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Normalization of 2-Week Postoperative Parathyroid Hormone Values in Patients with Primary Hyperparathyroidism: Four-Gland Exploration Compared to Focused-Approach Surgery

Peter J. Mazzaglia · Mira Milas · Eren Berber · Alan Siperstein · Jack M. Monchik

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Abstract
Background Elevation of parathyroid hormone (PTH) levels is commonly seen in patients with primary hyperparathyroidism (PHPT) who have undergone parathyroidectomy. This study evaluates differences in 2-week postoperative PTH levels in patients having focused-approach surgery versus four-gland exploration.
Methods Over 6 years, patients at Rhode Island Hospital (RIH) and the Cleveland Clinic (CCF) who had PHPT and underwent localization studies suggestive of single adenoma were analyzed. At RIH patients underwent focused-approach surgery, and at CCF routine four-gland exploration was performed. Postoperative calcium supplementation was routine at RIH and selective at CCF.
Results There were 308 patients at RIH and 370 at CCF. They were similar in age (59.2 ± 13.0 years at RIH and 60.4 ± 12.9 years at CCF), and sex (76.9 and 80.0% female at RIH and CCF, respectively). The mean preoperative serum calcium measured 10.9 ± 0.7 mg/dl at RIH and 11.1 ± 0.7 mg/dl at CCF ($P < 0.001$). Preoperative PTH values were similar, measuring 143.8 ± 104.8 pg/ml in the focused-approach group (RIH) and 157.6 ± 150.3 pg/ml in the four-gland exploration group (CCF). Preoperative 25-hydroxyvitamin D (vitamin D-25) levels were 24.1 ±12.0 ng/ml at RIH and 27.4 ± 10.6 ng/ml at CCF; and the prevalence of vitamin D-25 deficiency (level <20 ng/ml) was 43.9% at RIH and 27% at CCF ($P = 0.017$). The proportion of patients whose intraoperative PTH value dropped by ≥50% prior to completion of surgery was 95.0% at RIH and 95.5% at CCF. The total gland weight resected per patient was 942 mg at RIH versus 1,394 mg at CCF ($P = 0.003$). The 2-week postoperative serum PTH was >65 pg/ml in 18.8% at RIH and in 38.7% at CCF ($P < 0.001$). The 2-week postoperative serum calcium values dropped to 9.2 ± 0.6 mg/dl at RIH and to 9.5 ± 0.8 mg/dl at CCF ($P < 0.001$). The incidence of multigland disease was 5.8% at RIH and 21.9% at CCF ($P \leq 0.001$).
Conclusions Among patients with PHPT who underwent a localizing study indicating unilateral disease, a significant proportion had eucalcemic PTH elevation 2 weeks after parathyroidectomy. The elevation was more frequent in the four-gland exploration group and correlated most strongly with greater adenoma mass.

Introduction

The recognition of early primary hyperparathyroidism (PHPT) dramatically increased with the introduction of serum chemistry autoanalyzers during the early 1970s [1]. Today there is increasing awareness of the disease on the part of the general public and physicians alike, and this heightened awareness has resulted in earlier referral for surgery and lower preoperative serum calcium values [2, 3]. Despite these trends, however, most patients still have symptoms attributable to their disease, which are frequently alleviated by successful parathyroidectomy [4–6].

P. J. Mazzaglia (✉) · J. M. Monchik
Warren Alpert School of Medicine, Brown University, Rhode Island Hospital, 154 Waterman Street, Providence, RI 02906, USA
e-mail: pmazzaglia@lifespan.org

M. Milas · E. Berber · A. Siperstein
Endocrine Surgery Department/A80, Endocrinology and Metabolism Institute, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195, USA

Until the mid-1990s, a curative operation usually involved the traditional four-gland exploration. However, since the introduction of intraoperative parathyroid hormone (IOPTH) monitoring [7], many surgeons have adopted a focused approach to parathyroidectomy. Despite wide variations in the reported incidence of multigland disease, which range from <5 to >30% [8, 9], both approaches have been shown to produce surgical cure in ≥95% of patients [10–13], with reports of 5-year disease-free survivals of 97% based on Kaplan–Meier estimates [14]. Although the definition of surgical cure depends on the demonstration of normocalcemia at 6 months, many patients are often seen by their surgeons or endocrinologists at a 2-week follow-up visit, at which time serum calcium and parathyroid hormone (PTH) are measured.

