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Predicting the need for calcium and calcitriol supplementation after total thyroidectomy: Results of a prospective, randomized study

Ashley K. Cayo, MD, Tina W.F. Yen, MD, MS, Sarah M. Misustin, PA-C, Kimberly Wall, APNP, Stuart D. Wilson, MD, Douglas B. Evans, MD, and Tracy S. Wang, MD, MPH

Department of Surgery, Medical College of Wisconsin, Milwaukee, WI

Abstract

Background—The optimal protocol for the detection and treatment of post-thyroidectomy hypoparathyroidism is unknown. We sought to identify and treat patients at risk for symptomatic hypocalcemia based on a single PTH obtained the morning after surgery (POD1).

Methods—We performed a prospective, randomized study of total thyroidectomy patients who had POD1 calcium and PTH (pg/mL) levels. Randomization was based on POD1 PTH: if ≥ 10 , patients received no supplementation unless symptomatic; if <10 , patients were randomized to calcium, calcium and calcitriol, or no supplementation.

Results—Of 143 patients, 112 (78%) had a POD1 PTH ≥ 10 . Hypocalcemic symptoms were transiently reported in 11 (10%) and managed with outpatient calcium. Of 31 patients with PTH <10 , 15 (48%) developed symptoms, including 5 who required IV calcium. On multivariate logistic regression analysis, when adjusting for postoperative calcium level and performance of central neck dissection, predictors of hypocalcemic symptoms were younger age (OR 1.59, 95%CI 1.07 – 2.32) and a PTH <10 (OR 1.08, 95%CI 1.04 – 1.12). There were no patient or treatment-related factors that predicted a POD1 PTH <10 .

Conclusion—A single POD1 PTH level <10 can accurately identify those patients at risk for clinically significant hypocalcemia. All total thyroidectomy patients with a postoperative PTH ≥ 10 can be safely discharged without supplementation. Given the small number of patients with PTH <10 , it is unclear if both calcium and calcitriol are needed for these higher-risk patients.

Introduction

Postoperative hypocalcemia, as a result of hypoparathyroidism, is the most frequent complication after total thyroidectomy. Hypocalcemia occurs transiently in up to 50% of patients and permanently (>6 months) in 0.5–2% of patients; it may result from parathyroid devascularization, stunning, or incidental removal of the parathyroid gland(s).^{1–6} Factors that increase the complexity of surgery, such as Graves' disease, large goiters, thyroid cancer, malignant adenopathy in the central neck compartment, and previous neck operations, have been shown to increase the risk of hypoparathyroidism.^{2, 6–9}

The optimal protocol for the detection and treatment of post-thyroidectomy hypoparathyroidism is unknown. Determining predictors of symptomatic hypoparathyroidism is important as patients are frequently being discharged either on the day of or within 23 hours of surgery. Recent retrospective and prospective studies have shown that a single intact parathyroid hormone (PTH) level may predict the development of symptomatic hypocalcemia in patients who have undergone completion/total thyroidectomy.^{10–16} Current algorithms for the prevention or treatment of hypocalcemia include routine calcium and/or vitamin D supplementation or selective supplementation, based on intraoperative or postoperative PTH or serum calcium levels.^{1–5, 7, 11–19}

To our knowledge, there have been no prospective, randomized trials addressing the detection and treatment of hypoparathyroidism following total thyroidectomy. Herein, we report a single institution, prospective, randomized study which sought to identify patients at risk for hypoparathyroidism following completion/total thyroidectomy using postoperative day 1 (POD1) PTH levels and to determine the ideal algorithm of calcium and calcitriol supplementation in these at-risk patients.

Methods

This is a single-institution, prospective, randomized study of patients who underwent completion/total thyroidectomy. The protocol was approved by our institutional IRB. All patients scheduled for total thyroidectomy between February 15, 2010 and December 31, 2011 were asked to participate; patients who underwent concomitant parathyroid surgery were considered inevaluable. Preoperative serum calcium (mg/dL), intact PTH (pg/mL), and 25-OH vitamin D (ng/mL) levels were obtained. Patients with 25-OH vitamin D levels <32 were started on vitamin D supplementation (Ergocalciferol, 50,000 units weekly) prior to surgery. The duration of vitamin D supplementation varied, based on the time frame between the preoperative laboratory assessment and day of surgery; we did not require repletion of vitamin D levels prior to operation.

