Incidence and predictors of post-thyroidectomy hypocalcaemia in a tertiary endocrine surgical unit

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ABSTRACT

BACKGROUND Post-thyroidectomy hypocalcaemia is a common complication with significant short and long term morbidity. The aim of this study was to determine the incidence and predictors of post-thyroidectomy hypocalcaemia (as defined by a corrected calcium <2.1 mmol/l) in a tertiary endocrine surgical unit.

METHODS A total of 238 consecutive patients who underwent completion or bilateral thyroid surgery between 2008 and 2011 were included in this retrospective study. Clinical and biochemical data were obtained from electronic and hard copy medical records.

RESULTS The incidence of post-thyroidectomy hypocalcaemia on first postoperative day (POD1) was 29.0%. There was variation in the incidence of hypocalcaemia depending on the timing of measurement on the first postoperative day. At six months following surgery, 5.5% of patients were on calcium and/or vitamin D supplementation.

Factors associated with post-thyroidectomy hypocalcaemia were lower preoperative corrected calcium ($p=0.005$) and parathyroid gland (PTG) auto-transplant ($p=0.001$). Other clinical factors such as central lymph node dissection, inadvertent PTG excision, ethnicity, preoperative diagnosis and Lugol's iodine were not associated with post-thyroidectomy hypocalcaemia.

CONCLUSION The incidence of post-thyroidectomy hypocalcaemia was underestimated by 6% when only POD1 measurements were considered. The timing of measurement on POD1 has an impact on the incidence of post-thyroidectomy hypocalcaemia. Auto-transplantation and lower preoperative calcium were associated with post-thyroidectomy hypocalcaemia.

KEYWORDS

Endocrine surgery – Thyroid surgery – Hypocalcaemia

Accepted 6 December 2013

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Introduction

The reported incidence of post-thyroidectomy hypocalcaemia ranges from 3.1–100% depending on the definition used.^{1,2} The British Association of Endocrine and Thyroid Surgeons (BAETS) registry defines post-thyroidectomy hypocalcaemia as corrected calcium less than 2.10mmol/l on first post-operative day (POD1) and the fourth national audit reported a rate of 24.9%.³ Permanent hypocalcaemia (need of treatment to maintain normocalcaemia at six months) was found in 12.1% of patients.

Injury to the parathyroid glands (PTG) is generally accepted as the most common cause of post-thyroidectomy hypocalcaemia.⁴ This may be due to PTG devascularisation, obstruction of venous drainage or inadvertent PTG excision.⁵ Other mechanisms proposed for post-thyroidectomy hypocalcaemia include hungry bone syndrome and intraoperative haemodilution.^{4,6,7}

Establishing the incidence of post-thyroidectomy hypocalcaemia in individual centres would provide valuable

information to both clinicians and patients, therefore, facilitating informed consent.

Aims and objectives

The aim was to determine the incidence and predictors of post-thyroidectomy hypocalcaemia in patients undergoing bilateral thyroid surgery. The objectives were: to determine the incidence of post-thyroidectomy hypocalcaemia following bilateral thyroid surgery in Sheffield Teaching Hospitals (STH); to compare the above outcomes in STH with published national standards; and to determine predictors of hypocalcaemia in the above population.

Methods

Study design

This was a retrospective cohort study. The population included all patients who had first time bilateral thyroidectomy or a completion thyroidectomy between July 2008

and December 2011. Patients who underwent concomitant central neck lymph node dissection were also included. Patients who had prior/concomitant parathyroidectomy, known hyperparathyroidism and preoperative hypocalcaemia were excluded. The outcome studied was post-thyroidectomy hypocalcaemia in the immediate postoperative period and at six months following surgery. The STH operating theatre electronic database was used to identify patients.

Practice

The postoperative serum calcium was determined by two consecutive measurements in the morning and afternoon at approximately 9am and 3pm respectively. There was no standard protocol on measuring serum calcium after POD1 in normocalcaemic patients.

Variables

Patient characteristics (age, gender, ethnicity), preoperative diagnosis, treatment details (extent of surgery, parathyroid auto-transplant), peri-operative biochemistry (preoperative corrected serum calcium, 25-hydroxy vitamin D and post-operative parathyroid hormone (PTH) levels) and histopathology (diagnosis, weight of resected gland, presence of parathyroid tissue) were collected. All operations were performed or supervised by consultants.

