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# Postoperative Calcium Requirements in 6,000 Patients Undergoing Outpatient Parathyroidectomy: Easily Avoiding Symptomatic Hypocalcemia

Marie Vasher, MD, Arnold Goodman, MD, FACS, Douglas Politz, MD, FACS, FACE,  
James Norman, MD, FACS, FACE

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- BACKGROUND:** To determine the amount and duration of supplemental oral calcium for patients with varying clinical presentations discharged immediately after surgery for primary hyperparathyroidism.
- STUDY DESIGN:** A 4-year, prospective, single-institution study of 6,000 patients undergoing parathyroidectomy for primary hyperparathyroidism and discharged within 2.5 hours. Based on our previous studies, patients are started on a sliding scale of oral calcium determined by a number of preoperative measures (ie, serum calcium, body weight, osteoporosis) beginning 3 hours post-operation and decreasing to a maintenance dose by week 3. Patients reported all hypocalcemia symptoms daily for 2 weeks.
- RESULTS:** Seven parameters were found to have a substantial impact on the amount of calcium required to prevent symptomatic hypocalcemia: preoperative serum calcium >12 mg/dL, >13 mg/dL, and >13.5 mg/dL, bone density T score less than -3, morbid obesity, removal of >1 parathyroid, and manipulation/biopsy of all remaining glands (all  $p < 0.05$ ). Each independent variable increased the daily calcium required by 315 mg/day. Using our scaled protocol, <8% of patients showed symptoms of hypocalcemia, nearly all of whom were successfully self-treated with additional oral calcium. Only 6 patients (0.1%) required a visit to the emergency room for IV calcium, all occurring on postoperative day 3 or later.
- CONCLUSION:** After outpatient parathyroidectomy, a specific calcium protocol has been verified that eliminates development of symptomatic hypocalcemia in >92% of patients, identifies patients at high risk for hypocalcemia, and allows self-medication with confidence in a predictable fashion for those patients in whom symptoms develop. (J Am Coll Surg 2010;211:49–54. © 2010 by the American College of Surgeons)
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Monitoring patients in the hospital after parathyroidectomy has been standard practice for many decades. Although concerns about bleeding and airway compromise are present, most physicians will state that monitoring of calcium levels postoperatively is the primary reason these patients should be hospitalized. Patients undergoing a successful parathyroidectomy will show a substantial drop in serum calcium levels on postoperative day 1 that can last as long as 2 weeks.<sup>1</sup> Because of the fear of untreated hypocalcemia and tetany, many experienced physicians suggest

that patients remain in the hospital for 1 to 3 days for reasons of patient safety.

Parathyroid surgery has seen substantial changes since the mid 1990s. Mechanisms and techniques became available that allowed the experienced parathyroid surgeon—appropriately equipped—to make physiologic determinations within the operating room to establish cure before concluding the operation.<sup>2–6</sup> Surgeons are now able to use physiology and not just anatomy to determine cure. Our group was a pioneer in minimally invasive parathyroid surgery during this time.<sup>7,8</sup> Armed with intraoperative nuclear mapping, we could establish with >99% accuracy which patients are cured of their hyperparathyroidism within seconds of removal of the offending parathyroid gland(s).<sup>9,10</sup> This knowledge allows our group to perform most parathyroid operations in <20 minutes using much less anesthesia and a considerably smaller dissection than previously required. These quick and successful operations now allow virtually all patients to be sent home within an hour or 2 of

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From the Norman Parathyroid Center, Tampa, FL.

Correspondence address: James Norman, MD, Norman Parathyroid Center, 2400 Cypress Glen Dr, Wesley Chapel, FL 33544. email: jnorman@parathyroid.com

**Table 1.** Norman Postoperative Calcium Protocol

	Average preoperative calcium (mg/dL)	Calcium dose, day of operation	Daily calcium dose, postoperative week 1	Daily calcium dose, postoperative week 2	Daily calcium dose, maintenance
Adenoma	10.0–11.9	4	4	3	2
	12.0–12.5	5	6	4	2
	12.6–13.0	6	7	4	2
	13.1–14.0	7	8	5	3
	>14	8	10	6	3
Hyperplasia	10.0–11.9	4	5–6	4	2

Calcium tablets (Citracal+D Tablets, 315 mg calcium citrate per tablet) prescribed based on preoperative calcium levels and findings at surgery (adenoma versus hyperplasia). Tablets are spaced evenly throughout the day. Maintenance dose is anticipated to last 2 years or longer based on bone densitometry. Patients with an adenoma but undergoing biopsy of all 4 parathyroid glands during surgery are given 1 extra pill per day for the first 2 weeks. Postmenopausal females with T scores less than  $-2.5$  and all patients less than  $-3.0$  are given 1 extra pill per day for the 1<sup>st</sup> week. Morbid obesity increases calcium supplementation by 1 pill per day for the first 2 weeks.

the operation. In 1997, 80% of our parathyroid patients were sent home after their operation. By 2003, this number had grown to essentially 100%, with only a rare patient who required a concomitant and complex thyroid lobectomy being kept overnight.