Thyroidectomy was performed by one of three endocrine surgeons. The majority of patients who underwent thyroidectomy for a preoperative diagnosis of differentiated thyroid cancer received a prophylactic central compartment lymph node dissection. We considered a neck dissection prophylactic when there was no evidence of lymphadenopathy on preoperative ultrasound or intraoperative assessment of the central neck. Parathyroid autotransplantation was routinely performed whenever a parathyroid gland was identified (ex-vivo) within the thyroidectomy specimen; it is our practice to insert parathyroid fragments within a single pocket in either the sternohyoid or sternocleidomastoid muscle of patients without familial endocrinopathies. Following thyroidectomy, patients did not receive routine calcium or vitamin D supplementation (Figure 1). Serum calcium and PTH levels were obtained on the morning of POD1. If the patient reported symptoms which were consistent with hypocalcemia prior to the morning of POD1, serum calcium and PTH levels were obtained at that time; calcium supplementation was then initiated in all of these patients with overnight subjective symptoms of hypocalcemia and then subsequently discontinued only if the PTH level was <10.

Patients were randomized to one of five different supplementation regimens based on the POD1 PTH level (or earlier PTH result if symptoms were reported) (Figure 1). Threshold values of PTH <10 for calcium supplementation and <5 for the addition of calcitriol were chosen based on results of our previous study.¹⁹ Patients with a PTH <5 were randomized to calcium (Group A) or calcium and calcitriol (Group B). Patients with a PTH 5–10 were randomized to calcium (Group C) or no supplementation (Group D). All patients with PTH 10 (Group E) received no supplementation. Randomization occurred preoperatively via blinded selection from two boxes of prelabeled cards. If the POD1 PTH was <5, one card was chosen from the Group A/B box to determine if the patient would be randomized to Group A or B). Similarly, if the POD1 PTH was between 5 and 10, one card was chosen from the Group C/D box. Calcium supplementation consisted of elemental calcium (1 gm three times daily; calcium carbonate, 2500 mg). Calcitriol supplementation was 0.5 mcg twice daily. All patients were discharged, typically on the morning of POD1, with a templated record for documentation of symptoms and calcium/calcitriol supplementation and were extensively counseled on the recognition and management of symptomatic hypocalcemia.

At the first postoperative visit (approximately one week after surgery), serum calcium, PTH, and 25-OH vitamin D levels were obtained. Additional calcium and/or calcitriol supplementation was based on PTH levels and patient symptoms (Table 1). When necessary, calcitriol (0.5 mcg BID) was added to the supplementation of patients already on routine calcium; the dose of calcitriol was increased by 0.25 mcg per dose increments for patients already on both calcium and calcitriol. All patients who remained on any form of supplementation were provided detailed instructions for weaning one or both medications in the absence of recurrent symptoms. In brief, patients taking both calcitriol and calcium were first weaned from calcitriol by decreasing the dosage by 0.25 mcg every three days. Once weaned off of calcitriol, the dose of calcium carbonate was decreased by 1 gm of elemental calcium every three days. Serum calcium and PTH levels were not routinely obtained after the first postoperative visit.

Data collected included age, gender, preoperative and postoperative calcium, PTH, and 25-OH vitamin D levels, extent of surgery (concomitant central and/or lateral neck dissection, parathyroid autotransplantation), final pathology (including gland weight, benign disease vs. cancer, tumor size, parathyroid tissue removed, and number of malignant/total lymph nodes), and presence of hypocalcemic symptoms. Hypocalcemic symptoms were subjective and defined as any report of tingling, numbness, and/or cramping periorally or in the upper or lower extremities.

Statistical analysis was performed using SPSS software (version 19.0, Chicago, IL). Univariate analysis for risk factors of symptomatic hypocalcemia or PTH <10 were performed using Student's t-test and chi-square analysis. Significant factors on univariate analysis (p-value < 0.05) and variables of interest identified a priori were then tested by multivariate logistic regression analysis. Point estimates from the multivariable model are reported as odds ratios (ORs) along with the corresponding 95% CI for each OR.

