Incidental parathyroidectomy during total thyroidectomy is not a direct cause of postoperative hypocalcaemia

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Abstract

Background

Postoperative hypocalcaemia is the most common complication after total thyroidectomy, with a reported incidence of transient hypocalcaemia up to 50% and permanent hypocalcaemia 1.5-4%. The impact of incidental parathyroidectomy (IPE) on postoperative hypocalcaemia remains controversial. This study evaluated the risk factors for IPE following total thyroidectomy and compared postoperative calcium levels serially between patients with and without IPE.

Methods

A retrospective analysis of patients undergoing total thyroidectomy from January 2009 to October 2016 at Western Health was conducted. Histopathology reports were reviewed to identify specimens that included parathyroid tissue. Risk factors and dichotomous data were analysed by exact test of difference in binomial proportions. Group comparison of serial calcium levels (preoperative to 48 hours postoperative) between the no incidental parathyroidectomy (No IPE) and IPE patients were analysed by calculating the area under the curve (AUC) producing a time series summary.

Results

Four hundred and sixty-eight patients were included: 395 were females (81%), with a median age of 51 years. IPE was confirmed histologically in 84 patients (17.7%) and was more likely to occur in patients undergoing total thyroidectomy with central neck dissection ($p=0.0003$), and in patients with malignant disease ($p=0.0005$). The difference in AUC for serial postoperative

calcium levels between the No IPE and the IPE group was 0.61 ($p = 0.21$, 95% confidence interval (CI) -0.37 to 1.58).

Conclusion

Total thyroidectomy for malignancy and with central node dissection had a higher risk of IPE but did not result in significant changes in postoperative serum calcium levels.

Introduction

Total thyroidectomy is now a well-established, safe surgical procedure with relatively low morbidity ^{1,2}. Recurrent laryngeal nerve injury and postoperative hypocalcaemia are the most common complications after total thyroidectomy. In particular, symptomatic hypocalcaemia is a serious complication that may lead to emergency department presentations, **which may** require intravenous calcium infusion ³. Although most cases are transient, permanent hypocalcaemia can occur due to ongoing dysfunction of the parathyroid glands ^{4,5}.

The preservation of parathyroid glands during thyroid operations is a technical challenge due to difficulty in identification, fragile vascular supply and variation in location ^{4,6,7}. Iatrogenic hypocalcaemia post total thyroidectomy is a well-recognised complication. Following total thyroidectomy, the incidence of transient hypocalcaemia may be as high as 50% and that of permanent hypocalcaemia 1.5% to 4% ⁵⁻¹³. Hypocalcaemia may take 24 to 48 hours to manifest and for this reason many surgeons choose to either observe patients in hospital for one or two days, or routinely commence prophylactic calcium postoperatively. The prevention and treatment of post thyroidectomy hypocalcaemia remain areas of ongoing debate.

Hypocalcaemia is a direct result of low circulating parathyroid hormone levels. This is usually due to trauma to the vascular supply of the parathyroid glands, or their complete removal. A number of risk factors have been implicated in post thyroidectomy hypocalcaemia including: incidental

parathyroidectomy (IPE), extent of thyroidectomy, experience of surgeon and histopathology findings^{3-6, 8-12,14,15}

IPE is the inadvertent removal of one or more parathyroid glands during thyroid surgery, which are subsequently identified within the pathological specimen^{16,17}. IPE is a theoretical risk factor for postoperative hypocalcaemia.

This study aims to determine the incidence of incidental parathyroid excision in patients undergoing total thyroidectomy within a high volume specialist endocrine surgery unit in an Australian metropolitan hospital, and to assess risk factors for IPE and the relationship between IPE and transient postoperative hypocalcaemia in this patient group.

Methods

This is a retrospective review of all total thyroidectomies conducted at the Western Health, Footscray Victoria Australia between January 2009 and October 2016. This project was approved by the Western Health Low Risk Ethics Committee. All procedures were performed by consultants (or their trainees under close supervision) of the Endocrine Surgery Unit using a standard technique with particular attention to avoid devascularisation of parathyroids or IPE. In the event of intra-operatively recognised IPE, immediate auto-transplantation of the gland(s) into the sternocleidomastoid muscle was performed. Operations involving cervical lymph node dissections, and operations with specimens containing one or more parathyroid adenomas were excluded from the study. Patient details were anonymised and medical records were reviewed and data compiled in an Excel database.