Outcomes and definitions

The BAETS defines post-thyroidectomy hypocalcaemia as corrected serum calcium <2.10mmol/l (reference range 2.20–2.60mmol/l) on POD1. Permanent hypocalcaemia was defined as the need for calcium and/or vitamin D supplements to maintain normo-calcaemia at six months or more after the date of surgery.⁵ These definitions were used in this study. The lowest postoperative corrected calcium levels on POD1 were used to define post-thyroidectomy hypocalcaemia.

Data collection and statistical methods

Data were collected from hospital electronic records and case notes. A data collection form was developed, piloted for data entry using five medical records and revised accordingly. Data were collected on all included patients and transferred to an Excel® spreadsheet (Microsoft, Redmond, WA, US) spreadsheet. Where possible, the ‘data validation’ function in Excel® was used during data entry to prevent typographical errors. All biochemical data collected by one observer were independently checked by a second observer for inaccuracies. These were classified as misinterpretations and typographical or human error.

SPSS® (SPSS, Chicago, IL, US) statistical software was used for statistical analysis. Normally distributed data was presented as mean and standard deviation (SD), non-normally distributed data as median and interquartile range (IQR) and categorical data as frequencies and percentages. A paired *t*-test was used to examine the difference between morning and afternoon serum calcium measurement. The relationships between patient, disease and treatment characteristics and hypocalcaemia were examined by the chi-square test/Fisher’s exact test for

categorical variables and independent sample *t*-test or Mann–Whitney U test (depending on whether the continuous data is normally distributed) for continuous variables. A multivariate analysis (binary logistic regression) was performed on factors that were significant (or approached significance) in univariate analyses to determine independent predictors of post-thyroidectomy hypocalcaemia. The statistical significant level was set at 0.05. Approval for the study was obtained from the hospital clinical effectiveness unit.

Results

Data validation

A total of 3,185 data items were cross-checked by a second observer. Only 0.5% of items needed correction by the second observer, all of which were classed as misinterpretations.

Population demographics

Male and female patients represented 54/238 (22.7%) and 184/238 (77.3%) of the population respectively, with a mean age of 46.7 years (SD = 15.79). Among the patients included, 206/238 (86.6%) underwent total thyroidectomy, 27/238 (11.3%) underwent completion thyroidectomy and 5/238 (2.1%) underwent other bilateral procedures (including bilateral subtotal thyroidectomy and Dunhill procedure). These were carried out under the care of three consultant surgeons. A total of 51 of 242 (21.1%) patients underwent concomitant central lymph node dissection for thyroid cancer. Preoperative diagnosis included hyperthyroidism (44.1%), thyroid cancer (31.1%), and others (24.8%) including euthyroid nodule/goitre, Riedel’s thyroiditis and Pendred syndrome.

Hypocalcaemia

All patients had at least 1 serum calcium measurement recorded on the POD1, while 220/238 (92.4%) had serum calcium measured twice on POD1. The calcium level was not measured after POD1 in 11/238 (4.6%) of patients. At follow-up (=2 weeks), 221/238 (92.9%) patients had their calcium level monitored.

Table 1 shows the incidence of hypocalcaemia at various intervals. A difference of as much as 6.3% was observed between the BAETS definition of post-thyroidectomy

Table 1 Incidence of hypocalcaemia at various intervals	
Hypocalcaemia	Incidence
Overall first post-op day (<2.1mmol/l)	69/238 (29.0%)
First post-op day morning	58/236 (24.6%)
First post-op day afternoon	48/222 (21.6%)
Any point from first-op day	84/238 (35.3%)
Supplementation postoperatively	43/228 (18.9%)
Supplementation at ≥ 6 months	12/220 (5.5%)

Figure 1 Twenty patients who became normocalcaemic in the afternoon after being hypocalcaemic in the morning of the first postoperative day

Figure 2 Eleven patients who had hypocalcaemia in the afternoon despite being normocalcaemic in the morning of the first postoperative day

hypocalcaemia (which only includes calcium estimations from the first postoperative day) and any post-thyroidectomy hypocalcaemia regardless of when the calcium level was measured.

