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Preventing post-operative hypocalcemia in Graves' patients: A prospective study

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Abstract

Background—Hypocalcemia occurs after total thyroidectomy (TT) for Graves' disease via parathyroid injury and/or from increased bone turnover. Current management is to supplement calcium after surgery. This study evaluates the impact of preoperative calcium supplementation on hypocalcemia after Graves' TT.

Methods—A prospective study of Graves' patients undergoing TT was performed. Graves' patients managed over a 9 month period took 1gm of calcium carbonate (CC) three times a day for two weeks before TT. Those managed the previous year, without supplementation served as historic controls. Age-, gender-, and thyroid weight-matched, non-Graves' TT patients were procedure controls. Patient demographics, postoperative laboratory values, complaints and medications were reviewed. PTH based postoperative protocols dictated postoperative CC and calcitriol use.

Results—45 Graves' patients were treated with CC before TT, while 38 Graves' patients were not. 40 non-Graves' controls were identified. Age, gender and thyroid weight were comparable. Pre-operative calcium and PTH levels were equivalent. PTH values immediately after surgery, POD 1 and at 2 week follow-up were equivalent. Post-operative use of scheduled CC ($p=0.10$) and calcitriol ($p=0.60$) was similar.

Post-operatively, untreated Graves' had lower serum calcium levels than pre-treated Graves' or non-Graves' controls (8.3mg/dL vs. 8.6 vs. 8.6, $p=0.05$). Complaints of numbness and tingling were more common in non-treated Graves' (26%) than pretreated Graves' (9%) or non-Graves' controls (10%, $p<0.05$).

Conclusions—Calcium supplementation before TT for Graves' significantly reduced biochemical and symptomatic postoperative hypocalcemia. Preoperative calcium supplementation is a simple treatment that can reduce symptoms of hypocalcemia after Graves' TT.

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Keywords

Graves' Disease; Total Thyroidectomy; Post-Operative Hypocalcemia; Bone Hunger; Calcium Supplementation; Calcium Replacement; Symptomatic Hypocalcemia; Surgical Outcomes

Introduction

A well-known complication of bilateral thyroid surgery is compromise of the parathyroid glands resulting in transient symptomatic hypocalcemia or potentially even permanent hypoparathyroidism.¹⁻⁴ This complication has plagued thyroid surgeons, and throughout history, has led to modifications to the operative procedure, including subtotal thyroidectomy to minimize disruption to the parathyroid glands, as well as abandonment of central ligation of the inferior thyroid artery.⁵ As the blood supply to the parathyroid glands had become better understood, total thyroidectomy (TT) is now routinely performed with division of the vascular supply as it directly enters the capsule of the gland. In addition to surgical technique modifications, there are a variety of clinical practices to try to prevent symptomatic hypocalcemia, including selective calcium and vitamin D supplementation based on post-operative parathyroid hormone levels, and routine supplementation for all patients without evaluation of parathyroid hormone levels in the post-operative period.^{3,6-9}

Patients with Graves' disease have much higher rates of symptomatic hypocalcemia after TT than patients undergoing TT for other diagnoses.^{1,3,10-14} Factors contributing to this increased rate of hypocalcemia after surgery include increased bone hunger secondary to thyrotoxic osteodystrophy, increased release of calcitonin during gland manipulation during surgery, as well as the increased inflammation and friability of the gland making the procedure technically more demanding and therefore placing the parathyroid glands at increased risk for injury.^{1,12,15}

As TT is the operation of choice for the surgical management of Graves' disease, it is critical that the risk of symptomatic hypocalcemia is minimized.^{10,14,16,17} Some authors have proposed the use of calcium in the pre-operative period for Graves' patients, however none have reported on how this practice influences patient outcome.¹² The study hypothesis was that pretreatment of Graves' patients with calcium supplementation before TT decreases the frequency of symptomatic postoperative hypocalcemia.

