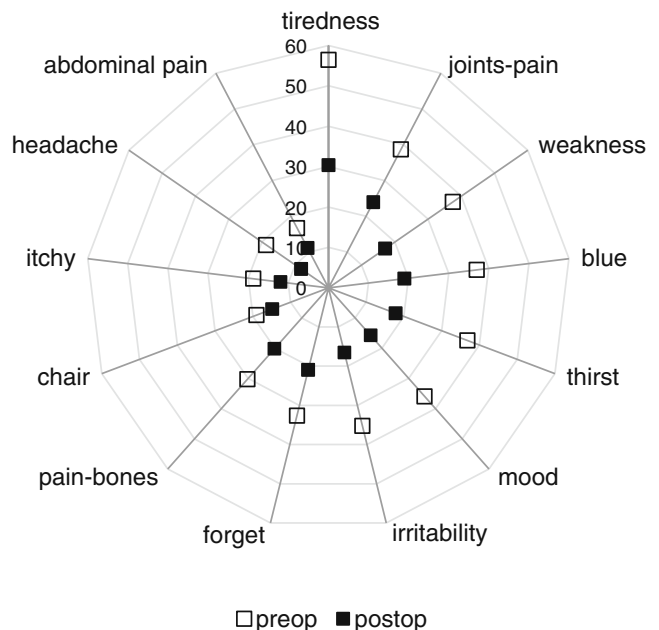


Fig. 3 Pre- and postoperative assessment of individual symptoms reported on Pasieka's parathyroid symptoms scores. Mean values for each of the items assessed on a visual analog score. Filled squares indicate preoperative values. Empty squares indicate postoperative values. Mean values for each of the items assessed by Pasieka's parathyroid symptoms score

Table 1 Changes in postoperative symptoms in a group of 107 patients with primary hyperparathyroidism

Percentage improvement ^a	Improved	No Change	Worsened
10%	75	8	24
25%	66	17	24
50%	55	28	24

^aThe ratio between postoperative and preoperative PPSS was used to identify patients who improved (i.e., postoperative score reduced by more than 10%, 25%, or 50%, respectively), had no change (i.e., postoperative score less than preoperative but less than 10%, 25%, or 50%), or who worsened (i.e., with postoperative scores higher than preoperative scores)

mental component scores (49.3±10.0 vs. 36.7±11.4) was more significant than the physical component scores (46.2±10.9 vs. 42.2±8.9; Fig. 4).

Discussions

This paper investigates the long-term postoperative outcome of a cohort of patients undergoing parathyroidectomy for primary hyperparathyroidism. The current data represents an extension of our previous report demonstrating symptomatic improvement at 3–6 months [17] and demonstrates that such benefits are maintained at over 12 months after the operation. The additional information provided by the current study is that rather than comparing the mean scores of the population before and after surgical cure for PHPT, we aimed to identify subgroups of patients based on their individual benefits (or lack of) after parathyroidectomy. We found that half of the patients experienced a decrease by 50% or more in the severity of their symptoms. If a lower threshold of 20% changes in preoperative PPSS, over two thirds of patients can expect a postoperative improvement in symptoms. Interestingly, we found no preoperative parameter that could predict which patients are going to experience a significant improvement in symptoms.

Our cohort of patients covered all age groups with the oldest patient being 89 years old and 28 patients being over 75 years old at the time of the operation. There was no correlation between the age of the patients’ and their symptomatic response. This data confirms our previous report that symptoms improve significantly at 6 months

Table 2 Changes in Pasieka’s parathyroid symptoms score at over 12 months postoperatively subgroup analysis was performed using the 25% threshold for the change in symptoms

	Improved symptoms	No change in symptoms	Worse symptoms
<i>N</i>	66	17	24
Preop Calcium (mmol/L)	2.89±0.21	2.91±0.19	2.89±0.24
Preop PPSS	423±193	459±271	199±198
Length of FU (months)	19±6	18±6	18±5
1 year PPSS	137±114	418±252	366±255

