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Timing of Symptom Improvement After Parathyroidectomy for Primary Hyperparathyroidism

Sara E. Murray, MD, Priya R. Pathak, David S. Pontes, David F. Schneider, MD, Sarah C. Schaefer, NP, Herbert Chen, MD, and Rebecca S. Sippel, MD

Section of Endocrine Surgery, Department of Surgery, University of Wisconsin, Madison, WI

Abstract

Background—The timing of symptom improvement after parathyroidectomy for primary hyperparathyroidism (PHPT) has not been well characterized.

Methods—This prospective study involved administering a questionnaire to patients with PHPT who underwent curative parathyroidectomy over an 11-month period. The questionnaire evaluated the frequency of 18 symptoms of PHPT on a 5-point Likert scale, and was administered pre-operatively, and 1 week, 6 weeks, and 6 months postoperatively.

Results—Of 197 eligible patients, 132 (67%) participated in the study. The questionnaires were completed at a rate of 91%, 92%, and 86% at 1 week, 6 weeks, and 6 months post-operatively, respectively. The most commonly reported pre-operative symptoms were fatigue (98%), muscle aches (89%), and bone/joint pain (87%). Improvement in symptom severity occurred across all symptoms and was separated into three categories based on the timing of improvement. Fatigue and bone/joint pain demonstrated ‘Immediate Improvement’ (>50% of patients reporting improvement by post-operative week 1), whereas the majority of symptoms showed peak improvement at 6 weeks (‘Delayed Improvement’). Symptoms categorized as ‘Continuous Improvement’ were those showing progressive improvement up to 6 months post-operatively (polydipsia, headaches, and nausea/vomiting).

Conclusions—Symptom improvement was most prominent 6 weeks post-parathyroidectomy, though some symptoms showed continued improvement at 6 months.

Background

Primary hyperparathyroidism (PHPT) is a common endocrine condition, which during recent decades, has typically been diagnosed on routine biochemical screening as opposed to the more classic presentation of overt manifestations of the disease. Despite this evolution of initial presentation, the majority of patients with PHPT remain symptomatic along a broad spectrum, and may have a variety of complaints involving the musculoskeletal, gastrointestinal, urinary, and neuropsychiatric systems.^{1–4} There is a large body of evidence that parathyroidectomy – the only definitive cure for PHPT – is beneficial in symptom relief

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Address for Correspondence: Rebecca S. Sippel, MD, University of Wisconsin, Department of Surgery, Section of Endocrine Surgery, K3/704 Clinical Science Center, 600 Highland Avenue, Madison, WI 53792, USA, Business, Tel.: 608-263-1387, Fax: 608-252-0912, sippel@surgery.wisc.edu.

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and increasing quality of life, and this observation has been equally demonstrated in patients who met the National Institutes of Health (NIH) criteria for parathyroidectomy and those that did not.^{1-3,5-20}

While numerous studies have reported that most patients with PHPT would benefit from operative cure, few have addressed the exact timing and sustainability of symptom improvement after parathyroidectomy using a disease-specific outcome tool.^{5,6,15} During surgical consultation, patients often inquire about the anticipated time course of post-operative symptom improvement and resolution. A better understanding of the improvement profile would aid clinicians in appropriately counseling patients on post-operative expectations and treatment efficacy. Therefore, the objective of this study was to more accurately characterize the timing of symptom improvement after parathyroidectomy for PHPT.

Methods

Patients

This is a prospective study that involved administering a questionnaire to patients with PHPT who underwent parathyroidectomy between November 2011 and October 2012 at a large tertiary care center in the Midwest. Identification of patients with PHPT was made by biochemical diagnosis, which is defined as hypercalcemia (serum calcium >10.2 mg/dL) with an elevated or inappropriately normal parathyroid hormone (PTH) level. Only patients who were biochemically cured as a result of parathyroidectomy were included in the study. Patients were excluded if they were <18 years old, had undergone a previous parathyroidectomy, required reoperation for persistent or recurrent PHPT, could not read or understand English, or declined to participate in post-operative follow-up questionnaires. Data collected included patient demographics, biochemical profile, operative procedure, and histologic information. Consent was obtained from patients for study participation during the initial surgical consultation, and specifically, all patients consented to receiving intermittent phone calls from our research team during the postoperative period.