Methods

With IRB approval, a retrospective review was performed on a prospectively maintained database of all patients undergoing thyroid surgery at a large university based endocrine surgery practice. As of January 2013, all patients with a diagnosis of Graves' disease undergoing TT were advised to take 1 g of calcium carbonate (CC) without vitamin D (TUMS, GlaxoSmithKline, Middlesex, UK) three times a day in the two weeks leading up to surgery. This dose and scheduling were selected as it was comparable to the post-operative dosing and schedule used for patients in a protocol driven fashion. Graves' patients who took preoperative calcium supplementation were identified as the study cohort. Graves' patients undergoing TT in the preceding calendar year (2012), who had not undergone any

preoperative calcium supplementation were identified and used as disease specific controls. Additional patients undergoing TT, alone, for other indications during the same time period (2012-2013) were selected to serve as contemporary procedure controls. Patients undergoing central neck dissection were excluded. The procedure controls were matched in a one to one fashion by age, gender and thyroid weight in efforts to control for surgical difficulty due to enlarged gland size.

Standard practice within the study institution includes the measurement of pre-operative calcium and parathyroid hormone (PTH) levels for patients undergoing thyroid surgery.¹⁸ Preoperative patient demographics and laboratory values were included. Saturated solution of potassium iodine (SSKI) 0.2 mL three times a day for 7 to 10 days prior to surgery is prescribed to the patients. Those patients who are pregnant or who have an allergy to iodine are not prescribed SSKI. Use of SSKI in patients unable to take anti-thyroid medications and/or still hyperthyroid is dependent on surgeon discretion, and differs between providers¹⁹. A PTH level was routinely sent on all patients in the immediate post-op period, whereas only those patients observed overnight had serum calcium levels checked four hours after surgery, along with both a serum calcium and PTH level the morning of post-operative day 1 at surgeon discretion. While Graves' patients were routinely placed on scheduled calcium after surgery, non-Graves' patients had supplementation of scheduled calcium based on a protocol driven, and determined, based on the post-operative PTH level (Table 1).^{7,8} Use of calcitriol was based on a post-operative PTH level protocol, regardless of the diagnosis. Immediate post-operative PTH levels were further characterized as >10 pg/mL, 2 to 10 pg/mL, and <2 pg/mL.

Pathology reports were reviewed for details regarding thyroid gland weight. Patient reported complaints during their hospital stay and at time of postoperative follow up were noted, as were any telephone calls, emergency room visits or readmissions for complaints specific to signs and symptoms of hypocalcemia (numbness, tingling, muscle cramping, tetany).

Statistical analysis was performed using IBM SPSS Statistics, version 21. Continuous variables were compared with ANOVA, and categorical variables were compared with chi-square. Variables following a non-parametric distribution were compared with Kruskal-Wallis. Serum calcium levels were plotted over time, and analyzed using a general linear model of repeated measures. A p-value of 0.05 was determined to be significant. Data are reported as mean $\pm$ standard deviation, or as number (percentage), unless otherwise stated.

Results

A total of 123 patients were identified for inclusion in the study. Between January and September of 2013, 45 patients with Graves' disease underwent TT and were pre-treated with CC for two weeks prior to surgery. In 2012, 38 patients with Graves' disease underwent TT, and were not given CC prior to surgery. Spanning both time periods, 40 patients undergoing TT only for a diagnosis other than Graves' disease were also identified as procedure controls. These patients were not given CC prior to surgery either. The patients serving as procedural controls had the diagnoses of well differentiated thyroid cancer (n=15, 38%), multi-nodular goiter (n=18, 45%), and benign adenoma (n=7, 18%).

The mean patient age was 42 years $\pm$ 16, and was comparable between groups ($p=0.51$, Table 2). The majority of patients were female (86%). Serum calcium ($9.2 \text{ mg/dL} \pm 0.6$) and PTH ($51.9 \text{ mg/dL} \pm 66$) levels at time of initial pre-operative consult, prior to any supplementation, were equivalent across the groups ($p=0.97$ and $p=0.83$, respectively). While no change in practice regarding SSKI use occurred during the study period, there was a noted difference in use between the Graves' cohorts. Only 62% of the pretreated Graves' patients were given SSKI, while 84% of the no pretreatment Graves' patients were given SSKI ($p=0.03$). Parathyroid auto-transplantation was required most often in the pretreated Graves' patients (22%), compared to the untreated Graves' (8%) and non-Graves' patients (3%, $p=0.01$). The mean thyroid specimen weight on final pathology was $37.5\text{g} \pm 36$, and was also similar between the groups ($p=0.72$).