Many series have documented eucalcemic postoperative PTH elevation in 10–40% of patients [15–18]. Multiple potential physiologic mechanisms for this phenomenon have been hypothesized, including relative hypocalcemia [19], vitamin D deficiency [5, 20, 21], bone remineralization [22], and PTH receptor down-regulation [23–25], but it remains poorly understood. Reassuringly, the finding of postoperative PTH elevation is not predictive of disease recurrence [19].

The goal of this study was to compare the normalization of PTH levels performed at the 2-week postoperative visit in a group of patients undergoing focused-approach parathyroidectomy versus a group undergoing routine four-gland exploration. Defining the impact that the extent of surgical exploration has on 2-week postoperative PTH levels may help clarify differing rates of postparathyroidectomy PTH elevation in various patient populations. Secondary endpoints included the incidence of vitamin D deficiency, number and weight of glands resected, and 2-week postoperative calcium levels.

Patients

The endocrine surgery databases at Rhode Island Hospital (RIH) and Cleveland Clinic Foundation (CCF) were examined to identify patients with sporadic PHPT who had undergone a preoperative localization study—sestamibi scan, ultrasonography (US), or both—that was highly suggestive of unilateral parathyroid adenoma. Inclusion criteria necessitated the availability of 2-week postoperative calcium and PTH levels. Patients undergoing parathyroid reexploration and those with suspected multigland disease were excluded. At CCF, from January 2000 to September 2006, a total of 1,010 patients with PHPT underwent parathyroidectomy. Among them, only 370 had both unilateral localization and availability of 2-week postoperative calcium and PTH levels. At RIH, from January 2004 to June 2009, a total of 797 patients with PHPT underwent parathyroidectomy, with only 308 meeting both criteria for inclusion: unilateral localization and availability of 2-week postoperative calcium and PTH levels.

Methods

All patients at both institutions underwent preoperative parathyroid sestamibi scans and parathyroid ultrasonography (US) examination. Sestamibi scans were primarily performed at the referral centers, although outside scans were sometimes used when available. At RIH the parathyroid US examination was performed in the radiology department, and at CCF all patients underwent surgeon-performed US during the preoperative consultation and again in the operating room after administration of general anesthesia and gentle neck hyperextension.

All parathyroidectomies at RIH were performed by one surgeon (J.M.M.), under either general or local anesthesia. Surgery is performed through a standard 3–4 cm Kocher incision, and dissection is focused to the anatomic location of the gland localized preoperatively. All blood samples to be assayed for IOPTH are obtained from a peripheral intravenous infusion line placed by the anesthetist. If the PTH level falls by 50% from the higher of the baseline or preexcision value, or into the normal range, surgery is concluded. Otherwise, dissection proceeds to identify additional enlarged glands and is terminated only when an appropriate decrease in the IOPTH level is achieved.

At CCF, all parathyroidectomies were performed by one of three surgeons (A.S., M.M., E.B.) with the patient under general anesthesia. A focused dissection is performed through a 3–4 cm Kocher incision based on results of preoperative localization studies. All blood samples to be assayed for IOPTH levels are obtained by the surgeon from an anterior jugular vein. As part of the standard operative technique, a full four-gland exploration is performed in all patients, even if the IOPTH falls appropriately after the first gland is removed. When additional enlarged glands are identified, they are excised, and the postexcision PTH assay is repeated.

At both institutions, patients are monitored overnight and discharged on the first postoperative day. Routinely at RIH, patients are prescribed calcium citrate 950 mg three or four times a day without vitamin D supplementation. Prior to the 2-week postoperative blood collection at the laboratory, the patients are instructed to fast and abstain from calcium after midnight. At CCF, calcium and/or vitamin D administration was not routine but selectively prescribed based on surgeon preference or if patients developed symptoms of hypocalcemia.