Results

Of the 158 patients who underwent completion/total thyroidectomy and initially consented to participate, 15 were excluded from the analysis: 10 patients withdrew, 2 underwent concomitant parathyroidectomy, and 3 underwent only thyroid lobectomy. The final study cohort consisted of 143 patients. The median age was 47 years (range, 18 to 82); 114 (80%) were female. Preoperative laboratory results included: median serum calcium, 9.4 (range, 8.4 to 10.9); median PTH level, 40.6 (range, 13.6 to 95.3); and median 25-OH vitamin D level, 29.1 (range, 4.6 to 74.6).

Of the 143 operations, 137 (96%) were total thyroidectomies and 6 were completion thyroidectomies. The indication for surgery was biopsy-proven thyroid cancer in 56 (39%) patients; the remaining 87 patients had either benign disease or indeterminate thyroid nodules on preoperative fine-needle aspiration biopsy. Of these 87 patients, 14 (16%) had an incidental thyroid cancer on final pathology. Central neck dissection was performed in 55 (38%) of 143 patients; this was a unilateral procedure in 30 cases, bilateral in 25 and prophylactic in 24 patients (Table 2). Parathyroid autotransplantation was performed in 63 (44%) of the 143 patients.

Figure 2 delineates the cohort by POD1 PTH level, supplementation regimen, development of hypocalcemic symptoms, and need for IV calcium. POD1 labs were drawn in 133 patients; the remaining 10 (7%) patients had labs drawn earlier due to symptoms consistent with hypocalcemia (mean PTH, 27.8 vs. 16.5; $p=0.04$). On POD1, 112 (78%) patients had a PTH >10 (group E). The remaining 31 (22%) patients had a POD1 PTH <10 and were randomized to calcium alone (Groups A [$n=5$] and C [$n=15$]), calcium and calcitriol (Group B [$n=7$]), or no supplementation (Group D [$n=4$]).

Predictors of the development of hypocalcemic symptoms

Symptoms consistent with hypocalcemia were reported by 26 (18%) of the 143 patients within the first 72 hours (Figure 2). No patient in any group developed clinically significant symptoms after this time period. Ten of these 26 patients reported symptoms on the night of surgery; of these ten, six had PTH <10 and received oral calcium supplementation; one eventually required IV calcium.

Symptoms consistent with hypocalcemia were reported by 11 (10%) of 112 patients with PTH ≥ 10 . Of these 11 patients, 7 had a POD1 serum calcium ≥ 8.0 ; of the remaining 4, 3 were 7.5–8.0, and 1 was 7.0–7.5. There was no difference in the mean percent change of preoperative to postoperative PTH between symptomatic and asymptomatic patients (22.6% vs. 23.0%; $p=0.98$). All 11 patients had transient symptoms that were successfully managed with outpatient prn oral calcium; no patient required scheduled calcium or calcitriol. At the one week follow-up visit, only three patients reported the continued use of intermittent calcium for transient symptoms; PTH levels remained >10 in all 11 patients.

In contrast, 15 (48%) of 31 patients with PTH <10 developed symptoms within 72 hours of operation. Of these 15 patients, 4 had a POD1 serum calcium ≥ 8.0 ; of the remaining 11, 7 were 7.5–8.0, 3 were 7.0–7.5, and 1 was <7.0 . The mean percent change of preoperative to

postoperative PTH was 86.3% in symptomatic patients and 82.6% in asymptomatic patients ($p=0.19$). For the 15 patients who developed symptoms, 10 were successfully managed with either the addition of calcium or calcitriol or with an increase in dose of supplementation. In the remaining five patients, administration of IV calcium was required due to the severity of symptoms.

Of the five patients who received IV calcium (5 of 143, 3.5%), four were readmitted (POD2–4) after discharge and one patient was still an inpatient at the time IV calcium was initiated (POD2). Of these 5 patients, 2 had a POD1 serum calcium ≥ 8.0 ; of the remaining 3, 2 were 7.0–7.5, and 1 was <7.0 . Length-of-stay for readmission was a median of 4 (range 3–5) days. After discharge, patients required an additional 16 (median, range 10–35) days of calcium supplementation and 21 (median, range 0–30) days of calcitriol supplementation. No patient had clinical or biochemical evidence of hypoparathyroidism longer than six weeks postoperatively. In unadjusted analyses of the 15 symptomatic patients with PTH <10 , no variables, including preoperative vitamin D levels, were associated with the need for IV calcium (data not shown).