This study was undertaken to examine our current postoperative calcium protocol, a protocol that was developed between 1992 and 2004 on patients sent home immediately after parathyroid surgery. This protocol outlines the administration of supplemental oral calcium so the precipitous and expected drop in serum calcium can be avoided and the ultimate dangers of severe hypocalcemia nearly eliminated. We wanted to test our previous observations that patients can be grouped into predictable cohorts that will require different amounts of supplemental calcium for different lengths of time, and that patients at high risk for hypocalcemia developing can be identified before discharge. Our overall goal in this study was to determine if our current protocol allowed the safe discharge of virtually all patients after parathyroidectomy for primary hyperparathyroidism, taking into consideration gender, menopausal status, and bone density.

## METHODS

### Study cohort

A total of 6,000 patients participated in the study during 4 years, ending in January 2009. All had a diagnosis of primary hyperparathyroidism, underwent parathyroidectomy, and were discharged within 2.5 hours of the operation. Women constituted 75.1% of patients and 24.9% were men. Mean age was 59.8 years, ranging from 14 to 95 years. Patients with secondary and tertiary hyperparathyroidism were not included in this study.

### Postoperative calcium protocol

Our postoperative calcium protocol is depicted in Table 1. Each patient is given a bottle of Citracal+D tablets (Bayer

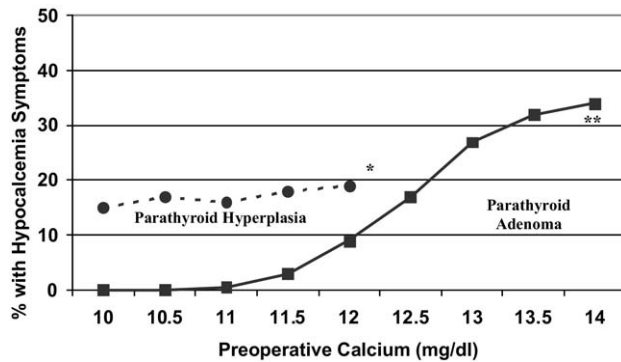
Healthcare LLC) and all instructions to the patient are in terms of the number of “calcium pills” to take rather than milligram dosage. Each tablet contains 315 mg calcium citrate and 200 IU vitamin D-3. A high dose of calcium is given, beginning on the day of surgery, that is highest during the first postoperative week and tapered during the next 2 weeks to a maintenance dose influenced by bone density. The first dose is to be taken within 3 hours of surgery. As published by our group previously, we have found that calcium citrate is preferable to other calcium formulations because it is tolerated very well by nearly all patients and is much less likely to be associated with some of the gastrointestinal maladies that can occasionally be seen when calcium carbonate is given in large doses.

Patients are segregated according to their observed serum calcium levels during the 3 to 6 months before the operation and assigned into 1 of 3 groups.<sup>11</sup> As shown in Figure 1, those with average calcium levels between 12.0 and 12.5 mg/dL are given more calcium tablets for the first postoperative week than patients with levels  $<12$  mg/dL. A similar increase is seen for additional increases in serum calcium (Fig. 1). We have previously shown that morbid obesity and severe osteoporosis (T score  $<3.5$ ) are both associated with an increase in calcium requirements and can influence a decision in this direction.<sup>12</sup>

Findings at surgery are also used to influence the dosage of postoperative calcium prescribed. Patients found to have 4-gland hyperplasia have their calcium dose increased more than those with an adenoma, despite having identical preoperative calcium values. If all remaining normal parathyroid glands require biopsy in a patient with an adenoma, then the number of pills prescribed for the first week is increased by 1 per day.