Results

Preoperative characteristics are outlined in Table 1. The percentage of females was 80.0% at CCF and 76.9% at RIH. The mean age was nearly identical: 59.2 years at RIH and 60.4 years at CCF. The mean preoperative serum calcium was 10.9 mg/dl at RIH and 11.1 mg/dl at CCF ($P < 0.001$). The mean preoperative PTH was 143.8 pg/ml at RIH and 157.6 pg/ml at CCF ($P = 0.18$). The mean 25-dihydroxyvitamin D (vitamin D-25) level at RIH was 24.1 ng/ml and at CCF 27.3 ng/ml ($P = 0.02$). Vitamin D deficiency, defined as a level <20 ng/ml, was present in 43.7% at RIH and 27.0% at CCF ($P = 0.04$). All patients had at least one positive localizing study. At RIH, the sestamibi scan was positive in 93.2% of patients, and US was positive in 73.4%; both studies were positive in 66.6%. At CCF, sestamibi was positive in 92.7%, US in 91.9%, and both studies in 84.9%.

Intraoperative and postoperative data are summarized in Tables 2 and 3. The proportions of patients whose IOPTH decreased by ≥50% from the baseline or preexcision level or that dropped into the normal range were 95.7% at RIH and 95.8% at CCF. At RIH, 68 (22.1%) operations were converted to a bilateral approach. In 11 of these cases the PTH did not fall appropriately in the 10-min postexcision blood sample. Among these 11 patients, 7 had double adenomas, 1 had hyperplasia, and 3 had a single adenoma. Nine patients underwent bilateral exploration because the IOPTH level was unavailable at the time of surgery. The other 48 patients experienced an appropriate PTH decrease at 10 min, and the decision to convert was based on intraoperative surgical decision-making, frequently done while awaiting the PTH result. At CCF, 100% of patients underwent four-gland exploration.

Multigland disease was identified in 5.8% of patients at RIH and in 21.9% of patients at CCF. The average total weight of resected gland(s) at RIH was 942 mg compared to 1,394 mg at CCF ($P = 0.003$); and the mean number of glands resected per patient at RIH was 1.07 compared to 1.34 at CCF. The percentages of patients with single and double adenomas as well as hyperplasia, defined as three or more enlarged glands, are given in Table 4. At 2 weeks postoperatively, serum calcium was 9.2 mg/dl at RIH and 9.5 mg/dl at CCF ($P < 0.001$), decreases of 15.6 and 14.4%, respectively. The mean 2-week postoperative PTH levels were 44.5 pg/ml at RIH and 66.0 pg/ml at CCF ($P < 0.001$). The proportions of patients with PTH levels >65 pg/ml were 18.8% at RIH and 38.7% at CCF.

Patients at each institution whose 2-week postoperative PTH was <65 pg/ml were compared to those whose PTH was ≥65 pg/ml to identify factors associated with a 2-week postoperative PTH elevation (Tables 5, 6). One factor at both institutions that was a statistically significant predictor of elevated postoperative PTH was a high preoperative PTH level. At CCF, the mean preoperative PTH was 54% higher, and at RIH it was 67% higher in those patients with elevated postoperative PTH. At both institutions, older patients and those with higher resected gland weights were more likely to have elevated postoperative PTH ($P < 0.05$ at CCF). Nonsignificant factors included preoperative and postoperative serum calcium as well as vitamin D-25 levels. The frequency of bilateral exploration did not differ

Table 1 Preoperative characteristics

Characteristic	RIH	CCF	*P*
Age	59.2 ± 13.0	60.4 ± 12.9	0.23
% Female	80.0	76.9	0.23
Preop. calcium (mg/dl)	10.9 ± 0.7	11.1 ± 0.7	<0.001
Preop. PTH (pg/ml)	143.8 ± 104.8	157.6 ± 150.3	0.18
Vitamin D-25 (ng/ml)	24.1 ± 12	27.4 ± 10.6	0.02
Vitamin D-25 (% <20 ng/ml)	43.8	27.0	0.04
Sestamibi-positive for single gland (%)	93.2	92.7	NA
US-positive for single gland (%)	73.4	91.9	NA
Sestamibi- and US-positive (%)	66.6	84.9	NA

RIH Rhode Island Hospital (focused-approach group), *CCF* Cleveland Clinic Foundation (four-gland exploration group), *PTH* parathyroid hormone, *vitamin D-25* 25-dihydroxyvitamin D, *US* ultrasonography, *NA* not available