Amongst the entire cohort of 143 patients, the specificity of a POD1 PTH <10 for the development of hypocalcemic symptoms was 86% (of the 117 asymptomatic patients, 101 had PTH ≥ 10); the negative predictive value was 90% (of all 112 patients with PTH >10 , only 11 developed symptoms). On univariate analysis, variables significantly associated with the presence of symptoms included younger age, lower postoperative calcium levels, and lower postoperative PTH levels. (Table 3) For every year increase in age, the likelihood of developing symptoms of hypocalcemia within 72 hours of total thyroidectomy is 4% lower; for every 10 years increase in age, there is a 36% decrease in the odds of developing symptoms (95% CI 0.45 – 0.91). Similarly, for every unit (pg/mL) increase in PTH, the odds of developing symptoms are 7% lower. On multivariate logistic regression analysis, when adjusting for postoperative calcium level and performance of a central neck dissection, independent predictors of hypocalcemic symptoms were younger age (OR 1.59, 95% CI 1.07 – 2.32) and lower postoperative PTH levels (OR 1.08, CI 1.04 – 1.12).

Predictors of POD1 PTH <10

The mean POD1 PTH level was 32.9 (SD, 15.1; range 10.4–85.5) for the 112 patients with POD1 PTH ≥ 10 and 5.8 (SD, 2.1; range 2.2–9.8) for 31 patients with POD1 PTH <10 . On univariate analysis, of the 12 variables assessed, only the POD1 calcium was associated with a POD1 PTH <10 ; for each 0.1 mg/dL increase in calcium, the odds of PTH <10 decrease by 31% (OR 0.69, 95% CI 0.61 – 0.79). In patients with a POD1 PTH <10 , mean POD1 calcium levels were significantly lower (7.7; SD 0.4; range 6.9–8.6) than in patients with a POD1 PTH ≥ 10 (8.5; SD 0.5; range 7.3–9.9; $p<0.001$). However, when analyzed with both postoperative calcium and postoperative PTH levels as continuous variables, there was only a weak correlation between these two variables (Spearman coefficient 0.46; $R^2=0.21$). Neither preoperative vitamin D levels ($p=0.6$) nor preoperative use of vitamin D supplementation ($p=0.26$) were associated with POD1 PTH levels. On multivariate logistic regression analysis, when adjusting for preoperative vitamin D levels, preoperative use of vitamin D supplementation, central neck dissection, and the number of parathyroid glands

that were incidentally removed or autotransplanted, there were no independent predictors of a POD1 PTH <10. There was a trend toward the removal or autotransplantation of more parathyroid glands as being predictive of POD1 PTH <10 (OR 0.47, 95% CI 0.21 – 1.04; $p = 0.06$).

Postoperative follow-up

For the cohort of 143 patients, the mean serum calcium was 9.2, PTH 32.6 and 25-OH vitamin D 30.4 at the first postoperative outpatient visit. The mean PTH at the time of the visit was 38.9 in patients with POD1 PTH ≥ 10 and 11.4 in patients with POD1 PTH <10 ($p < 0.001$). For the 31 patients with POD PTH <10, 13 (42%) had recovery of PTH levels to ≥ 10 . No patient with POD1 PTH ≥ 10 was on routine calcium or calcitriol supplementation at the time of the outpatient visit. Of the 31 patients with PTH <10, 26 (84%) were on supplementation at the time of their postoperative visit: nine were on calcium alone and 17 (55%) were on both calcium and calcitriol.

Overall, the median length of calcium supplementation was 22 days (range, 5 – 219) while median length of calcitriol supplementation was 15 days (range, 5 – 218). At the time of last follow-up (range, 59 – 219 days), only one patient (0.7% of the entire cohort) remained on calcium and calcitriol supplementation at 219 days of follow-up, at which time her PTH was 6.0. This patient underwent thyroidectomy for a goiter and was randomized to calcium and calcitriol (Group B) for a POD1 PTH of 2.6. There was no parathyroid tissue identified in the specimen.

