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ORIGINAL ARTICLE

Selective Prophylactic Calcium Supplementation reduces Length of Stay after Total Thyroidectomy

[1]Jake Osborne, [2]Alexander Papachristos, [3]Anita Skandarajah, [4]Alexandra Gorelik, [5]Daniel Hng, [6]Julie Miller

ABSTRACT

Introduction: Hypocalcemia is a common complication of thyroidectomy. We aimed to assess compliance with a targeted calcium and calcitriol supplementation protocol and hypothesized that it would allow safe early discharge without an increase in readmissions.

Materials and methods: In 2009, we instituted a targeted early postoperative calcium and calcitriol supplementation protocol based on postoperative parathyroid hormone (PTH). We retrospectively reviewed all patients who had a total or completion thyroidectomy over a 4-year period prior to protocol implementation (group I: 2005–2008) and over a 5-year period after protocol implementation (group II: 2010–2014), as well as all patients operated on in the private setting with the senior author over a 1-year period (group III: 2013). Endpoints for analysis were clinically significant hypocalcemia, protocol compliance, hospital length of stay (LOS), and readmission for hypocalcemia.

Results: Compliance with the protocol was high; however, the accuracy of supplementation prescription was significantly lower in group II than in group III ($p < 0.0001$). Mean corrected calcium on postoperative day 1 was significantly higher in groups II (2.29 mmol/L) and III (2.27 mmol/L) compared with group I (2.15 mmol/L; $p < 0.0001$). Forty (30.5%) patients had clinically significant hypocalcemia in group I, compared with 21 (10.8%) in group II, and 2 (3.3%) in group III ($p < 0.0001$). The LOS was significantly decreased after protocol introduction ($p < 0.0001$).

Conclusion: Selective prophylactic calcium supplementation reduces LOS after total thyroidectomy.

Clinical significance: Introducing a new management protocol in the public hospital system poses challenges with compliance; however, it was successful in lowering rates of symptomatic hypocalcemia and LOS without an increase in the readmission rate.

Keywords: Hypocalcemia, Parathyroid, Thyroid surgery, Thyroidectomy.

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[1]Medical Officer, [2,5]Registrar, [3,6]Consultant Surgeon, [4]Statistician

[1-6]Department of Endocrine Surgery, The Royal Melbourne Hospital, Melbourne, Victoria, Australia

Corresponding Author: Alexander Papachristos, Registrar Department of Endocrine Surgery, The Royal Melbourne Hospital, Melbourne, Victoria, Australia, Phone: +61393427000 e-mail: alex_papa4@hotmail.com

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INTRODUCTION

Hypocalcemia is a common complication of thyroidectomy, occurring in 20 to 35% of cases.[1-3] It occurs more frequently in patients who have had a central lymph node dissection, in those in whom the parathyroid glands are not identified intraoperatively, and in those for whom the indication for surgery is Grave's disease.[4-7] Symptomatic hypocalcemia may present with peripheral or perioral paresthesia, carpopedal spasm, confusion, or life-threatening seizures, and, depending on the degree of damage to the parathyroid glands, may be transient or permanent.[8]

Routine prescription of calcium and 1,25-dihydroxycholecalciferol has been shown to reduce the incidence and severity of hypocalcemia after total thyroidectomy.[9] Without calcium supplementation, serum calcium levels fall to a nadir between 24 and 48 hours postoperatively;[10] however, this may occur as late as day 4.[11] Prior to 2008, most patients at our institution remained in hospital for at least 2 days postoperatively to monitor for hypocalcemia, and supplementation was initiated, if required. In recent years, multiple studies have demonstrated that a low postoperative PTH can predict hypocalcemia;[12-16] however, its accuracy may be as low as 80%.[17] The half-life of PTH is approximately 2 to 3 minutes;[18] therefore, specimens sent from the recovery room should predict postoperative parathyroid status.[19] Based on this supposition, Raffaelli et al[20] demonstrated that a selective supplementation protocol using the postoperative PTH can minimize symptomatic hypocalcemia.

We hypothesized that the implementation of an early targeted calcium and calcitriol supplementation protocol at our institution would decrease the incidence of clinically significant hypocalcemia and allow safe early discharge without an increase in the readmission rate for symptomatic hypocalcemia.