Table 2 Operative findings

Parameter	RIH	CCF	*P*
IOPTH (% drop to ≥50% or normal)	95.7	95.8	1
Bilateral exploration (% of patients)	22.1	100	NA
Total gland weight resected (mg)	942 ± 1193	1394 ± 1761	0.003
Glands resected (no.)	1.1	1.4	<0.001
Average weight/gland (mg)	880	995	NA
Multigland disease (% of patients)	5.8	21.9	<0.001

IOPTH intraoperative PTH

Table 3 Two-week postoperative findings

Parameter	RIH	CCF	*P*
Calcium (mg/dl)	9.2 ± 0.6	9.5 ± 0.8	<0.001
PTH (pg/ml)	44.5 ± 31	66.0 ± 62.9	<0.001
PTH, % >65 pg/ml	18.8	38.7	<0.001

Table 4 Breakdown of single versus multigland disease, by institution

Institution	Single adenoma	Double adenoma	Hyperplasia
CCF	78.1	12.4	9.5
RIH	94.5	4.2	1.3

Results are the percent of patients

between patients with normal versus elevated PTH levels. In all, 100% of patients at CCF and slightly more than 20% of patients at RIH underwent bilateral exploration.

At CCF, patients with multigland disease were more likely to have a normal 2-week postoperative PTH level. Patients with normal 2-week PTH levels had an average of 1.5 glands resected, compared to an average 1.3 glands in patients with 2-week postoperative PTH elevation. Increased gland weight strongly predicted increased postoperative PTH levels. At CCF, the average gland resected from a patient with PTH $\geq$ 65 pg/ml at 2 weeks was 1,344 mg compared to 759 mg in the group of patients with PTH $<$ 65 pg/ml. At RIH the number and size of individual glands did not significantly differ between patients with normal and elevated 2-week postoperative PTH values.

To eliminate the possible role played by the different rates of multigland disease, all patients at both centers who had just a single adenoma resected—94.2% of patients at RIH and 78.1% of patients at CCF—were compared (Table 7) There were 290 patients from each center. The findings mirrored those of the entire populations. Age, sex, and preoperative PTH levels were similar. The preoperative calcium levels were slightly higher at CCF, as were the preoperative vitamin D-25 levels. The mean weight of single adenomas was 47.3% greater at CCF than at RIH: 1399 vs. 950 mg ($P = 0.001$). At the 2-week postoperative visit, the serum calcium and PTH levels were significantly higher at CCF than at RIH.

Discussion

The phenomenon of postparathyroidectomy PTH elevation in eucalcemic patients has been extensively studied, and many theories have been put forth as to its etiology. Significant predictors identified in prior studies include increased patient age, high preoperative PTH, larger adenomas, vitamin D deficiency, renal insufficiency, and high bone turnover [15–19, 21, 24, 26–29]. Recent analysis of more than 300 parathyroidectomy patients demonstrated

Table 5 Characteristics of patients with and without 2-week postoperative PTH elevation at CCF

Characteristic	PTH $\leq$ 65	PTH $>$ 65	*P*
Age (years)	58.9 ± 12.6	62.2 ± 13.1	0.02
Preop. calcium (mg/dl)	11.1 ± 0.7	11.1 ± 0.7	0.6
Preop. PTH (pg/ml)	131.3 ± 84.8	202.2 ± 212.1	<0.001
Vitamin D-25 (ng/ml)	27.7 ± 11.4	27.1 ± 15.7	0.82
Vitamin D-25 (% <20 ng/ml)	23.6	36.5	0.31
Postop. calcium (mg/dl)	9.6 ± 0.9	9.5 ± 0.7	0.11
Total gland weight (mg)	1063.4 ± 1337.9	1612.8 ± 2109.1	0.007
Glands excised (no.)	1.47 ± 0.95	1.27 ± 0.72	0.026
Weight per gland excised (mg), average	759	1344	NA

Table 6 Characteristics of patients with and without 2 week postoperative PTH elevation at RIH

