The incidence of post-thyroidectomy hypocalcaemia: a retrospective single-centre audit

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ABSTRACT

INTRODUCTION The aim of this single centre retrospective observational record-based audit was to assess the incidence of post-thyroidectomy hypocalcaemia. The setting was a district general hospital in Hertfordshire covering a population of 500,000 people. A total of 196 patients who had had total or completion thyroidectomy during a five-year period were included in the study.

MATERIALS AND METHODS The primary outcome measure was to determine the rate of biochemical and symptomatic hypocalcaemia in patients undergoing total or completion thyroidectomy. Secondary outcome measures assessed time taken for biochemical and clinical hypocalcaemia to resolve, whether malignancy affected the rate of hypocalcaemia and if removal of parathyroid glands during surgery were a predictor of hypocalcaemia.

RESULTS The overall incidence of post-thyroidectomy hypocalcaemia (PTHC) within 24 hours was 21.4%. The incidence increased from 6 hours (13.8%) to 24 hours post-thyroidectomy (15.8%) and there was evidence of both transient and delayed PTHC within the first 24 hours. By 6 months post-surgery, 3.6% remained hypocalcaemic and required continual oral supplementation. Patients with benign thyroid disease had a higher risk of PTHC ($P = 0.04$) and patients younger than 50 years of age had a higher risk of symptomatic hypocalcaemia ($P = 0.016$). Other clinical factors including sex, type of surgery, neck dissection, oral calcium and/or vitamin D supplementation and inadvertent histological parathyroid gland excision were not associated with an increased incidence of PTHC or symptomatic hypocalcaemia.

CONCLUSIONS Our audit shows that the rate of PTHC within our population was below the national average with higher risk in benign thyroid disease.

KEYWORDS

Hypocalcaemia – Thyroid diseases – Thyroidectomy – Endocrine surgical procedures

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Introduction

Post-thyroidectomy hypocalcaemia (PTHC) is a recognised postoperative complication with potential wide-ranging implications for patient experience and healthcare costs.¹ Hypocalcaemia can be asymptomatic; however, clinical manifestations such as paraesthesia and muscle spasms can be distressing for the patient, while persistent untreated hypocalcaemia can be life threatening.¹

Various mechanisms have been proposed to cause PTHC, the most accepted being secondary hypoparathyroidism due to parathyroid gland injury, devascularisation or inadvertent parathyroidectomy.² Other risk factors include type of surgery, experience of surgeon, female sex, malignancy and reoperation.³ However, owing to the inconsistency of data reported, many of these risk factors remain controversial.

Multiple studies have examined the incidence of PTHC, with their rates differing widely.^{1,4} The variation found is due to changes in the definition of PTHC used at these institutions and can be based upon different clinical, biochemical or therapeutic criteria.⁵ Furthermore, studies use various time intervals to define PTHC and often will include or exclude different thyroid procedures within their data.⁵

The British Association of Endocrine and Thyroid Surgeons (BAETS) define PTHC as serum adjusted calcium (SAC) of below 2.1 mmol/l within the first 24 hours with permanent hypocalcaemia defined as SAC less than 2.1 mmol/l beyond six months.⁶ As such, our aims were to investigate the incidence of PTHC within our unit and to compare this with national standards. We were also keen to determine which sub-groups or populations are at risk of developing post-thyroidectomy hypocalcaemia.

Materials and methods

Ethical considerations

This study took the form of an audit, so National Research Ethics Service approval was not necessary. The local audit and research department approved the study.

Study design

This was a single-centre retrospective record-based observational study. Our inclusion criteria were all patients who underwent total or completion thyroidectomy from 1 January 2012 to 31 December 2016, including those who underwent concomitant neck dissection. Patients who had previous or concomitant planned parathyroidectomy were excluded from the analysis.

Practice

In our unit, a single surgeon who performs more than 100 thyroid operations a year undertakes all thyroid surgery. Since 2011, the unit has implemented a protocol for all patients undergoing total or completion thyroidectomy. All patients must have SAC, phosphate, magnesium and parathyroid hormone measurement at six hours postoperatively and the morning of the next day. All patients must be discharged with one month's supply of vitamin D/calcium supplementation. All patients should be seen in outpatient clinic within two weeks with histology results. Parathyroid hormone levels take two to three days to process and therefore are not used in the immediate postoperative period for calcium monitoring.

Data collection

Data were collected retrospectively from patient case notes using a centrally standardised Microsoft Excel spreadsheet. The following data were collected:

- > demographics (age, gender)
- > type of thyroid surgery (completion, total)
- > histological diagnosis (malignant, benign)
- > parathyroid gland removal
- > SAC at 6 hours, 24 hours, 2–4 weeks and at 6 months if persistently hypocalcaemic
- > symptoms of hypocalcaemia
- > calcium supplementation.