MATERIALS AND METHODS

This study was a retrospective analysis of prospectively collected data. Prior to 2009, patients stayed in hospital 2 days following total thyroidectomy. Caltrate and calcitriol were prescribed in the event of hypocalcemic symptoms, such as acral or perioral paresthesia, muscle twitches, cramps or spasms or a skin-crawling sensation, or if the serum Ca^{++} was <2.0 mmol/L.

In 2009, we instituted a targeted prophylactic postoperative calcium and calcitriol supplementation protocol in patients undergoing total or completion thyroidectomy. The protocol requires measurement of serum intact PTH immediately after surgery (d0 PTH). Patients with a low PTH (<1.4 pmol/L) are prescribed prophylactic calcitriol 0.5 µg twice daily and calcium carbonate 600 mg (Caltrate) three times daily, starting on the day of surgery and continuing on discharge. The serum-corrected calcium level (Ca^{++}) is measured on the morning of the first postoperative day. We defined hypocalcemia on day 1 postoperatively as $Ca^{++} < 2.0$ mmol/L. Clinically significant hypocalcemia is defined as Ca^{++} <2.0 mmol/L or <2.1 mmol/L with hypocalcemic symptoms.

Prior to discharge, each patient is counseled and given an information sheet on the symptoms of hypocalcemia and how it should be managed. They are advised to take two Caltrate every 30 minutes until symptoms resolve, and if symptoms persist after three additional doses, they are advised to present to the emergency department for assessment.

In patients sent home on supplements, serum Ca^{++} and PTH are routinely measured at the first outpatient visit, 1 to 2 weeks postoperatively. Supplementation is ceased if the serum Ca^{++} is within normal limits. The patient is then reviewed at 6 weeks postoperatively with repeat serum Ca^{++} and PTH. In the case of hypocalcemia or hypoparathyroidism, the patient is then reviewed at 3 and 6 months postoperatively with repeat serum Ca^{++} and PTH. Permanent hypoparathyroidism was defined as low serum PTH and dependence on calcium supplementation >6 months after surgery.

We conducted a retrospective review of all patients that had a total or completion thyroidectomy over a 4-year period prior to protocol implementation (group I: 2005–2008) and over a 5-year period after protocol implementation (group II: 2010–2014). All cases were performed at our tertiary teaching hospital. A third group (group III: 2013) included all patients that underwent total or completion thyroidectomy in the private setting with the senior author over a 1-year period. This group was used as the gold standard for protocol compliance, as all blood test request forms and medication prescriptions were completed personally by the senior author. Patients operated on in 2009, during the pilot phase of the protocol introduction, were excluded.

All data were collected from medical records and included demographic details, operative indication and procedure, the number of parathyroid glands identified and preserved, the number of parathyroid glands in histology, the d0 serum PTH, the d1 corrected calcium level (Ca^{++}), the prescription patterns of calcium and calcitriol, LOS, and readmissions. To assess protocol compliance, the inpatient medication charts as well as discharge prescriptions were reviewed for each patient. All readmissions were verified.

Primary endpoints were clinically significant hypocalcemia, d1 Ca^{++}, protocol compliance, hospital LOS, and readmission for hypocalcemia. Prolonged hospitalization was defined as a LOS > 1 day. An intention to treat analysis was performed. Data were entered into a Microsoft Excel spreadsheet (Microsoft Corporation, Redmond, Washington, USA) and analyzed using Stat 13.0 (StatCorp LP, College Station, Texas, USA). Fisher's exact test was used to analyze categorical data and the Kruskal–Wallis test for continuous data. The p-values < 0.05 were considered statistically significant.

RESULTS

Demographic Details

Demographic and operative details are summarized in Table 1. A total of 385 patients were included in the analysis. There were 325 (84%) females and the median age (range) was 49 (17–88) years. Groups were well matched for age and gender. Preoperative diagnoses were similar for the groups I and II; however, a greater proportion of operations were performed for inflammatory conditions in group III. There were no significant differences between groups when comparing the rates of central lymph node dissection, the frequency of parathyroid autotransplantation, or the presence of parathyroid glands in the specimen histology. The proportion of patients with a low PTH on d0 was similar between groups. When analyzed by indication for surgery and performance of central lymph node dissection, there were no significant differences in early rates of low PTH and hypocalcemia.

