Modification, validation and implementation of a protocol for post-thyroidectomy hypocalcaemia

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ABSTRACT

INTRODUCTION The management of post-thyroidectomy hypocalcaemia should facilitate early discharge, and reduce risks of hypocalcaemia, readmission and treatment related hypercalcaemia. This paper describes the implementation, evaluation and revision a protocol for the optimal management of this condition.

METHODS Day 1 parathyroid hormone (PTH) measurements in addition to calcium measurements were commenced following review of the unit's outcomes and literature on post-thyroidectomy hypocalcaemia. Outcomes from a three-year cohort of patients undergoing thyroid surgery helped amend this protocol (revision 1) to reduce biochemical tests, stipulate the need, nature and dose of vitamin D/calcium supplements, and encourage early discharge. This was further validated over seven months to assess compliance, episodes of hyper and/or hypocalcaemia after discharge, readmissions and need for treatment changes. Further revisions were made (revision 2) and implemented.

RESULTS The temporary and long-term postoperative hypocalcaemia rates were 29.1% and 3.2% respectively. Repeat calcium measurements on the first day altered management in only 1.4% of cases.

The revised protocol was adhered to in 90% of cases. One patient had hypocalcaemia (due to non-compliance) and one had hypercalcaemia. Revision 2 involved reducing the dose of calcium.

CONCLUSIONS This is a good example of a unit protocol for post-thyroidectomy hypocalcaemia being developed and modified on the basis of the literature and local experience. Day 1 PTH and calcium levels determine the need for treatment and frequency of follow-up visits, facilitate early discharge, reduce risk of over and/or undertreatment, and are good indicators of permanent hypocalcaemia.

KEYWORDS

Thyroidectomy – Parathyroid – Hypocalcaemia – Hypercalcaemia – Calcium – Protocol

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Thyroid surgery is common, with over 13,000 operations performed annually in England.¹ It is indicated in the treatment of thyroid cancer, Graves' disease and compressive symptoms from large goitres. Hypocalcaemia is a common postoperative complication with a reported incidence of 27% of all total thyroidectomy operations in the UK.² Long-term hypoparathyroidism and hypocalcaemia occurs in around 12% of patients.

Postoperative hypocalcaemia is often attributed to partial damage or inadvertent excision of parathyroid glands, or compromise to their vasculature.^{3–5} In the short term, patients may have troublesome symptoms such as tingling and numbness of the extremities, cramps and nausea.⁶ The complication also prolongs hospital stay, increases the need for medications, frequent monitoring, hospital visits and readmissions, and increases healthcare costs related to the above.^{6–8} Patients who have long-term hypoparathyroidism have a greater incidence of hypercalciuria, renal stones, renal impairment, neuropsychiatric conditions, infections and seizures.⁹

Perioperative biochemistry measurements (including calcium, parathyroid hormone [PTH] and vitamin D) have been suggested as factors that can be used to help predict which patients will develop hypocalcaemia following total thyroidectomy.¹⁰ A systematic review and meta-analysis by Antakia *et al* identified factors that would prevent hypocalcaemia following total thyroidectomy.¹¹ They suggested that routine postoperative supplementation with calcium and vitamin D helps reduce the incidence of temporary hypocalcaemia. However, the routine use of prophylactic treatment is unnecessary in the majority of patients, masks the problem, delays the institution of appropriate (high dose) treatment in patients with severe disease and risks the rare occurrence of hypercalcaemia.

An accurate prediction of severe biochemical or symptomatic hypocalcaemia in the immediate postoperative period would enable selection of patients for appropriate treatment, and reduce the need for multiple biochemical testing, hospital visits and readmission for hypo or hypercalcaemia. A standard and consistent approach to this problem may be

facilitated by the adoption of protocols for the early detection and treatment of this problem.^{12,15} This has been demonstrated in the American and European literature. Currently, practice in the UK is varied, and there is a lack of national guidance on the use of appropriate predictors and management of this problem in the early postoperative period.