Patients had significantly lower corrected calcium levels in the morning than in the afternoon on POD1 (mean values of 2.17 and 2.18 respectively, $p=0.016$). 20/57 (35.1%) of patients with hypocalcaemia in the morning became normocalcaemic in the afternoon (Fig 1). A total of 11/48 (22.9%) patients who were hypocalcaemic in the afternoon had normal calcium in the morning (Fig 2).

Predictors of postoperative hypocalcaemia

Table 2 shows the influence of various clinical and biochemical variables on the risk of developing post-thyroidectomy hypocalcaemia. Factors that significantly increased the risk of developing post-thyroidectomy hypocalcaemia in univariable analysis were lower preoperative corrected calcium levels ($p=0.005$) and PTG auto-transplantation ($p=0.001$). Lower preoperative corrected calcium and PTG auto-transplantation remained significant after adjusting for central neck lymph node dissection and inadvertent parathyroid excision (Table 3). Patients’ demographics and other clinical variables studied did not seem to influence the development of post-thyroidectomy hypocalcaemia. The number of PTGs auto-transplanted and the number of PTGs inadvertently excised were not analysed owing to small numbers in subgroups. Preoperative vitamin D levels and postoperative PTH were only measured in a few patients. Therefore, the association between these

variables and post-thyroidectomy hypocalcaemia was not studied.

A subgroup analysis of patients with preoperative diagnosis of Graves’ disease was performed. Of the patients on preoperative Lugol’s iodine, 19/67 (28.4%) had post-thyroidectomy hypocalcaemia compared with 8/17 (47.1%) of patients who were not on Lugol’s iodine ($p=0.14$).

Discussion

Mehanna *et al* highlighted considerable variability (0–46%) in the incidence of post-thyroidectomy hypocalcaemia in the same cohort of patients, depending on which definition was used.⁸ In this hospital, serum calcium is traditionally measured twice on POD1 for the purpose of using the calcium slope to guide postoperative management. The current study found that the timing of measurement on POD1 also has an impact on the number of patients recorded as hypocalcaemic. Eleven patients with hypocalcaemia on POD1 afternoon had normal levels in the morning. Five of these eleven patients required calcium supplements; therefore, measuring calcium only on the morning of POD1 may miss patients who would subsequently require treatment. The incidence of post-thyroidectomy hypocalcaemia was underestimated by 6% when only POD1 measurement was used.

Outcomes were only compared with the BAETS dataset as there is considerable variability in the definitions of post-thyroidectomy and permanent hypocalcaemia in other publications. Incidence of post-thyroidectomy hypocalcaemia in this study was 29.0% (95% CI 23.2%, 34.8%) compared

Table 2 Influence of clinical and biochemical variables on first-postoperative day hypocalcaemia

Characteristics		Post-thyroidectomy hypocalcaemia		p-value
		Yes (n=69)	No (n=169)	
Age at surgery in years, mean (SD)		45.1 (15.62)	47.3 (15.86)	0.320
Gender	Male	17 (24.6%)	37 (69.6%)	0.646
	Female	52 (28.3%)	132 (71.7%)	
Ethnicity	White	57 (30.3%)	131 (69.7%)	0.610
	Non-White	8 (25.8%)	23 (74.2%)	
Preop diagnosis	Cancer	23 (31.1%)	51 (68.9%)	0.182
	Hyperthyroidism	34 (32.4%)	71 (67.6%)	
	Others	12 (20.3%)	49 (79.7%)	
Preop cCa mmol/l, mean (SD)		2.30 (0.076)	2.33 (0.094)	0.005
Type of surgery	TT	58 (28.2%)	148 (71.8%)	0.576
	CT	9 (33.3%)	18 (66.7%)	
Central neck dissection	Yes	20 (40.0%)	30 (60.0%)	0.054
	No	49 (26.17%)	139 (73.9%)	
First surgeon	Consultant	61 (31.1%)	135 (68.9%)	0.118
	Registrar	8 (19.0%)	34 (81.0%)	
Consultant scrub	Yes	6 (18.2%)	27 (81.8%)	1.000
	No	2 (22.2%)	7 (77.8%)	
PTG auto-transplantation	Yes	15 (55.6%)	12 (44.4%)	0.001
	No	54 (25.6%)	157 (74.4%)	
Histological diagnosis	Benign	50 (28.4%)	126 (71.6%)	0.739
	Malignant	19 (30.6%)	43 (69.4%)	
Inadvertent PTG excision	Yes	17 (41.5%)	24 (58.5%)	0.053
	No	52 (26.4%)	145 (73.6%)	
Weight of thyroid gland, g, median (IQR)		40 (56)	35 (78)	0.895