Upon reviewing medication records and discharge orders, a similar number of patients across groups were sent home with scheduled calcium supplementation (Table 3, $p=0.10$). Overall use of calcitriol was infrequent (24%), and comparable between groups ($p=0.60$). The overall rate of reported numbness or tingling symptoms attributed to symptomatic hypocalcemia was 15% for the entire study population. Preoperative supplementation with CC resulted in a rate of symptomatic hypocalcemia of only 10%, equivalent to the non-Graves' patients. However, Graves' patients who did not undergo pre-operative supplementation with CC reported symptoms of numbness and tingling 2.6x more often (26%)($p=0.049$).

The patients with Graves' disease who did not undergo pre-treatment with calcium prior to TT were noted to have significantly lower serum calcium levels four hours after surgery when compared to the Graves' patients pretreated with CC or patients undergoing TT for other diagnoses (8.3 mg/dL vs. 8.6 mg/dL , respectively, $p=0.05$) (Table 4). PTH levels immediately post-operative were equivalent between the groups ($p=0.42$). When PTH level was stratified as undetectable, low or normal, there was also no difference between groups ($p=0.84$). By post-operative day one, and at time of follow-up visits, serum calcium levels as well as PTH levels were equivalent. Plotting out the serum calcium levels over time, levels were not found to differ significantly, although this may be due to the overall low number of patients in each group with values drawn at all four time points ($p=0.18$, Figure 1).

Discussion

This study represents the first report of preoperative calcium supplementation for Graves' patients undergoing TT, and demonstrates its efficacy in minimizing symptomatic hypocalcemia in the postoperative period. While other authors have proposed this practice, none have reported on associated patient outcomes.¹² Given the multifactorial etiology of hypocalcemia after TT for Graves' disease, preoperative calcium supplementation allows for replenishment of whole body calcium stores which may be depleted secondary to the increased bone metabolism as a result of thyrotoxic osteodystrophy. With this contributing factor addressed in the preoperative period through calcium supplementation, Graves' patients undergoing TT are found to experience rates of symptomatic hypocalcemia equivalent to patients undergoing TT for other disease processes. The observed equivalence of PTH levels between the study cohorts further supports the non-parathyroid mediated

causes for increased hypocalcemia rates historically described in Graves' patients undergoing TT.^{1,12,13}

As previously mentioned, patients with Graves' disease have multiple proposed mechanisms which contribute to decreased serum calcium after TT separate from parathyroid function. Thyroid hormone has a direct effect on osteoclasts, which stimulates bone turn over. This, in turn, can lead to increased serum alkaline phosphatase, serum osteocalcin, urinary calcium, and urinary deoxypyridinoline.^{12,15} This continued bone destruction and subsequent loss of calcium via the urine results in depletion of whole body stores of calcium. Previous authors have also demonstrated concomitant vitamin D deficiency to place patients at increased risk for symptomatic hypocalcemia or tetany after TT for Graves' disease, but this was not necessarily a deficiency caused by the Graves' disease.²⁰ Given the influence vitamin D has on the absorption of calcium, underlying deficiency would understandably result in exacerbation of hypocalcemia, as well as make calcium replacement more difficult without also addressing the vitamin D deficiency. Lastly, it has also been postulated that during manipulation of the gland at time of surgery, calcitonin is released in an abnormal fashion.¹⁶ While measurements of alkaline phosphatase, osteocalcin, calcitonin, or urinary measures of calcium and deoxypyridinoline were not measured in the scope of this study, the similar post-operative PTH levels favor these alternative explanations.

Given the proximity of the parathyroid glands to the thyroid capsule, and the shared blood supply via the inferior thyroid artery, parathyroid damage still contributes to symptomatic hypocalcemia after TT for any diagnosis. The literature reports rates of transient hypocalcemia after TT range from 6 to 72% for all diagnoses.^{1-4,13,21,22} The wide range in the reported rates of transient hypocalcemia is, in part, due to the variability of definition from study to study. Additional factors noted to place patients at increased risk for transient and/or permanent hypoparathyroidism after thyroid surgery include the extent of thyroid resection, recurrent goiter, Graves' disease, hospital volume and female gender.²¹ In an additional study, Thomusch et al also found central ligation of the inferior thyroid artery to result in much higher rates of hypoparathyroidism due to compromise of the parathyroid blood supply.⁵ This technique has long since been abandoned. Specific to patients with Graves' disease, SSKI or Lugols solution is often administered in the pre-operative period in efforts to decrease vascularity and friability of the gland^{19,23}. More recently, the value of its use has been called into question.²⁴ It is unclear how the use or omission of SSKI would affect dissection and preservation of the parathyroid glands. While we observed a lower rate of SSKI use in the Graves' patients taking CC prior to surgery, it is unclear if this directly resulted in the increased rate of parathyroid auto-transplantation. Regardless, this did not result in alteration of the post-operative PTH levels and therefore did not negatively impact serum calcium levels. With a 15% overall rate of symptomatic hypocalcemia in the present study, these values fall well within the previously published rates of symptomatic hypocalcemia after TT for all diagnoses, not just Graves' disease.