Demographic data, indication for surgery and preoperative thyroid function tests were collected. Histopathology reports were reviewed to identify those with parathyroid tissue present, the number of parathyroid glands excised and their final histology. Only patients whose pathology reports identified one or more parathyroid glands in the histopathology specimen were considered as having had IPE. Operative data collected included the primary operator (trainee vs. consultant), the number of parathyroid glands identified intra-operatively and the number re-implanted. Patients who received prophylactic calcium carbonate supplementation postoperatively were excluded from the postoperative calcium analysis. Patients who were hypocalcaemic (clinically or biochemically) in the postoperative period received therapeutic calcium supplementation as directed by the treating consultant. Serum calcium levels were measured preoperatively, 6 hours and day 1 and 2 postoperatively. Hypocalcaemia was defined as a corrected serum calcium of less than 2.10 mmol/litre.

Statistical Analysis

Categorical data with cell count frequencies were analysed by exact test of difference in binomial proportions. Non-parametric Mann-Whitney test was used for unpaired group comparison for continuous data and summary measures expressed as median and inter-quartile range (IQR).

As the serum calcium levels were collected serially over time, the comparison between the non-incidental parathyroidectomy group (No IPE) and the incidental parathyroidectomy group (IPE) was analysed by calculating the area under the curve (AUC) for each subject, generating a time series summary for the whole period of observation¹⁸.

All analyses were performed with StatsDirect v. 3.0 (StatsDirect Ltd UK). Two-sided $p < 0.05$ was accepted as statistically significant.

Results

Total thyroidectomy was performed in 468 patients during the study period. A total of 83 patients were identified as having IPE (17.7%). Patient characteristics are shown in Table 1. In both groups (No IPE vs. IPE) the majority of patients were female, with a median age of 51 years.

None of the patients in the IPE group had more than two parathyroid glands excised. Intra-operative re-implantation of parathyroid glands occurred in 31.0% of patients (No IPE $n=110$, IPE $n=35$). No patients experienced permanent hypoparathyroidism. The majority of patients underwent surgery for benign thyroid disease ($n=399$, 85.3%), with 69 patients undergoing surgery for fine needle aspiration (FNA) proven malignancy on preoperative assessment. Patients underwent total thyroidectomy with central neck dissection in 34 patients (7.3%). IPE was more likely to occur in patients undergoing thyroid surgery for malignancy ($p=0.0003$) and with central neck dissection ($p=0.0005$). The patient age, specimen weight and primary operator (consultant vs. trainee) did not affect the incidence of IPE (Table 1).

Patients who received routine calcium carbonate supplementation in the post-operative period were excluded from calcium data analysis, leaving a total of 315 patients (260 No IPE, 55 IPE). Table 2 shows a time series summary of area under the curve (AUC) for patients with IPE vs. patients No IPE. The mean AUC for patients without IPE was 107.68 (SD 0.22) and for patients with IPE was 107.07 (SD 0.44). The AUC difference between the two patient groups was not significant at 0.61 ($p=0.21$, CI -0.37 to 1.58). Figure 1

shows the curves joining the mean serum calcium levels (used for calculating AUC) over the whole period of observation for the IPE and No IPE patients.

Discussion

In this study, analysis of changes in serial calcium levels over the whole period of observation rather than at each time point¹⁸ showed no significant difference between patients who sustained incidental parathyroidectomy and those who did not.

Hypoparathyroidism is known to result in hypocalcaemia, but there is no strong evidence that links incidental parathyroidectomy to postoperative hypocalcaemia following thyroid surgery². Most published studies on this relationship are retrospective reviews with notable heterogeneity and limitations. Indeed, a review of the literature shows that twelve of sixteen publications, published between 1961-2014, found no association between IPE and hypocalcaemia following thyroidectomy^{2,7,16,17,19-26}. Four of sixteen publications suggested that IPE did result in a statistically significant increase in the incidence of transient hypocalcaemia; only Khairy *et al.* found any association between IPE and permanent hypocalcaemia but this was not statistically significant^{12,27-29}.