Discussion

We report the first prospective, randomized controlled study to evaluate calcium and calcitriol supplementation following total thyroidectomy. Based on our findings, a single PTH level, obtained the morning after surgery, is highly specific for predicting those patients at risk for symptomatic hypocalcemia. If the POD1 PTH is ≥ 10 , 90% of patients will be symptom free; the remaining patients may develop mild, transient symptoms that can be effectively managed with outpatient oral calcium supplementation, as needed. Further, of the 10% of patients whose symptoms were interpreted as hypocalcemia, 64% (7/11) had serum calcium levels ≥ 8.0 and in such patients, the reported symptoms were perhaps unrelated to calcium-PTH physiology. Indeed, a POD1 PTH of ≥ 10 is a very powerful indicator that parathyroid function has been preserved and will not be a clinically significant concern for the patient or the treating physicians.

Several studies support the use of postoperative PTH in identifying patients likely to develop symptomatic hypocalcemia following thyroidectomy.^{5, 11–16, 19, 20} Sywak et al.⁵ measured PTH levels four hours after total thyroidectomy and found that a PTH ≥ 10 provided a 90% sensitivity for the absence of hypocalcemia, defined as serum calcium ≥ 8.0 . In pooled data from 458 patients by the Australian Endocrine Surgeons, a normal postoperative PTH had a specificity of 71% for predicting normocalcemia. Low PTH values were less predictive of hypocalcemia (specificity 92.6%), and 16% of patients with an undetectable PTH required no calcium supplementation.¹⁶ Youngswirth et al.¹⁰ showed that institution of a protocol for routine calcium and calcitriol supplementation for all patients with a PTH <10 resulted in a

lower rate of symptomatic hypocalcemia (7% vs. 17%; $p=0.005$) and fewer emergency room visits (1.8% vs. 8%; $p=0.008$). However, in all these studies, all patients received routine calcium supplementation, with selective use of calcitriol.

In contrast, selective supplementation of both calcium and calcitriol for only patients at risk for symptomatic hypocalcemia can prevent unnecessary supplementation in low risk patients, allow for a simplified discharge plan, and may allow for earlier discharge and potential cost-savings. We have previously demonstrated that a POD1 PTH had a higher positive predictive value than a POD1 calcium in predicting the need for calcitriol at one month following surgery.¹⁹ More recently, Landry et al.¹² demonstrated that limiting calcium and calcitriol supplementation to patients with a PTH <6 or a calcium <8 could eliminate unnecessary supplementation in up to 58% of patients. While cost analyses have suggested that routine supplementation may be more cost-effective, prospective data has been lacking and further validation is needed.²¹

In our current study, the only significant predictors of symptomatic hypocalcemia were younger age and lower PTH level. In our cohort, there was no difference in the number of central neck lymph nodes removed between symptomatic and asymptomatic patients. Although the postoperative PTH level predicted the development of hypocalcemic symptoms, we were unable to identify any clinical, laboratory or surgical factors that predict a POD1 PTH <10 . In contrast to the work of Landry et al.¹², extent of surgery (central neck dissection or removal of parathyroid tissue) did not predict either a PTH <10 or hypocalcemic symptoms. Our study is comparable in the number of resected parathyroid glands; therefore, our findings may reflect a lower rate of parathyroid stunning at the time of surgery as autograft function will protect against long-term, but not short-term, hypoparathyroidism.

This study has several limitations. First, due to the small number of patients with a POD1 PTH <10 , we were unable to adequately assess predictors of hypocalcemic symptoms or determine the need for calcitriol supplementation in this high-risk group. Secondly, while patients with low 25-OH vitamin D were started on ergocalciferol preoperatively, the duration of supplementation was not uniform and we cannot conclude that low preoperative vitamin D levels may predispose to postoperative hypocalcemia. Finally, we only obtained a PTH level on POD1, therefore the ability to apply this data to patients discharged on the day of surgery may not be feasible. However, previous studies have found no difference between PTH levels drawn 4 or 23 hours postoperatively in the detection of symptomatic hypocalcemia, suggesting that our data may be applicable to patients who have a PTH level drawn shortly after surgery and are discharged on the day of surgery.^{5, 14} The physiology of parathyroid stunning is not well described. Whether all (or most) stunned parathyroids have recovered function by the morning following surgery is not known, but one would assume that the stunning effect would be more pronounced immediately after surgery and decline with time.