Outcome measures

The primary outcome measures were the rate of biochemical hypocalcaemia (less than 2.1 mmol/l) at 24 hours, 4 weeks and 6 months, and the rate of clinical hypocalcaemia at any point following thyroidectomy.

Secondary outcome measures assessed the impact of other factors on the rate of biochemical hypocalcaemia. These included sex, age, histological diagnosis, inadvertent parathyroid gland removal, type of operation and oral calcium supplementation.

Statistical analysis

Statistical analysis was performed using SPSS statistical software. Chi-square testing was performed on all

categorical data and multiple regression analysis was used to determine significant independent predictors of PTHC. A *P*-value of less than 0.05 was taken to indicate statistical significance.

Results

A total of 196 patients met the inclusion and exclusion criteria of the study. The mean age of the patients at surgery was 50.3 years, with a range of 16–85 years (standard deviation $\pm$ 16.32). The patient demographics are demonstrated in Table 1.

Calcium measurements

All patients had at least one SAC measurement within 24 hours of the operation; 194 patients (98.98%) had SAC measurement at 6 hours, with only 12 patients (6.12%) not having SAC levels measured at 24 hours. All patients who did not have their second measurement had SAC levels above 2.10 mmol/l.

Within the two- to four-week postoperative interval, 160 patients (81.6%) had a follow-up SAC check; 178 patients (90.8%) had their first follow-up SAC by 8 weeks postoperatively and 13 patients (6.62%) had no further SAC level measurements following discharge from hospital. This population of patients had no recorded incidence of biochemical hypocalcaemia within 24 hours of surgery. Some 186 patients (94.9%) received calcium supplementation prior to and following discharge from hospital.

Primary outcome measures

The average SAC in all patients was found to be (2.22 mmol/l $\pm$ 0.13 95% confidence interval, CI) at 6 hours postoperatively and (2.24 mmol/l $\pm$ 0.17 95% CI) at 24 hours. Table 2 indicates the level of biochemical hypocalcaemia at various intervals.

Table 1 Demographics of 196 patients included in the study.

Factor	Patients	
	(n)	(%)
Sex:		
Male	33	16.9
Female	163	83.1
Surgery:		
Total thyroidectomy	143	73.0
Completion thyroidectomy	53	27.0
Selective neck dissection:		
Performed	25	12.8
Not performed	171	87.2

Table 2 Incidence of biochemical hypocalcaemia at various intervals.

Interval	Incidence	
	(n)	(%)
At 6hrs postoperatively	27/196	13.8
At 24 hours postoperatively	31/196	15.8
Overall Incidence Day 1	42/196	21.4
2–4 weeks	17/196	8.67
4 weeks – 6months	10/196	5.1
> 6 months	7/196	3.6

Of the 27 patients who were hypocalcaemic at 6 hours, 11 were normocalcaemic at 24 hours. Of the remaining 16 patients who remained less than 2.1 mmol/l at 24 hours, 8 patients suffered a further drop in SAC levels; 5/31 patients who were normocalcaemic at 6 hours were noted to be hypocalcaemic at 24 hours.

Our study found only seven patients (3.6%) with continued hypocalcaemia beyond six months despite supplementation; this included one patient who unfortunately died of a non-related condition. The demographics of these seven patients are noted in Table 3.

Seventeen (8.7%) patients had documented clinical hypocalcaemia at any time postoperatively; 14 (82.4%) of these patients were biochemically hypocalcaemic within 24 hours. Of the remaining three (17.6%), one was biochemically hypocalcaemic within two days postoperatively and this patient remained permanently hypocalcaemic beyond six months.

Secondary outcome measures

Table 4 demonstrates the various epidemiological, clinical and pathological variables that were tested to determine influence on the occurrence of post-thyroidectomy hypocalcaemia within the first 24 hours. The overall regression model was not significant ($F [7,188] = 1.82$, $P > 0.05$, $R^2 = 0.06$), meaning that, as a group, the variables did not significantly impact biochemical hypocalcaemia within 24 hours. However, it did find that a benign histological diagnosis can significantly affect the rate of PTHC ($P = 0.04$). No statistical differences were noted with sex, age, surgery type (completion vs total thyroidectomy), concomitant neck dissection, inadvertent parathyroid gland excision and postoperative oral calcium/vitamin D supplementation.