### Patient education, symptom recognition, and follow-up

All patients are given a preprinted instruction sheet that outlines in detail the number of calcium pills they are to



**Figure 1.** Incidence of hypocalcemia symptoms during 1<sup>st</sup> week after successful parathyroidectomy when taking supplemental calcium. Six thousand patients were maintained on the Norman postoperative calcium protocol. Percentages of all patients with parathyroid hyperplasia or adenomas are shown compared to their preoperative average calcium levels.

take each day for the subsequent 2 years. Considerable time is spent counseling the patient and their family member(s) about the importance of calcium supplementation, which is emphasized by providing a box of calcium directly to the patient. Symptoms of hypocalcemia are described in detail on the instruction sheet and are reviewed in more detail with at-risk patients. Patients with calcium levels <12 mg/dL and found to have an adenoma are not allowed to increase their calcium intake without calling the surgeon directly. Patients with calcium levels >12 mg/dL and patients found to have hyperplasia are allowed to increase their calcium intake to a maximum of 10 pills (3.1 g) per day should symptoms arise. Our protocol is for the patient to increase calcium intake by 2 pills every 2 hours if symptoms are present. No patient is allowed to take >10 calcium pills per 24-hour period without contacting the surgeon directly; all patients are given the surgeon's home phone and cell phone numbers for this purpose. All calls to the office or to the surgeon about complications or calcium symptoms are noted and tracked.

Postoperative laboratory results are obtained for all patients from 1 to 4 weeks postsurgery, at the discretion of the referring endocrinologist and/or primary care physician.

**Table 3.** Incidence and Timing of Hypocalcemia Symptoms

	Average preoperative calcium (mg/dL)	Postoperative hypocalcemic symptoms (%)	Postoperative day symptoms appear	Need for ER visit for IV calcium (%)
Adenoma	10.0–11.9	2	3	0
	12.0–12.5	12	3	0
	12.6–13.0	21	2–3	0
	13.1–14.0	31	1–2	0
	>14	35	2–3	5
Hyperplasia	10.5–11.8	16	2–3	3.5

Six-thousand outpatients started on the Norman Postoperative Calcium Protocol. Symptoms requiring additional calcium developed in 460 patients. ER, emergency room.

**Table 2.** Relative Frequency of Specific Hypocalcemic Symptoms

Subjective symptoms	% of Symptomatic patients*
Hand paresthesia	81
Perioral tingling	39
Mental fog	35
Hand cramping	4.1

Symptoms of hypocalcemia occurred in 7.7% of patients discharged immediately after successful parathyroid surgery and managed on oral calcium as outlined.

\*Because some patients have more than 1 symptom, percentage sum to >100%.

No results are routinely obtained on any patient before this time. Thirty-day postoperative follow-up was available for 100% of patients in this study.

### Statistical analysis

Data were analyzed by using the Sigma Stat Program (SPSS Inc). All results are expressed as mean  $\pm$  SD. Differences in mean values were assessed by use of Student's *t*-test and the Mann-Whitney rank sum test.

## RESULTS

### Symptomatic postoperative hypocalcemia

Symptomatic hypocalcemia occurred in 460 (7.7%) patients taking supplemental calcium according to our protocol. Seven of these patients (0.1%) required a visit to the emergency room for IV calcium, all occurred between postoperative days 3 and 5. Table 2 shows the relative frequency of the most common subjective reports of those with symptomatic hypocalcemia. Hand "tingling" and paresthesia occurred most frequently (82% of those with symptoms), followed by perioral tingling and mental fog. Cramps of the hands occurred in only 19 patients (4.1% of patients with symptoms, and 0.3% of all patients).

Timing of the onset of symptoms after successful parathyroid surgery, when taking oral calcium with the outlined protocol, is shown in Table 3. The incidence of symptoms developing varies according to the findings at surgery (hyperplasia versus adenoma) and the degree to which the

serum calcium level was elevated preoperatively. Importantly, the preoperative parathyroid hormone (PTH) level did not correlate with the need for additional calcium ( $p = \text{NS}$  at all PTH levels). Onset of symptoms almost always occurred on postoperative day number 2 or later, with patients having extreme elevations of calcium preoperatively being the only patients who occasionally presented with symptoms on postoperative day 1. There were only 16 patients of the 6,000 on this protocol (0.2%) who reported symptoms of low calcium on postoperative day 1. No patient had symptoms the day of surgery.

The relationship of preoperative calcium levels to incidence of symptoms of hypocalcemia developing (when taking oral calcium supplements as outlined) is shown in Figure 1. Patients with serum calcium levels  $<11.5$  mg/dL and found to have a single (or double) adenoma as the cause, have a  $<5\%$  chance of symptomatic hypocalcemia developing when maintained on oral calcium as outlined. As the average preoperative calcium level increases beyond 12 mg/dL, however, the incidence of symptoms developing increases to near 33% in patients with calcium levels  $>13$  mg/dL ( $p < 0.05$ ; calcium  $<11.5$  mg/dL versus calcium  $>12.5$  mg/dL). It is important to emphasize that although symptoms develop in these patients on this protocol, the symptoms are mild and can almost always be managed with additional oral calcium supplementation.