In the ATA guidelines for the management of hyperthyroidism, TT, radioactive iodine ablation (RAI), and anti-thyroid medications are listed as the "three effective and relative safe initial treatment options" for patients diagnosed with Graves' disease.¹⁰ Despite this recommendation, a recent survey of the membership of three major international

endocrinology organizations demonstrated that surgery as first line therapy is used only 0.7% of the time worldwide, and for only 0.9% of cases in the United States.⁹ However, there were selective instances when TT was the preferred first line treatment: patients with severe ophthalmopathy (18.5%), and for women wanting to conceive in the near future (20.3%). For those patients who do not achieve remission after 12 to 18 months of anti-thyroid medications, TT has also proven to be more cost effective in the definitive management of Graves' than either life-long anti-thyroid medication or RAI.²⁵ The data presented here add to the growing literature demonstrating that TT for Graves' disease does not pose any greater risk of hypoparathyroidism than TT for benign causes.^{13,14,26-28} With a failure rate of RAI between 10 and 38%, the documented cost effectiveness of TT as definitive management, and the severe, life-threatening side effects from anti-thyroid medications, it is surprising that surgical management of Graves' disease has not become more widely adopted.^{10,14,29-32}

Another caveat to the ATA guidelines, is that near-total or TT should be performed by a high volume surgeon to ensure optimal outcomes, and minimize risk of permanent complications.¹⁰ This recommendation is based on several studies showing superior patient outcomes for both benign and malignant thyroid conditions when thyroid surgery is performed by a high volume thyroid surgeon.³³⁻³⁵ The study institution is a high volume practice, and thus the rates of transient hypocalcemia are low and reflect this expertise. As a result of our growing institutional experience, nearly half of all patients within our institution are referred for surgical management at time of initial Graves' diagnosis for definitive therapy. Other authors have also observed excellent outcomes after TT for Graves' disease, as well as lower rates of disease recurrence or persistence when compared to non-surgical therapies.^{27,28}

While this study reflects a prospective alteration in clinical practice, it uses a historic cohort for comparison, which may cause some limitations to our conclusions. It also reflects the practice at a single high volume institution, where the surgical management of Graves' disease makes up a significant proportion of the thyroid surgical volume. Despite the relative high volume of surgery for Graves' disease, the cohort groups are still relatively small which may lead to under-powering of our analysis. Additionally, our results regarding equivalent PTH levels may not be applicable to lower volume centers. As not all patients had serum calcium and/or PTH levels drawn both on the day of surgery and on post-operative day one, our assessment on the patient trends over time are based on a limited number of patients. This is in part due to differences in surgeon practices regarding overnight observation versus same day surgery, as well as differences in laboratory evaluation preferences. We suspect these observed changes in serum calcium levels would reach significance with a larger patient population, however additional studies are needed. Also, patients did not have thyroid function measured on the day of surgery to determine if the degree and/or the duration of hyperthyroid or euthyroid state influenced the severity of bone hunger experienced by the patient, and therefore influenced the degree of serum calcium alteration in the post-operative period. As serum albumin and vitamin D are not checked as part of the pre-operative laboratory evaluation for thyroid surgery at the study institution, it is possible that additional variables which influence calcium metabolism and measurement are not captured.

Conclusion

Preoperative supplementation of Graves' patients with calcium prior to TT minimizes the drop in serum calcium after surgery, and reduces the number of episodes of symptomatic hypocalcemia during the post-operative period. As immediate post-operative PTH levels were equivalent across groups, the mechanism resulting in a greater incidence of symptomatic hypocalcemia after TT for Graves' disease is not due to increased injury to the parathyroid glands at a high volume endocrine surgery practice. Counseling patients to taking 1 g of CC three times a day is a simple intervention to add to the pre-operative preparation for the Graves' patient.