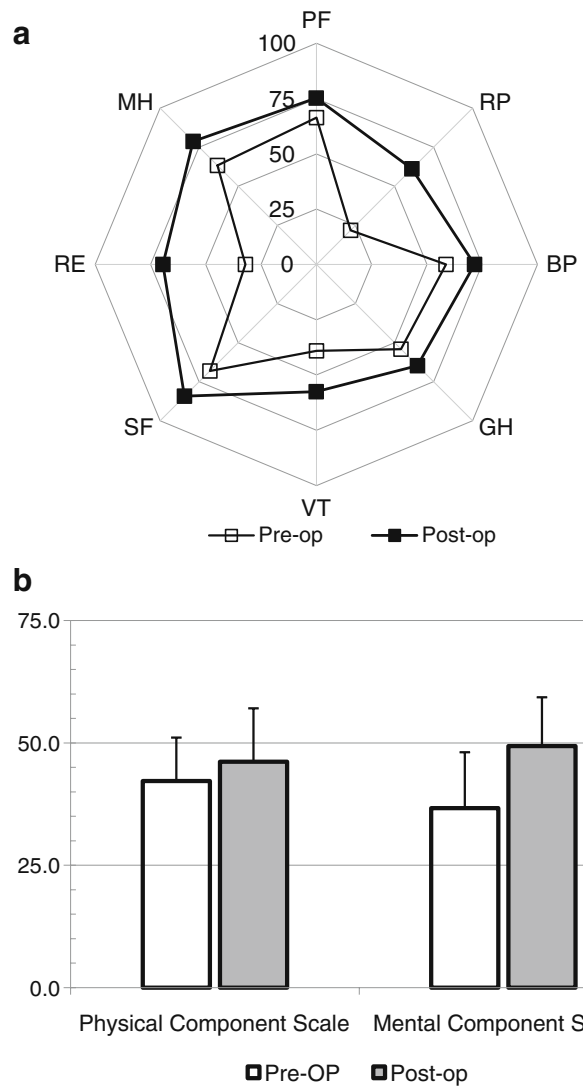


Fig. 4 Scores of SF-36 components in the subgroup of patients reporting an improvement on Pasieka’s questionnaire. **a** Mean scores for each component of SF-36 questionnaire in patients with a decrease in PPSS by at least 25%. *PF* physical functioning, *RP* role physical, *BP* bodily pain, *GH* general health, *VT* vitality, *SF* social functioning, *RE* role emotional, *MH* mental health. Data from individual patients at different time points were compared by using Mann–Whitney *U* test. **b** Physical and mental component scores in the subgroup of patients with a decrease in PPSS by at least 25%

postoperatively in all age groups [19]. Similarly, in a study of 50 patients, octogenarians and nonagenarians, greater than 60% reported improved physical functioning, social

functioning, and/or mental health and reduction of bodily pain after parathyroidectomy [20]. Marked improvements in depressive mood, psychomotor inhibition, anxiety, and somatic symptoms after PTX were also reported in a small study of octogenarians assessed using Hamilton Rating Scale for Depression [21]. This is an important clinical observation as PHPT is increasingly common in older patients, many of whom might be denied such symptomatic benefits if physicians fail to refer them for surgical treatment. While some still consider this to be a debatable issue [22], there is increasing evidence in support of a more proactive approach.

The severity of symptoms generally associated with PHPT was quantified using the PPSS [14, 15]. As an alternative, others have used a 12-item short-form health survey (SF-12; [23]) or a more elaborate 53-question survey based on the Health Outcomes Institute Health Status Questionnaire 2.0 [24], but the experience with these alternative assessment tools remains very limited. In contrast, the feasibility of using the Pasieka's score has been reported by several groups. Very recently, Dr. Pasieka's own group reported the 10-year follow-up data on 78 PHPT patients and showed persistent symptomatic benefits, with the average PPSS decreasing from 318 preoperatively to 177 at 1-year postoperatively and 189 at 10 years postoperatively [25].

As in our initial report [17], we found no significant difference in symptoms scores between those who had minimally invasive parathyroidectomy or bilateral cervical exploration. Others consider that minimally invasive parathyroidectomy leads to better score reduction compared with bilateral cervical exploration because of patients' perception of having had a "less invasive" surgical procedure [26]. Possibly, this perception is influenced by social factors and medical tradition that are difficult to assess and compare between centers on different continents.

Several aspects of the current report can be open to debate or criticism.

Firstly, in this prospective cohort study parathyroidectomy was offered to all patients with firm biochemical diagnosis of PHPT. A similar prospective but nonrandomized design characterizes most studies that have investigated this topic [8, 11, 16, 17, 23–25, 27]. In two randomized controlled trial involving 53 American patients [7, 10] and 50 Italian patients [9] who did not fulfill the NIH criteria for operation of "asymptomatic PHPT," those randomized to parathyroidectomy showed improved QoL at 1 year after operation, but these findings were not replicated in a larger RCT of 191 Scandinavian patients [12]. Despite the small number of level I RCTs addressing the impact of parathyroidectomy on QoL in patients with PHPT, there are supportive data to suggest that most such patients benefit from operative cure (reviewed in [3, 13]).

Secondly, we found no correlation between severity of hypercalcemia and the symptoms scores. Some would therefore argue that Pasieka's score is not specific for PHPT. In contrast, others found a significant correlation between the changes in serum calcium and intact parathyroid hormone levels and improvement in symptoms [24]. It remains likely that this issue could only be settled in a much larger study group that would be feasible only through a multicenter collaboration.

In conclusion, these data contribute to the growing evidence that the majority of patients with primary hyperparathyroidism derive significant and persistent symptomatic benefits after parathyroidectomy. This is an area insufficiently explored or quantified in the absence of routine use of specific assessment tools for quality of life and severity of symptoms. In view of its much simpler way to administer and quantify, the Pasieka's symptoms score should be incorporated on the regular pre- and postoperative assessment of patients with primary hyperparathyroidism who are offered surgical intervention or choose to continue with surveillance or medical supportive therapy.

Conflicts of interest None.

Financial support None

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