Patients found to have 4-gland hyperplasia as the cause of the hyperparathyroidism and who are treated with an appropriate subtotal parathyroidectomy have a higher incidence of symptoms of low calcium developing than patients with an adenoma(s) as the cause (Fig. 1;  $p < 0.01$  hyperplasia versus adenoma). Unlike those patients with an adenoma, the incidence of symptoms developing in the hyperplasia group is not related to the preoperative calcium level but rather to a function of the necessary parathyroid tissue debulking.

### Management of symptomatic hypocalcemia

Only 7 (1.5%) of 460 patients with hypocalcemic symptoms required IV calcium as a treatment for hypocalcemia (0.1% of all patients, Table 3). All of these patients had all of the symptoms of hypocalcemia, including hand cramps. All other patients with symptoms were adequately managed by increasing the amount of oral calcium intake for several days. All first visits to the emergency room for IV calcium occurred between postoperative day numbers 3 and 5. Five of the seven who required IV calcium were patients with 4-gland hyperplasia who were treated with a subtotal parathyroidectomy. There were only 2 patients with adenomas who required IV calcium, both of whom required more than 1 trip to the emergency room, with 1 patient requiring hospital admission for multiple doses of

IV calcium. Both of these patients had single adenomas  $>3$  cm and serum calcium levels  $>14$  mg/dL before surgery. No patients in this study were rendered hypoparathyroid. All patients receiving IV calcium did so in the emergency department of their local hospital and all patients experienced a dramatic and sudden resolution of symptoms and were sent home within 2 hours of receiving IV calcium.

### DISCUSSION

Although outpatient parathyroid surgery has become commonplace, a number of endocrinologists and surgeons still have reservations about the safety of this practice. Fear of severe symptomatic hypocalcemia has led to the longstanding practice that patients have their calcium levels monitored at least overnight.<sup>1,13-15</sup> The purpose of this study was to evaluate the safety of immediate discharge of patients after parathyroidectomy and to develop mechanisms to identify which patients are more likely to have calcium difficulties in the postoperative period.

An individual patient's postoperative calcium requirements were shown to be very predictable based on factors known preoperatively and observations made during the operation. Without exception, all patients believed to be cured should be put on supplemental calcium postoperatively and this should begin within 3 hours of surgery. Only those patients who the surgeon does not believe to be cured should have their calcium withheld to avoid the potential of iatrogenic postoperative hypercalcemia. We routinely measure PTH in the recovery room 1 hour postoperation just before discharge. A cured patient should have a dramatic decrease in their PTH, much greater than the 50% drop typically associated with cure when this test is performed during the operation. Recently, several authors advocated using the drop in intraoperative PTH levels as a predictor of postoperative hypocalcemia.<sup>16,17</sup> In our experience, a cured patient will typically have a PTH level  $<15$  pg/mL at 1 hour after a successful operation.

Complications of hypocalcemia substantial enough to warrant a patient visit to the emergency room are particularly rare when patients are well-educated, given the calcium supplements directly, and managed appropriately. Patients must be educated about their calcium requirements postoperation and we believe that this education should be verbal as well as written. We have found that providing a box of calcium pills directly to the patient, followed by a physician's phone call to the patient the night of surgery, increases compliance to near 100%. Simply giving the patient a prescription for calcium or making a verbal recommendation will result in a substantial percentage of patients who never obtain or take their required calcium.

Fewer than 8% of all patients sent home immediately after a parathyroid operation on the outlined calcium pro-

tocol will experience symptoms of hypocalcemia, with nearly all being able to be self-managed with additional oral calcium. Just 1 in 850 patients required a visit to the emergency room for IV calcium (0.1%), with only the most extreme cases of hyperparathyroidism at risk of needing hospitalization. Importantly, we have never had a patient require a trip to the emergency room for IV calcium before the 2<sup>nd</sup> postoperative day; it typically occurs on day 3.

As shown in [Figure 1](#), the most important factor determining the amount of calcium required is the patient's preoperative calcium levels (measured when the patient is not taking any calcium supplementation). It is important to note that the level of PTH preoperatively was not a predictor of postoperative calcium requirements. The vast majority of patients will have average calcium levels <12 mg/dL and will be found to have a single adenoma as the cause. These patients are quite easy to manage and almost never experience postoperative symptoms attributable to low calcium levels when managed with oral calcium supplements as outlined. However, substantial symptoms will develop even in these patients if they do not take any oral calcium, or take less than outlined. Patients with a single (or rarely, a double) adenoma and calcium levels >12 mg/dL have an increasing incidence of subjective symptoms of hypocalcemia developing, despite being placed on a higher dose of calcium supplementation. These patients can be managed with additional oral calcium supplementation, often adding calcium carbonate to the high dose of calcium citrate already being taken.