The results of this prospective, randomized study suggest that a single PTH level the morning following surgery can identify patients who are (PTH <10) and are not (PTH ≥ 10) at risk for hypocalcemia following total thyroidectomy. Only 10% of patients with a PTH

10 developed symptoms and all were managed as outpatients with calcium alone. Therefore, we currently discharge all patients with POD1 PTH levels ≥ 10 without supplementation. In contrast, a POD1 PTH level of <10 identifies a patient at high risk for short-term symptomatic hypoparathyroidism, 50% of whom will require supplementation for symptomatic hypocalcemia. More information is needed regarding the importance of calcitriol (in addition to calcium) in this patient subset.

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Figure 1.
Algorithm for postoperative calcium supplementation

Figure 2.
Breakdown of the cohort by POD1 PTH level, supplementation regimen, hypocalcemic symptoms, and need for intravenous calcium.

Table 1

Protocol for calcium and/or supplementation, if needed, based on PTH obtained at postoperative clinic visit.

POD#1 PTH	PTH at visit	Plan
<5	<5	Continue supplementation. Repeat labs in 2 weeks.
	5–10	Wean supplementation.
	10	Wean supplementation.
5–10	<5	If asymptomatic, wean supplementation. If symptomatic, continue and repeat labs in two weeks.
	5–10	Wean supplementation.
	10	Wean supplementation.
10	<5	---
	5–10	---
	10	---

Table 2

Extent of surgery for patients undergoing total thyroidectomy, based on postoperative symptoms of hypocalcemia.

	Number of patients (%)		p-value
	Symptoms (n = 26)	No symptoms (n = 117)	
Median no. central lymph nodes removed (range)	5.5 (1–26)	9.0 (1–29)	0.52
Median no. malignant central lymph nodes (range)	0.5 (1–17)	0 (0–22)	0.76
Number of parathyroid glands removed*			
None	19 (73)	102 (87)	
1	7 (27)	14 (12)	
>1	0 (0)	1 (1)	
Parathyroid autograft performed	11 (42)	52 (44)	1.0

* Number of parathyroid glands detected in final pathology specimen.

Table 3
Unadjusted analysis of characteristics of 143 patients, by report of hypocalcemic symptoms*

	No Symptoms (n=117)	Symptoms (n=26)	Odds Ratio	95% Confidence Interval		p-value
				Lower	Upper	
Age (years)						
Mean (SD; range)	49 (14; 18–82)	41 (11; 23–64)	0.96	0.92	0.99	0.03
0–37	26 (22%)	13 (50%)				
38–48	32 (27%)	6 (23%)				
49–56	27 (24%)	4 (15%)				
>56	32 (27%)	3 (12%)				
Postoperative calcium						
Mean (SD; range)	8.4 (0.5; 6.9–9.6)	7.9 (0.6; 6.9–9.9)	0.16	0.07	0.41	<0.0001
<8.1	27 (23%)	17 (65%)				
8.1–8.6	54 (46%)	7 (27%)				
>8.6	36 (31%)	2 (8%)				
Postoperative PTH						
Mean (SD; range)	29.8 (17.2; 3.9–85.5)	14.6 (13.0–44.5)	0.93	0.89	0.96	<0.0001
<10	16 (14%)	15 (58%)				
10	101 (86%)	11 (42%)				
Number of CN nodes						
Mean (SD; range)	9.0 (7.4; 0–29)	8.3 (7.4; 1–26)	0.88	0.77	1.01	0.75

* Gender, preoperative laboratory values (calcium, PTH, and 25-OH vitamin D), extent of surgery (central neck dissection, parathyroid autotransplantation), and final pathology (diagnosis, gland weight, tumor size, parathyroid tissue removed and number of malignant lymph nodes) were not associated with the development of hypocalcemic symptoms.
Abbreviations: CN, central neck; PTH, parathyroid hormone