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Synopsis

Transient hypocalcemia is a common issue after total thyroidectomy due to direct injury to the parathyroid glands. As patients with Graves' disease have also struggled with hyperthyroidism prior to surgery with resultant high bone turn over, they have a potential second etiology to contribute to and/or exacerbate hypocalcemia in the postoperative period independent of parathyroid function. A simple period of preoperative calcium supplementation decreases the incidence and severity of hypocalcemia experienced by Graves' patients after total thyroidectomy.

Figure 1. Serum calcium levels over time. Only patients with values for all time points were included in this analysis.

Table 1

Protocol for calcium and calcitriol supplementation based on post-operative parathyroid hormone level.

	PTH <2 pg/mL	PTH 2 to 10 pg/mL	PTH 10 to 20 pg/mL	PTH >20 pg/mL
Calcitriol	0.5 mcg twice a day	0.25 mcg twice a day	None	None
Calcium Carbonate	1 to 1.5 gm three times a day. 2 gm every 30 minutes as needed for symptoms.	1 to 1.5 gm three times a day. 2 gm every 30 minutes as needed for symptoms.	1 to 1.5 gm three times a day. 2 gm every 30 minutes as needed for symptoms.	Scheduled calcium at attending discretion. 2 gm every 30 minutes as needed for symptoms.

Table 2

Patient demographics, pre-operative laboratory evaluation (prior to any supplementation) and thyroid weight.

	Pre-Op CC Graves'	No Pre-Op CC Graves'	No Pre-Op CC Non-Graves'	P-value
N	45	38	40	
Age (Years)	44 ± 17	40 ± 15	43 ± 14	0.51
Female	38 (84%)	33 (87%)	35 (88%)	0.91
Pre-Operative				
Calcium (mg/dL)	9.2 ± 0.59	9.2 ± 0.58	9.2 ± 0.57	0.97
PTH (pg/mL)	51 ± 35	48 ± 38	56 ± 102	0.83
SSKI Drops	28 (62%)	32 (84%)	N/A	0.03
Thyroid Weight (g)	39 ± 43	40 ± 35	34 ± 28	0.72
Parathyroid Autotransplantation	10 (22%)	3 (8%)	1 (3%)	0.01

CC – Calcium carbonate

Table 3

Post-operative use of routine calcium carbonate (CC) and calcitriol, and reported symptoms of hypocalcemia.

	Pre-Op CC Graves'	No Pre-Op CC Graves'	No Pre-Op CC Non-Graves'	P-value
N	45	38	40	
Scheduled CC	41 (91%)	36 (95%)	32 (80%)	0.10
Scheduled Calcitriol	10 (22%)	8 (21%)	12 (30%)	0.60
Reported Symptoms of Numbness or Tingling	4 (10%)	10 (26%)	4 (10%)	0.049

Table 4

Post-operative calcium and PTH levels.

		Pre-Op CC Graves'	No Pre-Op CC Graves'	No Pre-Op CC Non-Graves'	P-value
N		45	38	40	
Day of Surgery					
Calcium (mg/dL)		8.6 ± 0.4	8.3 ± 0.7	8.6 ± 0.4	0.05
PTH (pg/mL)		30 ± 27	30 ± 30	21 ± 17	0.42
PTH Group	>10	33 (73%)	27 (73%)	26 (65%)	0.84
	2 to 10	6 (13%)	6 (16%)	9 (23%)	
	<2	6 (13%)	4 (11%)	5 (13%)	
Post-Operative Day 1					
Calcium (mg/dL)		8.3 ± 0.6	8.0 ± 1.7	8.5 ± 0.4	0.36
PTH (pg/mL)		26 ± 17	25 ± 21	20 ± 20	0.62
PTH Group	>10	14 (70%)	21 (75%)	15 (65%)	0.96
	2 to 10	3 (15%)	3 (11%)	4 (17%)	
	<2	3 (15%)	4 (14%)	4 (17%)	
Post-Operative Visit					
Calcium (mg/dL)		9.1 ± 0.8	8.9 ± 0.7	8.9 ± 0.8	0.44
PTH (pg/mL)		36 ± 26	35 ± 28	29 ± 25	0.47
PTH Group	>10	36 (86%)	31 (91%)	32 (82%)	0.14
	2 to 10	4 (10%)	0	1 (3%)	
	<2	2 (5%)	3 (9%)	6 (15%)	
Patients with four time point measurements		16 (36%)	26 (68%)	20 (50%)	

CC- Calcium carbonate