As displayed in Table 2, the measurement of postoperative serum PTH and corrected calcium occurred in almost all patients in groups II and III. According to the protocol, 126 patients in group II should have received supplementation and 120 (95%) were prescribed Caltrate or calcitriol. However, only 87 (69%) patients received the doses specified by the protocol. On discharge, 112 (89%) received Caltrate or calcitriol, whereas 83 (66%) were prescribed both correctly. In contrast, compliance was 100% in group III. Totally, 27 of group II patients (14%) received Caltrate or calcitriol supplementation despite a d0 PTH >1.4. In contrast, no patient in group III with PTH >1.4 was supplemented. Three (1.5%) patients in group II

Table 1: Demographics and operative details

	Group I	Group II	Group III	
	Public	Public	Private	
	2005–2008	2010–2014	2013	p-value
Patients	131	194	60	
Age	50.1 (14.0)	48.3 (15.7)	46.7 (15.0)	NS
Sex (% female)	86.2	83	85	NS
Preoperative diagnosis				
Benign	70 (53.4)	91 (46.9)	18 (30.0)	
Inflammatory	16 (12.2)	36 (18.6)	23 (38.3)	
Suspicious/malignant	45 (34.4)	67 (34.5)	19 (31.7)	
Central lymph node dissection	18 (13.7)	36 (18.6)	12 (20.0)	NS
Parathyroid tissue in histology				NS
0	108 (82.4)	153 (78.9)	52 (86.7)	
1	17 (13.0)	32 (16.5)	6 (10.0)	
≥2	6 (4.6)	9 (4.6)	2 (3.3)	
Parathyroids autotransplanted				NS
0	92 (70.2)	131 (67.5)	38 (63.3)	
1	31 (23.7)	42 (21.6)	14 (23.3)	
≥2	8 (6.1)	21 (10.8)	8 (13.3)	

NS: Not significant

Table 2: Protocol compliance

	Group I	Group II	Group III	
	(n = 131)	(n = 194)	(n = 60)	p-value
Calcium measured d1 postoperative	130 (99.2)	193 (99.5)	60 (100.0)	NS
PTH measured in recovery	39 (29.8)	191 (98.5)	59 (98.3)	NS
PTH <1.4 in recovery	23 (59.0)	126 (66.0)	28 (47.5)	0.01
Protocol indicates supplementation	N/A	126 (64.9)	28 (46.7)	
Protocol correctly followed		77 (61.1)	28 (100.0)	<0.0001
In-hospital compliance				
Patients prescribed calcium or vitamin D		120 (95.2)	28 (100.0)	NS
Patients correctly prescribed calcium and vitamin D		87 (69.0)	28 (100.0)	0.0002
• Caltrate		97 (76.9)	28 (100.0)	
• Calcitriol		95 (75.4)	28 (100.0)	
Discharge medication compliance				
Patient prescribed calcium or vitamin D		112 (88.9)	28 (100.0)	NS
Patients correctly prescribed Caltrate and vitamin D		83 (65.9)	28 (100.0)	<0.0001
• Caltrate		90 (71.4)	28 (100.0)	
• Calcitriol		89 (70.6)	28 (100.0)	

p-value compares groups II and III; NS: Not significant

and 1 (0.8%) patient in group I developed asymptomatic hypercalcemia on supplementation.

Comparing prescriptions patterns before and after protocol introduction, there was no significant difference in the use of Caltrate on discharge, with 53 and 64% of patients discharged on Caltrate in groups I and II respectively. However, calcitriol was significantly more frequently utilized after the introduction of the protocol; 28% in group I and 58 % in group II were discharged on calcitriol, $p < 0.0001$. Overall, 76% of group II patients received some form of calcium or calcitriol supplementation, compared with 60% in group I, $p = 0.002$.

As demonstrated in Table 3, mean Ca^{++} on postoperative day 1 was significantly higher in groups II and III compared with group I. Also, significantly more patients in group I were hypocalcemic on day 1, and had clinically significant hypocalcemia while in hospital. In group II, 21 of the 126 patients with a low PTH developed clinically significant hypocalcemia and 1 patient with clinically significant hypocalcemia had a normal PTH, resulting in a sensitivity of 95% and a specificity of 39%. The absolute risk reduction for events of clinically significant hypocalcemia was 19.2%, resulting in a number needed to treat of 5.2.