Questionnaire

The questionnaire utilized in this study asked patients to rate the frequency of 18 recognized symptoms associated with PHPT (Table 1). The severity of symptom occurrence was reported by patients according to a 5-point Likert scale (0 = never, 1 = rarely, 2 = occasionally, 3 = frequently, 4 = very frequently). The questionnaire was administered during the initial surgical consultation pre-operatively, which served as the baseline assessment, and again post-operatively at 1 to 2 weeks, 6 to 10 weeks, and 6 to 10 months. Herein these time periods will be referred to as 1 week, 6 weeks, and 6 months for ease of presentation, although the median questionnaire completion times were 8 days (interquartile range [IQR], 7 to 12 days), 7.1 weeks (IQR, 6.1 to 7.9 weeks), and 6.4 months (IQR, 6.1 to 7.3) days after surgery, respectively. It is our practice to have patients who undergo a parathyroidectomy follow-up in clinic 1 week and 6 months post-operatively. Therefore, questionnaires at these time points were often completed in person, whereas the 6-week questionnaire was done over the telephone by one of two trained research assistants. If patients did not follow-up in clinic at the 1-week or 6-month post-operative time period, they were contacted via telephone and asked to complete the questionnaire in this manner.

Statistical Analysis

Data were analyzed using Stata version 12 software (StataCorp, College Station, TX), and are expressed as either mean with standard deviation for continuous, normally distributed variables, or as the median with IQR for non-normally distributed variables. Frequency

distributions were calculated for each symptom pre-operatively. Likert scale severity data was dichotomized for each symptom into patients experiencing symptoms at any severity (rarely to very frequently) versus those reporting no symptoms pre- and post-operatively. This was utilized to determine the resolution of symptoms after parathyroidectomy. Likert scale data was also dichotomized into those symptoms showing improvement post-operatively (i.e. a decrease in the severity of symptoms), versus those who did not. Rather than imputing missing responses, individual unreported values were excluded from the analyses. The institutional review board from the University of Wisconsin approved this study.

Results

A total of 197 patients who underwent a parathyroidectomy were eligible for the study, and 132 (67%) participated. All 132 patients completed the questionnaire pre-operatively, and 91%, 92%, and 86% of patients completed the post-operative questionnaires 1 week, 6 weeks, and 6 months after surgery, respectively. In total, 100 patients completed the questionnaire at all time points.

The mean age of the cohort was 59.7 ± 1.1 years, and 80% (n=105) were female. Pre-operative mean serum calcium and PTH levels were characteristically elevated (10.8 ± 0.7 mg/dL, 106 ± 58 pg/mL), and normalized after parathyroidectomy (9.0 ± 0.6 mg/dL, 43 ± 24 pg/mL). The majority of patients had a single parathyroid adenoma excised (n=103, 77%), whereas 14 patients had double adenomas and the remaining 15 patients had four-gland hyperplasia. Two patients experienced transient hypocalcemia post-operatively, and one patient had transient hoarseness. There were no occurrences of permanent complications.

Of the 18 symptoms queried, patients pre-operatively reported a mean of 13 ± 4 symptoms, ranging in frequency from rarely to very frequently. No patients in the series were truly asymptomatic, and the lowest number of patient-reported symptoms was three. Alternatively, over half of the patients presented with 12 or more symptoms, and 24 patients (18%) in the series reported experiencing all symptoms at some level of severity. The most commonly reported pre-operative symptoms were fatigue (98%), muscle aches (89%), bone/joint pain (87%), memory problems (86%), and difficulty concentrating (86%) (Figure 1).

A modest percentage of patients experienced symptom resolution by postoperative week 1, and this was observed across nearly all symptoms queried (Figure 1). However, a much steeper decline in symptom incidence occurred at the 6-week time point. From 6 weeks to 6 months there was a subsequent slight increase in symptom occurrence; however, for all 18 symptoms the incidence remained lower at 6 months compared to the pre-operative baseline.