Table 5 demonstrates the various epidemiological, clinical and pathological variables that were tested to determine influence on the incidence of documented clinical hypocalcaemia at any stage postoperatively. The overall regression model was not significant ($F [7,188] = 1.38$, $P > 0.05$, $R^2 = 0.05$), meaning that, as a group, the variables did not significantly affect rates of symptomatic hypocalcaemia. However it did find that an age less than 50 years can significantly impact the rate of clinical hypocalcaemia

Table 3 Results of seven patients who remained biochemically hypocalcaemic beyond six months.

Factor	Patients	
	(n)	(%)
Sex:		
Male	1	14.3
Female	6	85.7
Surgery:		
Total thyroidectomy	5	71.4
Completion thyroidectomy	2	28.6
Neck dissection:		
Performed	1	14.3
Not performed	6	85.7
Histological diagnosis:		
Benign	2	28.6
Malignant	5	71.4
Parathyroid on histology:		
Present	3	42.9
Absent	4	57.1

($P = 0.016$). No statistical differences were noted with sex, surgery type (completion vs total thyroidectomy), concomitant neck dissection, inadvertent parathyroid gland excision and postoperative oral calcium/vitamin D supplementation.

Discussion

Synopsis of key findings

Our study has found a low incidence of biochemical PTHC within the first 24 hours of 21.4% (95% CI 15.7–27.2%) and that the only factor that significantly influenced the rate was the benign nature of the thyroid gland. Several other factors including age, sex, surgery, oral calcium supplementation and parathyroid removal had no impact on the rate of PTHC. An age of less than 50 years is a predictor for clinical hypocalcaemia.

Comparison with previous studies

One of the aims of this study was to compare data from this single centre to national standards reported in BAETS fifth national audit, however there are large differences in varying practices and populations between the two cohorts, making direct comparisons somewhat difficult. Nevertheless, consecutive national audits by BAETS have reported a gradual decrease in reported rates of PTHC from 29.6% in 2009 to 23.5% in 2017.⁷ Our results compare favourably with 2017 results and fall within the confidence margin of 95%. We do, however acknowledge that that data from BAETS are not independently verified and are therefore susceptible to reporting bias,⁷ potentially affecting its

Table 4 Impact of various characteristics on incidence of post-thyroidectomy hypocalcaemia within 24 hours.

Characteristic	Overall incidence of post-thyroidectomy hypocalcaemia within 24 hours				P-value ^a
	Yes (n = 42)		No (n = 154)		
	(n)	(%)	(n)	(%)	
Sex:					P = 0.973
Male	7	21.2	26	78.8	
Female	35	21.5	128	78.5	
Age (years):					P = 0.123
< 50	25	25.5	73	74.5	
> 50	17	17.3	81	82.7	
Surgery:					P = 0.188
Total thyroidectomy	34	23.3	112	76.7	
Completion thyroidectomy	8	16	42	84	
Level VI neck dissection:					P = 0.737
Yes	6	37.5	10	62.5	
No	36	20	144	80	
Histology:					P = 0.049
Benign	31	26.1	88	73.9	
Malignant	11	14.3	66	85.7	
Parathyroid excision:					P = 0.090
Yes	14	28	36	72	
No	28	19.2	118	80.8	
Postoperative supplementation:					P = 0.090
Yes	40		144		
No	0		0		
^a P-value was determined using chi-square test.					

^a *P*-value was determined using chi-square test.

accuracy. We did, however, compare our results to those available in the literature from other centres (Table 6).

Few studies have correlated age with PTHC.^{15,14} Theoretically, it would be expected that the physiological changes brought with increasing age would result in higher rates of PTHC because of the reduced availability of calcium ions.¹⁵ We postulate that our observed phenomenon may be a consequence of the younger generation feeling more comfortable in voicing their symptoms and concerns in comparison to their seniors.

Clinical applicability of the study

The higher rates of PTHC in benign thyroid disease are well reported in the literature.^{7,15} This is likely to be a reflection of the intraoperative challenges frequently encountered in common benign thyroid diseases such as Graves and multinodular goitre where the vascularity and size of the gland can cause technical difficulties. There is correlation between the size and weight of the thyroid

gland and PTHC,¹⁶ as well as evidence that protecting the vasculature of the parathyroid glands during surgery will reduce the rate of PTHC.¹¹ It is thus not uncommon for parathyroid glands to be bruised during the dissection which may result in an immediate hypocalcaemia.⁷ Our hypotheses is supported by the fact that the vast majority of the PTHC recovered within six months (Table 2) and the inadvertent removal of parathyroid glands had minimal effect (Table 4).