Characteristic	PTH $\leq$ 65 pg/ml	PTH $>$ 65 pg/ml	*P*
Age	58.6 ± 12.9	61.8 ± 13.4	0.09
Preop. calcium (mg/dl)	10.9 ± 0.6	10.9 ± 0.9	0.45
Preop. PTH (pg/ml)	127.8 ± 68.7	214.9 ± 181.1	<0.001
Vitamin D-25 (ng/ml)	24.6 ± 12.5	21.4 ± 9.2	0.10
Vitamin D-25 (% <20 ng/ml)	43.2	46.9	0.78
Postop. calcium (mg/dl)	9.2 ± 0.6	9.1 ± 0.5	0.06
Total gland weight (mg)	968 ± 1194	1022 ± 983	0.11
Glands excised (no.)	1.07	1.10	0.52
Weight per gland excised (mg), average	880	929.1	NA
% Bilateral exploration	22.5%	21.0%	0.65

the predictive value for failure of an elevated PTH at 1 week to be just 14% [19] and over months to years a high postoperative PTH level declines in many but not all [20, 26].

This study provides a large-scale comparison of two surgical approaches to hyperparathyroidism and their relation to postoperative PTH elevation. Because the groups are geographically separate, their preoperative traits were not identical. Both populations were similar in age and sex as well as preoperative PTH levels. At CCF, preoperative calcium and vitamin D-25 levels were slightly higher. Unfortunately, the vitamin D levels were available for only 31% of the CCF patients, in contrast to 85% of those at RIH. This was simply a limitation of the database. Although it is unlikely that this introduced bias, the possibility of significant vitamin D deficiency in the rest of the CCF patients would provide a plausible explanation for the higher rate of 2-week postparathyroidectomy PTH levels.

The intraoperative findings differed significantly between institutions. The focused approach at RIH identified multigland disease in only 5.8% of patients, whereas routine four-gland exploration at CCF identified it in 21.9%. The total gland weight resected per patient was also significantly higher at CCF. However, this was not related to the number of glands resected. In fact, it has recently been shown that total gland weight correlates more with preoperative PTH levels than with the number of enlarged glands. In a review of nearly 500 CCF patients, total abnormal gland weight was similar in patients with single adenomas versus multigland disease and was directly related to preoperative PTH levels [30].

To eliminate the potential bias introduced by the different rates of multigland disease in the two groups, the individual gland weights of only patients with final diagnoses of single adenoma were compared. The mean weight of single adenomas at CCF was still significantly higher: 1399 vs. 951 mg (Table 7). The explanation for this finding in our study population may be related to the duration of disease prior to diagnosis. The longer a parathyroid adenoma is present, the longer it has for potential growth. If the patients in the midwestern United States are being diagnosed later in their disease course than patients in the New England region, or if the time between diagnosis and surgical referral is longer in Ohio than in Rhode Island, higher gland weights would be expected. Examination of the operative findings for the two groups reveals that the clearest difference between them is the increased weight of the parathyroid adenomas in patients at CCF. Prior studies have also shown that increased gland size, along with higher preoperative calcium and PTH [15, 18, 22], both of which were seen in the CCF patients, are factors predictive of postparathyroidectomy PTH elevation.

Table 7 Comparison of patients with a single adenoma

Parameter	RIH	CCF	*P*
Age	60.0 ± 13	60.9 ± 13	0.08
% Female	76.6	79.0	0.06
Preop. calcium (mg/dl)	10.9 ± 0.7	11.1 ± 0.7	<0.001
Preop. PTH (pg/ml)	144.1 ± 104.7	162.1 ± 164.5	0.11
Vitamin D-25 (ng/ml)	24.1 ± 12.1	27.5 ± 12	0.02
Vitamin D-25 (% <20 ng/ml)	43.8	25.3	0.002
2-Week calcium (mg/dl)	9.2 ± 0.6	9.6 ± 0.8	<0.001
2-Week PTH (pg/ml)	44.3 ± 30.9	65.3 ± 38.8	<0.001
Gland weight (mg)	951 ± 1221	1399 ± 1925	0.001

The most widely accepted theory behind these associations is that patients with large adenomas produce more PTH and therefore have more severe bone disease. When hyperparathyroidism is cured by resection of the abnormal parathyroid gland(s), bone remineralization occurs, causing a relative calcium deficit, which then drives the PTH levels higher [18, 19, 29]. This calcium deficit may not always be reflected in the measured serum values; and in this study the 2-week postoperative calcium levels were actually higher at CCF than at RIH. Unfortunately, true measures of bone turnover were unavailable for comparison. The mean 2-week postoperative PTH was 66 pg/ml at CCF versus 44 pg/ml at RIH.