Length of stay was significantly decreased after protocol introduction, with no increase in readmissions for hypocalcemia. Median LOS was 2 days in group I, compared with 1 day in groups II and III. In group I,

Table 3: Outcomes

	Group I	*Group II*	*Group III*	*p-value*
Ca^{++} d1 postoperative mean (SD)	2.15 (0.17)	2.29 (0.15)	2.27 (0.12)	<0.0001
Hypocalcemic d1 postoperative*	32 (24.6)	10 (5.2)	0 (0)	<0.0001
Clinically significant hypocalcemia^ in hospital	36 (27.5)	15 (7.7)	1 (1.7)	<0.0001
Clinically significant hypocalcemia^ post-discharge	9 (6.9)	10 (5.2)	1 (1.7)	NS
Total clinically significant hypocalcemia*	40 (30.5)	21 (10.8)	2 (3.3)	<0.0001
LOS				
Median (IQR)	2 (1–2)	1 (1–1)	1 (1–1)	<0.0001
≤1 day	52 (39.7)	130 (67.0)	52 (86.7)	
≥2 days	79 (60.3)	64 (33.0)	8 (13.3)	
Prolonged LOS due to hypocalcemia#	53 (40.5)	13 (6.7)	0 (0.0)	<0.0001
Readmission for hypocalcemia	8 (6.1)	6 (3.1)	0 (0.0)	NS
Intravenous calcium	10 (7.6)	7 (3.6)	1 (1.7)	NS
Permanent hypocalcemia	N/A	7 (3.6)	0 (0.0)	NS

*Ca^{++} < 2.0 mmol/L; ^Ca^{++} < 2.0 mmol/L or < 2.1 mmol/L with symptoms consistent with hypocalcemia; #Includes patients who did not develop clinically significant hypocalcemia, but remained in hospital > 1 day for calcium monitoring; SD: Standard deviation; IQR: Interquartile range; NS: Not significant; N/A: Not applicable

53 (40.5%) patients had a prolonged hospitalization for calcium monitoring or replacement, compared with 13 (6.7%) in group II, and none in group III. There was no significant difference between groups in the number of patients who had clinically significant hypocalcemia after discharge, nor was there an increase in the readmission rate. There was a trend to fewer readmissions in group II. However, this was not statistically significant. Among the six readmissions in group II, one was not supplemented as they did not meet protocol criteria. The other five were correctly prescribed supplementation on discharge. However, only one patient was compliant. There were no readmissions in group III.

DISCUSSION

Predicting postoperative hypocalcemia using PTH has been extensively studied in recent years[8,12-14,17,20] and various authors have attempted to ascertain the optimal time point at which to measure the PTH level. Noordzij et al[13] analyzed the pooled data from nine studies, finding that the PTH level 6 hours after surgery had the highest accuracy for predicting hypocalcemia. Based on the analysis of published Australian data,[21-23] The Australian Endocrine Surgeons Guidelines currently recommends the routine measurement of PTH 4 hours after total thyroidectomy to guide postoperative calcium supplementation.[24] Schlottman et al[25] suggested that the greatest sensitivity and specificity in predicting hypocalcemia are achieved when looking at the decline in PTH from baseline rather than the absolute value, demonstrating that no patient with a decrease in PTH <35% developed hypocalcemia and all patients with a decrease >80% (14% of the cohort) became hypocalcemic in a study of 106 patients.

