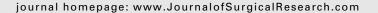


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Elevated parathyroid hormone after parathyroidectomy delays symptom improvement



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ABSTRACT

Background: Curative parathyroidectomy for primary hyperparathyroidism (PHPT) resolves various nonspecific symptoms related to the disease. Between 8% and 40% of patients with normocalcemia after parathyroidectomy have persistently elevated parathyroid hormone (ePTH) levels at follow-up. We investigated whether ePTH in the early postoperative period was associated with the timing of symptom improvement.

Materials and methods: This prospective study included adult patients with PHPT who underwent curative parathyroidectomy from November 2011 to September 2012. Biochemical testing at 2 wk postoperatively identified ePTH (defined as PTH > 72 pg/mL) versus normal PTH (nPTH). A questionnaire administered pre- and post-operatively at 6 wk and 6 mo asked patients to rate the frequency of 18 symptoms of PHPT on a five-point Likert scale. Student t-tests were used to compare pre- with postoperative changes in scores for individual symptoms.

Results: Of 194 patients who underwent parathyroidectomy, 129 (66%) participated in the study. Preoperatively, all patients were symptomatic, with a mean of 13 ± 4 symptoms. Two weeks postoperatively, 20 patients (16%) had ePTH. The percentage of patients with postoperative improvement for individual symptoms was compared between groups. At the early time point (6 wk), the ePTH group showed less improvement in 14 of 18 symptoms. This difference reached statistical significance for four symptoms: anxiety, constipation, thirst, and polyuria. By the 6-mo time point, these differences had resolved, and symptom improvement was similar between groups.

Conclusions: ePTH after curative parathyroidectomy may result in a delay in symptom improvement 6 wk postoperatively; however, this difference resolves in 6 mo.

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1. Introduction

Primary hyperparathyroidism (PHPT) is one of the most common endocrine disorders in the United States, with approximately 100,000 new cases diagnosed each year [1,2]. Parathyroidectomy is the definitive treatment. It restores normocalcemia—the criteria by which cure is defined—and also generally alleviates the numerous typical and nonspecific

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symptoms of PHPT. Nontraditional symptoms associated with PHPT include musculoskeletal pain and fatigue, insomnia, gastrointestinal and urinary problems, and neuropsychiatric complaints such as depression, anxiety, and irritability [1,3–12].

Interestingly, between 8% and 40% of patients with normocalcemia after parathyroidectomy have persistently elevated parathyroid hormone (ePTH) levels at follow-up, ranging anywhere from 1-2 wk to 5 y postoperatively [2,13-15]. The pathophysiology and significance of this phenomenon are unclear, although several studies have investigated possible etiologies, which include impaired renal function, bone remineralization, and vitamin D deficiency [14,16-18]. Factors associated with ePTH are varied and inconsistent across studies but include: high preoperative PTH, low preoperative vitamin D, advanced age, and higher adenoma volume [2,14,18]. Studies investigating whether ePTH confers a higher risk of persistent or recurrent PHPT also have inconsistent conclusions. Evidence supports that a great majority of ePTH patients do not develop recurrent disease; however, comparatively, their risk of developing recurrent disease may be higher than patients with normal PTH (nPTH)

Despite the research focusing on ePTH and the risk of recurrence of PHPT, no studies have investigated the association between postoperative ePTH and symptom improvement after curative parathyroidectomy for PHPT. A better understanding of the relationship of ePTH and symptom frequency and improvement would aid clinicians in more effectively counseling patients in the postoperative period, as well as determining an appropriate follow-up strategy. Therefore, the objectives of this study were to: (1) determine the incidence of postoperative ePTH in patients with normocalcemia after curative parathyroidectomy for PHPT; (2) investigate whether ePTH in the early postoperative period was associated with changes in the extent or timing of symptom improvement; and (3) determine if ePTH affects overall symptom improvement.

2. Materials and methods

2.1. Patients

This is a prospective study of patients with PHPT who underwent parathyroidectomy between November 2011 and October 2012 at a large academic 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 ePTH or inappropriately nPTH level. Patients were excluded if their operation was not curative, which was defined as patients with continued hypercalcemia (serum calcium level >10.2 mg/dL) at 6 mo after parathyroidectomy. Additional exclusion criteria included patients aged <18 y, those having undergone a previous parathyroidectomy, those unable to read or understand English, or those who declined to participate in postoperative follow-up questionnaires. There were no significant differences in gender, age, or parathyroid pathology between study participants and nonparticipants (Table 1). Data including patient age and gender, biochemical profile, operative

Table 1 — Comparison of demographic and pathologic profile of study participants and non-participants showed no significant differences.

	Study participants $(n = 129)$	Study nonparticipants $(n = 65)$	P value
Sex			0.59
Male	26 (20%)	11 (17%)	
Female	103 (80%)	54 (83%)	
Age (y)	59.7	59.7	0.99
Pathology			0.24
Single adenoma	101 (78%)	43 (68%)	
Double adenoma	14 (11%)	9 (14%)	
Four-gland hyperplasia	14 (11%)	12 (18%)	

procedure, and histologic information were collected at the preoperative visit and two follow-up appointments at approximately 2 wk and 6 mo after surgery. Consent was obtained from patients for study participation during the initial surgical consultation, and specifically, all patients consented to receive phone calls from our research team intermittently during the postoperative period.

2.2. Questionnaire

The questionnaire (Appendix) is a disease-specific tool previously developed and applied by this institution [11] and was used to assess the extent of 18 varied nonspecific symptoms associated with PHPT. Patients reported the frequency of symptom occurrence according to a five-point Likert scale (0 = never, 1 = rarely, 2 = occasionally, 3 = frequently, and 4 = very frequently). The questionnaire was administered during the initial surgical consultation preoperatively and again at the two follow-up appointments 2 wk and 6 mo after surgery. In addition, patients were contacted by telephone by one of two trained research assistants 6 wk postoperatively and asked to complete the questionnaire over the phone. For ease of presentation, the postoperative time points herein will be referred to as "6 wk" and "6 mo", although the median questionnaire completion time was 7.1 wk (interquartile range [IQR], 6.0-7.8 wk) and 6.9 mo (IQR, 6.0-7.3 mo). Of note, the 6 mo questionnaire was typically completed at the postoperative appointment; however, in a few instances, it was collected over the telephone if the patient did not return to clinic.

2.3. Statistical analysis

Statistical analysis was performed using the SPSS packages (SPSS version 12.0 for Microsoft Windows; SPSS Inc, Chicago, IL). Data are expressed either as 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 preoperatively. Rather than imputing missing responses, individual unreported values were excluded from the analyses.

Student t-test, Fisher exact test, and chi-squared analysis were used to identify possible factors associated with ePTH or

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