Previous investigators have suggested that the performance of a bilateral dissection could produce more transient ischemia of the normal remaining glands, leading to lower levels of PTH and serum calcium during the immediate postoperative period [27, 28]. This relative hypocalcemia should then stimulate PTH production and secretion from the remaining functioning glands, leading to a rebound elevation. One of the only published randomized trials comparing four-gland exploration to a unilateral approach did in fact show lower levels of calcium on postoperative days 1–4 and an increased incidence of early severe symptomatic hypocalcemia in the bilateral group [31]. In that study, however, PTH levels at 6 weeks were similar for both groups, and 2-week postoperative PTH levels were not published.

Despite the potential association of four-gland exploration with higher 2-week postoperative PTH levels, there are several significant findings that do not support this theory. First, patients at CCF with normal postoperative PTH levels had significantly more glands resected, 1.5 versus 1.3 in the patients with postoperative PTH elevation. Second, at RIH the frequency of bilateral neck exploration was nearly identical in patients with both normal and elevated 2-week PTH levels. If a bilateral exploration were responsible for the differences in postoperative PTH

between RIH and CCF, its effect should also be evident in a comparison of RIH patients with and without such an exploration. Finally, significant differences were discovered in the disease phenotypes at CCF and RIH.

The patients at each institution were also grouped by postoperative PTH levels and compared (Tables 5, 6). At both CCF and RIH, patients with elevated postoperative PTH had preoperative PTH levels that were nearly double the values seen in patients whose postoperative PTH was normal. The other predictor of postoperative PTH elevation at CCF was a large adenoma size, but this was not significant at RIH. Although some investigators have suggested that high preoperative PTH levels may only be a marker of worse vitamin D deficiency [20], this was not seen at either institution. There were trends between lower serum vitamin D-25 levels and postoperative PTH elevation at both CCF and RIH, but neither was statistically significant. There was also no significant relation seen between preoperative and postoperative serum calcium levels and postoperative PTH levels at either institution.

The potential impact of postoperative calcium and/or vitamin D replacement is difficult to compare between these two groups of patients. Whereas all patients at RIH were discharged home on calcium supplementation, most of the patients at CCF were not. By repleting a relative calcium deficit, those patients at RIH may not have experienced the same degree of relative hypocalcemia, thus lowering the stimulus for PTH secretion. The practice of routine calcium supplementation in the focused-approach group, in contrast to selective replacement in the four-gland exploration group, may have contributed to the differences seen. For this reason, many surgeons now recommend routine postoperative vitamin D and calcium replacement for their patients, as well as preoperative vitamin D replacement in those known to be deficient [15, 20, 21, 27]. Because vitamin D-25 deficiency is one of the most commonly cited causes of postparathyroidectomy PTH elevation [18, 21, 22], its lower prevalence in patients treated at CCF was an unexpected finding.

Two other potential differences between these populations that warrant further investigation include (1) the level of bone disease, as measured by bone densitometry or urinary assay for markers of bone turnover; and (2) the degree of renal dysfunction in each of the groups. Both have been shown to be associated with postparathyroidectomy PTH elevation [18, 22] but were not available for analysis.

From a technical perspective, both groups of patients experienced high initial cure rates with minimal complications. Additional follow-up data available for patients at CCF was recently published: they show that persistent PTH elevation at 6 months is present in just 15% of patients, and the frequency of persistent and recurrent hyperparathyroidism is just 3% [32].

Conclusions

This study examining the likelihood of 2-week postoperative PTH elevation in patients with PHPT who underwent unilateral localization demonstrates that PTH elevation during the early postoperative period is significantly associated with large parathyroid adenomas and high preoperative PTH levels. The prevalence of elevated postoperative PTH was greater in the group of patients undergoing routine four-gland exploration; however, the significant differences in the disease phenotypes between the two groups make it difficult to infer a role when deciding on the operative approach.

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