Although parathyroid removal during thyroidectomies has been shown to significantly affect PTHC,¹⁶ our results in Tables 3 and 4 were supported by Zhou *et al*'s retrospective review,¹⁷ where only 2.7% of 78 patients with inadvertent parathyroidectomy during thyroidectomy suffered long term PTHC. This would suggest that the preserved parathyroid glands have decent compensatory mechanisms to ensure a normocalcaemic state. We feel that further subgroup analysis of the BAETS data may help to shed further light on the effects of parathyroid gland injury.

Table 5 Impact of various characteristics on incidence of symptomatic hypocalcaemia postoperatively.

Characteristic	Overall incidence of post-thyroidectomy hypocalcaemia within 24 hours				P-value ^a
	Yes (n = 42)		No (n = 154)		
	(n)	(%)	(n)	(%)	
Sex:					P = 0.926
Male	3	10.0	30	90.0	
Female	14	8.6	149	91.4	
Age (years):					P = 0.016
< 50	13	13.7	82	86.3	
> 50	4	4.0	97	96.0	
Level VI neck dissection:					P = 0.527
Yes	3	12.0	22	88.0	
No	14	8.2	157	91.8	
Histology:					P = 0.758
Benign	11	9.2	109	90.8	
Malignant	6	7.9	70	92.1	
Parathyroid excision:					P = 0.121
Yes	3	6.0	47	94.0	
No	14	9.6	132	90.4	
Postoperative oral supplementation:					P = 0.317
Yes	42	22.6	144	77.4	
No	0	0	0	100	
^a P-value was determined using chi-square test.					

^a P-value was determined using chi-square test.

We feel that the low rates of PTHC may be a consequence of prophylactic post-operative vitamin D and calcium supplementation. Our practice stems from well-documented evidence on the association between prophylactic calcium and Vitamin D supplementation and a reduction in postoperative hypocalcaemia.^{18,19} This was also noted in our comparison with BAETS, where 94.9% of patients within our study were supplemented prior to and following discharge from hospital in contrast to 40% reported in BAETS.⁷ We therefore theorise that many of our patients with decreased parathyroid function may not have developed PTHC within 24 hours. Furthermore, our low rate of clinical hypocalcaemia (8.7%) further complements the benefits of prophylactic supplementation found in other studies.^{18,19} We do however appreciate that a real benefit of supplementation cannot be established from this study, as such comparisons were not clinically tested as part of our study design. Overall, we feel that our results may provide a stepping stone to formally test such a hypothesis.

Limitations

One of the major limitations is the retrospective nature of the study. Consequently, there were missing data on the

Table 6 Rates of post-thyroidectomy hypocalcaemia (PTHC) in other studies at single centres.

Study	Rates of PTHC (< 2.1 mmol/l) (%)
Edafe <i>et al</i> (2014) ⁸	29.0
Noureldine <i>et al</i> (2014) ⁹	52.3
Vani <i>et al</i> (2017) ¹⁰	24.0
Aqtashi <i>et al</i> (2017) ¹¹	33.0
Stedman <i>et al</i> (2018) ¹²	29.1
Arman <i>et al</i> (2018)	21.4

SAC levels performed within 24 hours and post-hospital discharge, which may have affected our overall primary and secondary outcomes. We may be missing further instances of clinical hypocalcaemia that have not been recorded in patient notes. A prospective study can also shed further light on the effects of postoperative calcium supplementation, as it appears that the protocol was not as

strictly adhered to during the earlier years following its implementation; it is difficult to know why this has occurred and this lack of randomisation in our current comparison, as outlined in Table 4, is thus unlikely to be a true reflection of how postoperative supplementation can influence PTHC.

We also acknowledge that the size and weight of the thyroid gland, which has been shown to affect PTHC, was not measured on removal.¹⁶

Lastly, our study was hampered by the speed of our biochemistry department turning around serum parathyroid hormone levels. As these hormones have been shown to be a good predictor of long-term calcium levels,⁷ we feel that the immediate availability of parathyroid hormone levels may have further guided our management and helped educate the 21.4% of patients who had PTHC at day 1 on the likely course of their calcium levels post-discharge.

Conclusions

Using a standardised definition of PTHC, we report a lower overall incidence of PTHC at 24 hours of 2.1% compared with national rates and 2.6–30.9% lower than previous single centred studies.^{8–12} Our study demonstrates that the presence of benign pathology is associated with a higher rate of PTHC and, unlike previous reports, inadvertent parathyroid gland removal has no significant impact on rates of PTHC.¹⁷ Our results shed further light on factors that influence PTHC, although further subgroup analysis on nationally collected BAETS data may be of greater help.

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