Next we evaluated the improvement in symptom severity (i.e. a decrease in the frequency of symptoms reported on the Likert scale) as opposed to complete symptom resolution. Post-operative improvement was observed in all symptoms and ranged from occurring in 33% (urinary incontinence) to 72% (fatigue) of patients at their peak. The 18 queried symptoms were separated into three categories based on the timing of their improvement (Table 2). These were determined by comparing the percentage of patients with symptom improvement compared to the pre-operative baseline at 1 week, 6 weeks, and 6 months post-operatively. Only two symptoms (fatigue and bone/joint pain) demonstrated 'Immediate Improvement', defined as >50% of patients reporting improvement by post-operative week 1. Not surprisingly, similar to the observation of symptom resolution demonstrated in Figure 1, the greatest improvement in symptom severity occurred at the 6-week post-operative time period. Symptoms meeting these criteria were categorized as 'Delayed Improvement' and showed peak improvement at 6 weeks with a slight decline at 6 months. Alternatively, three

symptoms (polydipsia, headaches, and nausea/vomiting) exhibited the greatest improvement 6 months postoperatively and were labeled as 'Continuous Improvement'. The specific percentages of improvement for all 18 symptoms at all post-operative time points are depicted in Figure 2, and are separated by the timing of improvement category.

Discussion

This study describes the timing of symptom improvement after parathyroidectomy for PHPT. As documented previously in the literature, we confirmed that the majority of symptoms associated with PHPT, both classic and nonspecific, improve after parathyroidectomy.^{1–3,5,7,11,13,15,16,19} However, this study is novel in that it outlines the timing of symptom improvement of individual symptoms after surgical cure. Symptom improvement began as early as post-operative week 1, but was most prominent 6 weeks post-operatively. The majority of symptoms stabilized by 6 months time, while a few symptoms showed continual improvement, allowing the categorization of symptoms by the specific timing of post-operative improvement. This information can be utilized to counsel patients during the initial surgical consultation, as well as to guide post-operative surveillance and management.

Generalized, non-specific tools have been frequently utilized to assess symptom improvement following parathyroidectomy, such as the SF-36 Health Survey^{7–10,12,15,17,18}. These studies have shown that symptom improvement occurs and that it is associated with a sustained increase in quality of life.^{7–10,15,17,21} Several other studies have been done which have focused on individual symptoms and have used validated questionnaires to assess symptom resolution. Weber and colleagues examined neuropsychological problems, including depression and anxiety, and found that symptom severity correlated with the degree of hypercalcemia and that the severity of symptoms improved significantly after curative parathyroidectomy.²² Perrier and colleagues utilized a validated sleep assessment tool and functional MRI to show that sleep symptoms improved after parathyroidectomy; interestingly they also showed peak improvement at 6 weeks, with a slight degradation at 6 months.²³ We have previously shown, using a validated questionnaire, that symptoms of gastroesophageal reflux disease improve significantly after parathyroidectomy.²⁴ However, we only examined symptom resolution at 6 months and did not look at an earlier time point. In this study we used a disease-specific questionnaire evaluating symptoms related to PHPT, that included a broad range of symptoms attributable to primary hyperparathyroidism. Our findings were consistent with these prior studies, although we were able to further delineate the timing of disease and symptom-specific improvement. In general, the majority of pre-operative symptoms from PHPT showed significant improvement following curative surgical resection.

Although post-operative symptom improvement has been well documented, the specific timing of individual symptoms improvement is less well known. Several prior studies have utilized disease-specific tools to examine symptom frequency longitudinally, and the results are conflicting.^{5,15} Pasieka and colleagues reported continual improvement in nearly all symptoms through 7 days, 3 months, and 12 months postoperatively.⁵ Calliard *et al.* examined symptom frequency at 3, 6, and 12 months postoperatively and found peak improvement at 6 months, which persisted out to 12 months for many symptoms.¹⁵ In a large prospective study by Roman *et al.*, in which they used a variety of validated instruments to demonstrate neurocognitive symptom improvement longitudinally, they showed results similar to ours, in which the greatest symptom improvement was seen early at about 1 month, with some symptoms showing mild continued improvement out to 6 months.²⁵ Our study aimed to clarify the timing of symptom improvement for a variety of different symptoms and resolution following parathyroidectomy by narrowing the time

windows of symptom assessment. We demonstrated that symptoms actually showed peak improvement earlier than previously described, and then remained relatively stable out to 6 months. As mentioned, Pasieka found continued, active improvement in most symptoms as far as 12 months out from surgery.⁵ Although it may be difficult to attribute changes in nonspecific symptoms to a surgical intervention 12 months prior, three symptoms in our study demonstrated a similar profile with continual improvement out to 6 months (polydipsia, headaches, and nausea/vomiting). Perhaps if we were to assess symptom frequency 12 months postoperatively, we would see a similar improvement profile for these three symptoms. However, the majority of symptoms queried plateaued at 6 months in our study. There was no reason to suspect that symptoms would deteriorate beyond this time frame for patients who underwent a curative resection, with symptom stability being demonstrated up to 10 years post-resection.²⁶