It has been our experience that preoperative calcium levels >12.0 mg/dL require more supplemental calcium than patients with lower levels. When patients have  $\geq 12$  calcium levels >12.5 before surgery, the daily Citracal tablets are increased to 7 per day for the first week, but are tapered to 4 during the 2<sup>nd</sup> week. This need for more calcium for patients with very high preoperative calcium levels has been noted by some authors<sup>18,19</sup> and refuted by others.<sup>14,20</sup> Regardless of the patient's preoperative calcium levels, we have found that it is uncommon for any patient with a single or double adenoma (not hyperplasia) to require >4 calcium pills per day for the 2<sup>nd</sup> week. This observation suggests that almost all patients will get acclimated to their new, lower, normal calcium level during the 1<sup>st</sup> postoperative week, as long as 1 or more normal parathyroid glands were not biopsied. If all glands are manipulated and biopsied (mandatory in patients with hyperplasia), this process can be expected to take an additional week, or even 2. Managed as outlined, the need for a patient with parathyroid adenoma(s) to visit the emergency room for IV calcium is near 0.

Although patients with 4-gland hyperplasia make up a small minority of all patients with primary hyperparathyroidism, they have a different need for calcium postoperatively, one that does not vary with the degree of hypercalcemia preoperatively.<sup>13,14</sup> The reason for this difference is that these patients undergo a different operation, which is designed to debulk the total amount of parathyroid tissue to a level sufficient for long-term homeostasis. By virtue of their disease process, patients with hyperplasia will usually require the identification, mobilization, and removal of 3 glands, with the other biopsied (debulked). These patients must be counseled more carefully about the signs of hypocalcemia than patients with adenomas. Except in patients with MEN syndromes, this more extensive counseling will be conducted postoperatively after hyperplasia is discovered at operation.

An important observation is that the manipulation and biopsy of all 4 parathyroid glands in a patient with a single adenoma increases the chances of hypocalcemia symptoms developing during the 1<sup>st</sup> postoperative week. The standard, old-fashioned parathyroid operation, which dictates that all 4 parathyroid glands are mobilized and biopsied for frozen-section histologic analysis, is inherently and predictably associated with poor function of the normal (but disturbed and transected) parathyroid glands for as long as 7 to 10 days. Leaving 1 or more normal glands undisturbed decreases the chances of symptomatic hypocalcemia for the vast majority of patients with an adenoma to near 0. It is our protocol to biopsy (for permanent histology, not frozen section) all parathyroid glands identified, we simply increase the number of calcium pills for the 1<sup>st</sup> week by 1 per day as shown in [Table 1](#).

We believe that all patients should be discharged on postoperative calcium to more rapidly resume normal calcium homeostasis. Several studies have shown that as many as 25% of patients will show a persistent elevation of PTH, despite curative parathyroid surgery.<sup>21,22</sup> It is our belief that this can largely be avoided by proactive calcium supplementation beginning immediately after surgery, because our patients rarely show elevated PTH levels at any time postoperation. All articles describing this phenomenon are from authors who do not routinely give calcium to patients after parathyroidectomy, electing to give it only to patients who become symptomatic.

Patients undergoing an uneventful parathyroid operation for primary hyperparathyroidism can be discharged immediately. All patients should start oral calcium within 3 hours of surgery in an amount that decreases during several weeks. Postoperative calcium requirements are predictable according to preoperative calcium levels, bone density, and findings at surgery. When managed as outlined, symptoms

of low calcium will not develop in the vast majority of patients. For the small number of patients who will display symptoms, the addition of more calcium pills in an educated and orderly fashion will safely eradicate the symptoms. It is a very rare patient who will require a trip to the emergency room on postoperative days 3 or 4, and the identification of these high-risk patients should be easy before discharge. Verbal and written patient education is essential for compliance, as is providing the necessary calcium pills directly to the patient.

### Author Contributions

Study conception and design: Vasher, Politz, Norman

Acquisition of data: Vasher, Politz, Norman

Analysis and interpretation of data: Vasher, Goodman, Politz, Norman

Drafting of manuscript: Vasher, Goodman, Politz, Norman

Critical revision: Vasher, Goodman, Politz, Norman

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