Preop = preoperative; cCa = corrected calcium; TT = total thyroidectomy; CT = completion thyroidectomy; SD = standard deviation; IQR = interquartile range; g = grams

with reported BAETS rates of 24.9%. The reported BAETS incidence of post-thyroidectomy hypocalcaemia falls within STH's 95% CI margin, indicating that the incidence of post-thyroidectomy hypocalcaemia in this unit was comparable

Table 3 Binary logistic regression

	Test statistics	Df	p-value
Preoperative corrected calcium	10.746	1	0.001
PTG auto-transplantation	6.212	1	0.013
Inadvertent parathyroid excision	3.078	1	0.079
Central Neck Dissection	0.244	1	0.621
Constant	11.569	1	0.001
Df = Degree of freedom			

with national data. However, rate of long term hypocalcaemia (5.5%; 95% CI 3.1%, 9.4%) in this study was lower than BAETS (12.1%).⁵

Although the incidence of post-thyroidectomy hypocalcaemia in this study was comparable to the BAETS audit, the practice and the population in the two cohorts may differ significantly for the following reasons:

- > Calcium levels were measured twice on POD1 in this study, increasing the likelihood of detecting hypocalcaemia.
- > It is unclear what proportions of BAETS members routinely administer calcium/vitamin D supplements postoperatively; patients at STH are not routinely supplemented after surgery.
- > In the current study, 21.0% of patients underwent concomitant central neck dissection compared with 11.6% in BAETS audit; this is known to increase the risk of transient hypocalcaemia.⁹

- > The BAETS dataset has not been independently verified; it contains self (surgeon) reported outcome data, which is susceptible to 'reporting bias'.

With regard to the incidence of hypocalcaemia or need for calcium or vitamin D at six months, variation in protocols for weaning or withdrawing patients from calcium and/or vitamin D supplements may contribute to the difference observed in the long term rates of hypocalcaemia between STH and BAETS.

In this study, a lower preoperative serum calcium was associated with post-thyroidectomy hypocalcaemia. The association between lower preoperative calcium and postoperative hypocalcaemia has also been found by others.^{10,11} This could be a surrogate marker for vitamin D deficiency, although the association between low preoperative vitamin D and post-thyroid hypocalcaemia is unclear.^{12–14} The use of preoperative calcium alone to identify patients at risk of hypocalcaemia has a relatively low sensitivity (29–58%).^{15–16}

PTG auto-transplantation and the number of PTGs auto-transplanted have been shown to be risk factors for post-thyroidectomy hypocalcaemia.^{16–19} PTG auto-transplantation into the sternocleidomastoid muscle was performed in 27/238 (11.3%) of patients in this series. This represents selective (for inadvertently removed or devascularised gland) as opposed to routine auto-transplantation. In this study, selective PTG auto-transplantation was found to be associated with post-thyroidectomy hypocalcaemia. After PTG auto-transplantation, only one patient required supplements at six months following surgery.

A limitation of this study is the potential impact of missing data on variables and outcomes. 4.6% of patients did not have calcium measured after POD1. Data on treatment details at six months were missing for 18/238 (7.6%) patients. Of these 18 patients, 8/18 had post-thyroidectomy hypocalcaemia. There was no standard protocol to attempt weaning of calcium/vitamin D supplements in patients who developed post-thyroidectomy hypocalcaemia. The small number of patients on supplement at six months limited the ability to assess predictors of permanent hypocalcaemia.

Conclusion

The incidence of post-thyroidectomy hypocalcaemia was underestimated by 6% when only POD1 measurements were considered. The timing of measurement on POD1 has an impact on the incidence of post-thyroidectomy hypocalcaemia. To enable detection of all patients with this complication, a calcium check beyond POD1 (at the first follow-up visit or earlier in symptomatic patients) is recommended. Alternatively, measurement of PTH levels may be used to predict a later fall in serum calcium. Parathyroid auto-transplantation and lower preoperative calcium

are associated with increased risk of post-thyroidectomy hypocalcaemia. The need for a clear definition of post-thyroidectomy hypocalcaemia is highlighted in this study. This will facilitate a fair comparison between different populations.

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