Previous work in our unit revealed an incidence of first postoperative day hypocalcaemia of 29.0% and a 6-month rate of 5.5% in 238 patients over a 3-year period (2008–2011).¹⁴ During this time, postoperative hypocalcaemia was detected using serum calcium measurements in the morning and afternoon of day 1. Based on this work and systematic reviews of the literature performed in the unit,¹¹ a new protocol was proposed that involved measurement of PTH in the morning of day 1 along with calcium. Repeat calcium checks were carried out in the afternoon and at around day 5. Decisions regarding supplementation were made in view of the results of these tests. Routine perioperative supplements were not used.

The aims of the current study were to monitor rates of temporary and permanent hypocalcaemia following bilateral thyroid surgery, assess and optimise the protocol for management, and implement changes according to ongoing experience in the local population.

Methods

Following introduction of the protocol to measure PTH and calcium levels on the first postoperative day, data were collected from all patients who underwent first time total thyroidectomy, near total thyroidectomy or completion thyroidectomy procedures in the endocrine surgery unit at Sheffield Teaching Hospitals NHS Foundation Trust between 2012 and 2014 (inclusive). Patients undergoing 're-do' thyroid surgery were excluded.

Variables collected as part of this study included patient characteristics (age and sex), diagnosis, preoperative biochemistry results (corrected serum calcium, vitamin D and thyroid status when available), postoperative adjusted serum calcium and PTH levels, histological diagnosis and weight of excised thyroid tissue. Data were collected from electronic databases and recorded on an Excel® spreadsheet (Microsoft, Redmond, WA, US) adapted from the data collection sheets of the previous audit.¹⁴

All calcium results in this report refer to adjusted or corrected calcium levels. Postoperative hypocalcaemia was defined as any postoperative adjusted serum calcium of <2.10mmol/l on day 1 and long-term hypocalcaemia was defined as hypocalcaemia necessitating supplementation to maintain normal adjusted serum calcium concentrations at around six months after surgery. These definitions are consistent with those used in our previous audit¹⁴ as well as with the British Association of Endocrine and Thyroid Surgeons (BAETS) fourth national audit definitions.²

Outcomes in relation to postoperative hypocalcaemia for the cohort in the present study were compared with those for the cohort from our previous audit.¹⁴ Differences were assessed using the chi-squared test. A *p*-value of <0.05 was considered statistically significant.

As this was a service improvement project and the design was observational in nature, permission from patients and approval from the ethics committee were not deemed to be required. The study was registered with the audit and service evaluation unit of Sheffield Teaching Hospitals NHS Foundation Trust.

Results

Data were collected from 287 patients (56 male [19.5%], 231 female [80.4%]). The median age was 44 years (range: 16–83 years). The common preoperative diagnoses were Graves' disease (46.0%), cancer (34.5%) and multinodular goitre including retrosternal goitre (19.5%). Operative procedures included 260 total or near total thyroidectomies (90.6%) and 27 completion thyroidectomies (9.4%). Sixty-four patients (22.3%) had a central neck dissection performed. Histological examination confirmed that 130 patients (45.3%) had Graves' disease, 85 (29.6%) had cancer, 57 (19.9%) had multinodular goitre and 15 (5.2%) had other pathologies. Of the patients with cancer, 60 had papillary thyroid cancer, 22 had follicular thyroid cancer and 3 had medullary thyroid cancer. Thirty-five patients were found to have parathyroid glands in the excised tissue, one of whom was documented to have had an intentional excision.

Five patients were excluded from further analysis as postoperative biochemistry results were not available. Of the remaining 282 patients, 82 (29.1%) were hypocalcaemic on day 1. Of these, 19 had low serum calcium levels in the morning but normal calcium in the afternoon, and 13 had normal morning and low afternoon calcium concentrations. One hundred and forty-three according to raw data patients (50.7%) had calcium measured on day 5. Of these, only five (3.5%) were hypocalcaemic, and only one of these five patients had a normal day 1 and a low day 5 calcium level.