There are several limitations to this study. First, there is potential non-responder bias given that only 67% of patients who underwent parathyroidectomy during the study period participated in the study. However, there were no significant differences in age, gender, or parathyroid pathology between responders and non-responders, leading us to believe that our study sample is generalizable. Second, parathyroidectomy was performed on all patients with a biochemical profile suggesting PHPT, regardless of meeting NIH criteria for surgical intervention. However, multiple studies have documented equivalent post-operative improvement in patients meeting the NIH criteria and those who do not.^{2,15,16} It is unknown whether the timing of symptom improvement and resolution is different in these two groups, and warrants further study. Third, this study did not have a true control group. It has been well documented in the literature that many disease-related symptoms of PHPT significantly improve after parathyroidectomy.^{1-3,5,7,11,13,15,16,19,23} Therefore, because our primary objective was to describe the *timing* of symptom improvement and not necessarily to reconfirm that symptoms improve post-operatively, we opted to use patients' pre-operative questionnaire as the control for each patient. The non-specific nature of PHPT-associated symptomatology has historically made it difficult to quantify the extent of pre- and postoperative incidence. Because PHPT is defined by a collection of non-specific, often subjective symptoms, there are no objective or pathognomonic measures that have 100% sensitivity or specificity for the disease. Confounding this problem, the instrument utilized in this study was not validated. However, our questionnaire used well-recognized symptoms related to PHPT – symptoms that have been utilized in previous studies and incorporated into validated tools widely used to assess post-operative improvement.¹ In addition, the internal validity of the instrument was improved by allowing patients to serve as their own individual controls. Lastly, we did not adjust for patient sociodemographics or co-morbidities, and the extent to which these factors potentially affect the timing of symptom improvement or resolution is not known.

In conclusion, this study confirms the significant disease burden in patients with PHPT, and offers further evidence that curative parathyroidectomy results in the sustained improvement of many classic and nonspecific symptoms related to PHPT. While certain symptoms exhibited improvement or resolution as early as 1 week postoperatively, the majority demonstrated peak improvement at 6 weeks that then persisted out to 6 months. The timing of individual symptom improvement must be discussed with patients during the initial surgical consultation to provide realistic expectations for postoperative improvement. Although it is important for both patients and clinicians to be aware of the extended time frame of symptom improvement beyond the immediate postoperative period, it is uncommon for symptoms to show significant improvement or resolution beyond 6 weeks.

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Abbreviations

PHPT	Primary hyperparathyroidism
NIH	National Institutes of Health
PTH	Parathyroid hormone

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Figure 1. Incidence of patient-reported symptoms at any level of severity pre-operatively and 1 week, 6 weeks, and 6 months post-operatively.

Figure 2.

Percentage of patients with improvement in symptom severity 1 week, 6 weeks, and 6 months post-operatively compared to pre-operative baseline, separated by the timing of symptom improvement category: a) Immediate Improvement, b) Delayed Improvement, c) Continuous Improvement.

Table 1**Items in prospective questionnaire**

Fatigue
Joint or bone pain
Muscle aches
Difficulty concentrating
Memory problems
Feeling depressed
Feeling anxious
Irritability
Difficulty sleeping
Headaches
Abdominal pain
Nausea or vomiting
Constipation
Heartburn
Increased thirst
Frequent urination
Nighttime urination
Difficulty controlling urine

Table 2

Timing of symptom improvement categories

Category	Description	Symptoms
Immediate Improvement	>50% of patients improved by post-operative week 1	Fatigue Bone/joint pain
Delayed Improvement	Peak improvement occurred 6 weeks post-operatively, with a slight decline in improvement at 6 months	Concentration Irritability Muscle aches Memory problems Anxiety Nocturia Sleep problems Depression Polyuria Abdominal pain Dyspepsia Constipation Urinary incontinence
Continuous Improvement	Peak improvement occurred 6 months post-operatively	Polydipsia Headaches Nausea/vomiting