It is generally accepted that a normal postoperative PTH is good predictor of postoperative normocalcemia. A low postoperative PTH level, however, is a common finding after thyroidectomy with a sensitivity of 48.4% and a positive predictive value of 83.8% in predicting hypocalcemia; 16% of these patients will remain normocalcemic without treatment.[24] As such, the cost-effectiveness of introducing a supplementation protocol based on postoperative PTH has been questioned by Wang et al,[26] who reported that routine supplementation was more cost-effective than selective supplementation. However, this did not consider the potential adverse effects of supplementation and the cost associated with managing these. In addition to hypercalcemia, delayed diagnosis of hypoparathyroidism may occur if the patient is not monitored closely on an outpatient basis. Further, Albuja-Cruz et al[27] compared a group of post-thyroidectomy patients after the introduction of a protocol similar to ours with an earlier group that had routine calcium supplementation and found that there was no difference in symptomatic hypocalcemia, LOS, or readmissions. Only two patients that did not receive supplements developed mild hypocalcemia. This reinforces the notion that a PTH-based protocol can effectively predict which patients will not develop hypocalcemia and, hence, can avoid supplementation.

At our institution, the introduction of an early postoperative calcium supplementation protocol significantly reduced the rates of symptomatic and biochemical hypocalcemia, LOS, and there was a trend to a decreased readmission rate for hypocalcemia. Prior to protocol introduction, we supplemented selectively based on calcium levels and hypocalcemic symptoms, and as such, the median LOS was 2 days, with a prolonged hospital stay in 53 (40.5%) patients for calcium monitoring or replacement. Using the protocol, this decreased to 1 day without an increase in the readmission rate or events of hypocalcemia postdischarge. Therefore, despite the suboptimal protocol compliance, the protocol was successful in minimizing in-hospital hypocalcemia as well as preventing it from occurring after discharge.

Our measured specificity of 95.5% for a normal PTH as a predictor of normocalcemia was similar to that reported by Grodski et al.[24] However, our sensitivity of 39.0% was lower. The larger proportion of patients with an undetectable PTH and, hence, higher rate of false negative results may be due to the fact that the PTH was measured immediately postoperatively, rather than at the 4 to 6 hour mark, supporting the findings of Noordzij et al,[13] who found the mean PTH of normocalcemic and hypocalcemic patients increased from immediately post thyroid gland removal to 6 hours postoperative by 25 and 27% respectively. The decision to perform the test in the recovery room rather than 4 to 6 hours after the procedure was made to maximize compliance with the introduction of a new protocol.

Overall protocol compliance with biochemical testing was excellent, and this translated to similar corrected calcium levels between groups II and III on postoperative day one and similar rates of hypocalcemia. The compliance with calcium carbonate and calcitriol supplementation was more variable. Although the majority of patients who required supplementation according to the protocol were prescribed calcium carbonate or calcitriol, the dosage and combination were often incorrect, probably due do the junior level of staff actually writing the prescriptions. This may explain the lower rates of hypocalcemia seen in group III, although these differences were not statistically significant. Introducing a new management protocol in the public hospital system poses many challenges, including the dependence on a large number of frequently rotating junior staff members to maintain its integrity. In contrast, the operating surgeon manages all in-hospital tests, prescriptions, and discharge medications in the private system. These differences and challenges were clearly demonstrated in our results.

When examining the six patients in group II, who were readmitted with hypocalcemia, one patient had a normal PTH and corrected calcium level postoperatively and, hence, was not supplemented. On representation 3 days later, her PTH was undetectable and corrected calcium was 1.85. Measuring the PTH at 4 to 6 hours postoperatively or the following morning may have prevented this false negative from occurring. In the other five patients, the protocol was prescribed correctly. However, on discharge, only one patient was compliant. This finding emphasizes another important difference between groups II and III and a challenge that introducing such a protocol presents. Although patients are given an instruction sheet on discharge, the education they receive on what to do in the event of hypocalcemic symptoms often depends on the junior staff responsible for their ward management, who are less experienced in conveying these messages than the operating surgeon. From our results, it appears that improved patient education prior to discharge may reduce readmissions.

The study has a number of limitations. It is retrospective and, hence, only data recorded in the medical record were available. Reporting and documentation of hypocalcemic symptoms were inconsistent. Readmissions to other hospitals or to a primary care provider for management of hypocalcemic symptoms may not have been captured. Patient compliance with discharge medication was not directly assessed.

CONCLUSION

Selective prophylactic calcium supplementation reduces LOS after total thyroidectomy.

CLINICAL SIGNIFICANCE

Introducing a new management protocol in the public hospital system poses challenges with compliance. However, it was successful in lowering rates of symptomatic hypocalcemia and reducing LOS without an increase in the readmission rate.

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