Of 198 patients who had PTH measured on the first postoperative day, 28 (14.1%) had low levels (<20ng/ml). Twenty-four (85.7%) of these patients were hypocalcaemic on day 1. PTH results were available for 68 patients who were hypocalcaemic on day 1. Of these, 45 (66.2%) had a normal serum PTH concentration.

Forty-three patients (15.0%) were discharged with postoperative calcium and/or vitamin D supplementation. Of these, 29 (10.1%) were on short-term supplementation (<180 days) and 9 (3.1%) required long-term supplementation. The data were not available for five patients. The outcomes in this cohort were similar to those for in our unit's previous audit (Table 1).¹⁴

Following the above analyses, the existing protocol was revised (Fig 1a). This included measurement of PTH and calcium levels on the morning of the first postoperative day as well as the avoidance of routine day 1 afternoon and day 5 measurements. This was because no patient had a fall from a normocalcaemic day 1 morning sample to a hypocalcaemic afternoon/day 5 sample necessitating a change in supplementation.

Once implemented, the amended protocol was again assessed, over a seven-month period. Of the 49 patients included in this audit, the protocol was followed in 44

Table 1 Comparison of outcomes in relation to postoperative hypocalcaemia between the cohort from a previous audit¹⁴ and the cohort in the present study

	2008–2011 (n=238)	2012–2014 (n=282)	p-value
Day 1 hypocalcaemia (adjusted calcium <2.1mmol/l)	69/238 (29.0%)	82/282 (29.1%)	0.983
Need for postoperative supplements	42/228 (18.4%)	44/277 (15.9%)	0.450
Need for supplements at 6 months	12/220 (5.5%)	9/277 (3.2%)	0.225

patients (90%). Eighteen patients were discharged with supplements and returned for a check at around the fifth post-operative day. One of the forty-nine patients developed hypocalcaemia (as a result of poor compliance with supplements) and one developed hypercalcaemia. In order to further optimise management in the interval between surgery and the first follow-up outpatient visit, and to decrease the occurrence of hypo or hypercalcaemia, the protocol was amended again to reduce the amount of calcium supplementation given (Fig 1b). The three protocols are summarised in Table 2.

Discussion

Identification and appropriate treatment of hypocalcaemia following bilateral thyroid surgery is a key part of managing patients who have undergone this procedure. Inadequate treatment can lead to significant symptoms, longer hospital stay and returns to hospital, thereby increasing morbidity.⁸ At the same time, overtreatment has the potential to cause hypercalciuria and hypercalcaemia, and impairment of renal function.¹⁵ Establishing a protocol to detect and treat hypocalcaemia appropriately will help reduce morbidity.

Figure 1 Schematic diagrams illustrating the management of post-thyroidectomy hypocalcaemia: based on analysis of a previous audit¹⁴ (A) and further validation (B). The latter is currently used in our unit.

Table 2 Summary of the original protocol and the two subsequent revised protocols for monitoring and treating postoperative hypocalcaemia following total thyroidectomy

	Original protocol	Protocol revision 1	Protocol revision 2
Day 1 AM	Bloods: Ca + PTH	Bloods: Ca + PTH	Bloods: Ca + PTH
Day 1 AM		Discharge +/- supplementation* based on protocol revision 1 (Fig 1a)	Discharge +/- supplementation* based on protocol revision 2 (Fig 1b)
Day 1 PM	Bloods: Ca		
Day 1 PM	Discharge +/- supplementation based on senior review		
Day 5 AM	Bloods: Ca	Bloods: Ca only on patients requiring supplementation* at discharge	Bloods: Ca only on patients requiring supplementation* at discharge

Ca = calcium; POD = postoperative day; PTH = parathyroid hormone
 *Patients requiring supplements were reviewed in clinic earlier than usual (ie at 2–3 weeks instead of 6–8 weeks).

A number of other groups have proposed different protocols for identification of postoperative hypocalcaemia. The Society for Endocrinology in the UK suggests initial treatment with calcium supplements and repeated daily checks in patients with post-thyroidectomy hypocalcaemia until the concentrations are normalised.¹⁶ In patients where the adjusted calcium is $>2.1\text{mmol/L}$, further checks within a week are recommended. The advice does not include the use of PTH results to optimise treatment. The BAETS audit has clearly demonstrated that hypocalcaemia has the potential to delay discharge.² Postoperative PTH can accurately predict hypocalcaemia and need for treatment.^{17–20} For this reason, early measurement of PTH and treatment based on a combination of PTH and calcium levels can enable early and safe discharge of patients after thyroid surgery. Husein *et al* also suggested the use of early calcium monitoring (6 hours and 12 hours) to identify hypocalcaemia postoperatively.⁷

Analysis of the data collected in our study showed that repeated adjusted serum calcium measurements are not necessary. Thirteen patients (4.6%) developed hypocalcaemia in the afternoon of the first postoperative day following a normal morning adjusted serum calcium concentration. This fall in calcium only affected the decision to start postoperative supplementation in four patients (1.4%). Only one patient who was previously normocalcaemic was mildly hypocalcaemic (adjusted calcium of 2.06mmol/L) on day 5; however, this did not necessitate supplementation.

Our study has demonstrated the importance of monitoring PTH postoperatively in addition to calcium for the early identification of patients likely to develop temporary and permanent hypocalcaemia. Eighty-six per cent of patients who had low PTH on morning samples were hypocalcaemic. Furthermore, of the 169 patients with normal PTH levels on the first postoperative day, only 2 (1.2%) required long-term supplementation.

Several studies have suggested different protocols for the use of PTH measurements to identify patients who will develop hypocalcaemia.^{17,19–29} Protocols focused on

intraoperative^{21–26} and postoperative^{17,19,20,27–29} PTH monitoring have strengthened our study's conclusions that PTH can be used as a sensitive and specific marker for the development of postoperative hypocalcaemia. Nevertheless, the data collected in this study show that PTH monitoring alone cannot be relied on as a sole indicator for the development of hypocalcaemia as 65% of hypocalcaemic patients had normal PTH results on the first postoperative day.

We have developed a safe and efficient protocol for the early identification and management of hypocalcaemia following bilateral thyroid surgery. Changes in the protocol based on the data collected have reduced the number of blood tests performed, allowed for early discharge of patients and reduced the need for routine reassessment of calcium within the first week after discharge. Initial evaluation of the protocol led to minor adjustments in dosage of supplementation. Further work will be needed to assess the impact of these changes.

Comparison of hypocalcaemia rates with published figures are complicated by the variations in definitions used for both transient and long-term hypoparathyroidism. However, the BAETS national registry reports a day 1 hypocalcaemia rate of 27.4% and a long-term hypocalcaemia rate of 12.1%.² A systematic review from 2014 demonstrated temporary hypocalcaemia rates of 19–38% and long-term rates of 0–3%.¹⁰

In this cohort, 34 (11.8%) of 286 patients had an inadvertent parathyroidectomy. This compares favourably with rates of between 13.8% and 20.2% in other recently published studies.^{30–32}

The limitations of this study include the retrospective nature of the design and the small number of patients in whom the protocol was re-evaluated. It is also possible that other biochemical parameters such as the differences between preoperative and postoperative PTH and magnesium levels may aid in prediction of the recovery of parathyroid function but these have not been evaluated in this study. The prevalence of vitamin D deficiency in the population

may also have had an influence on the degree of postoperative hypocalcaemia and the dose of medications used. This has not been studied either.

Conclusions

This paper presents a protocol that can be used for the early identification and management of post-thyroidectomy hypocalcaemia and hypoparathyroidism. This protocol can be used in similar centres in the UK and elsewhere, and it can be modified to suit local practices. Ongoing audit and protocol driven care will improve the efficiency of care pathways and reduce the problems associated with under and overtreatment.

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