To our knowledge, this is the first published Australian study to investigate the relationship between IPE in thyroid surgery and postoperative hypocalcaemia. Our series of 383 patients found that there is no significant difference in postoperative serum calcium levels in patients with parathyroid glands incidentally removed during surgery. This supports the findings of the majority of the published literature in concluding that IPE does not directly

cause transient postoperative hypocalcaemia. Even the few studies that found a statistically significant increase in transient post-operative hypocalcaemia in patients with IPE were not able to conclude that this was a direct result of IPE; rather these were simply observations of association^{12,27-29}.

The incidence of IPE for patients undergoing total thyroidectomy at Western Health in this study is 17.7% and comparable to that published in the literature of 2.9% - 21.6%^{15,19}. Variation in incidence of IPE between studies is likely due to numerous variables including patient demographic, operative technique, pathology reporting, and data collection and is not a direct reflection of surgical skill².

Visualisation of the parathyroid glands during surgery may often be difficult due to their variable location, small size and amorphous appearance. Many surgeons would argue that identification of parathyroid glands *in situ* during total or completion thyroidectomy results in a lower incidence of IPE, despite lack of supporting evidence². In fact, even though identification of parathyroid glands during surgery has been shown not to increase the incidence of IPE, all surgeons endeavour to identify the parathyroid glands intra-operatively¹⁶. Some authors also recommend careful inspection of the surgical specimen for the presence of parathyroid glands and auto-transplant any that may have been excised²⁸.

From first principles, it is presumed that only one of four parathyroid glands is necessary to provide adequate levels of circulating parathyroid hormone to avoid hypocalcaemia. Thus, it seems unlikely that IPE of one, two or even three parathyroid glands would directly result in hypocalcaemia. In the

hands of a skilled surgeon, IPE of all four parathyroid glands should be considered exceptionally rare and a serious complication of an otherwise low morbidity surgical procedure. Certainly, in our study no histopathology specimen contained more than two incidentally excised parathyroid glands. IPE may be an indicator of a difficult procedure or the presence of aberrant anatomy; it may occur more frequently in high-risk patients²⁷. It is likely that hypocalcaemia post thyroid surgery is multi-factorial. Potential causes include: trauma to or devascularisation of multiple parathyroid glands, haemodilution, pre-existing hyperparathyroidism and hyperthyroidism, with associated 'bone hunger'³⁰.

Conclusion

Our study confirms that there is no evidence to suggest that IPE directly causes post-operative hypocalcaemia following total thyroidectomy. Although thyroid surgeons should be aware of all potential risk factors for postoperative hypocalcaemia, the clinical management of patients should not be altered solely based on whether IPE has occurred. There is certainly no need for prolonged admission, additional investigations or calcium supplementation unless other indications exist.

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Table 1. Patient characteristics and univariate analysis for patients undergoing total thyroidectomy without and with IPE

	No IPE (<i>n</i> =385)	IPE (<i>n</i> =84)	p-value
Gender			
Female	325 (82.28%)	70 (17.72%)	
Male	60 (81.08%)	14 (18.92%)	0.81
Age[†]			
	51 (40-63)	51.5 (43-60)	0.492
Histology			
Benign	323 (85.22%)	56(14.78%)	0.0005
Malignant	62 (68.89%)	28 (31.11%)	
Weight[†]			
	59 (36-107)	51 (27-106)	0.234
Procedure			
Total thyroidectomy	366 (84.14%)	69 (15.86%)	
Total thyroidectomy and central neck dissection	19 (55.88%)	15 (44.12%)	0.0003
Primary operator			
Consultant	242 (80.94%)	57 (19.06%)	0.40
Registrar	143 (84.12%)	27(15.88%)	

† Median and inter-quartile range (IQR)

Table 2 Time Series Summary: Area Under Curve (AUC)

	Time (hours)	Observations (n)	s-Ca ²⁺ mmol/litre (mean ± SD)	AUC† (mean ± SD)
No IPE	0	260	2.37 (0.09)	107.68 (0.22)
	6	260	2.27 (0.10)	
	24	260	2.24 (0.15)	
	48	260	2.18 (0.10)	
IPE	0	55	2.39 (0.09)	107.07 (0.44)
	6	55	2.26 (0.13)	
	24	55	2.20 (0.11)	
	48	55	2.20 (0.13)	

† AUC difference 0.61; p = 0.21; 95% CI; -0.37 to 1.58; No IPE: no incidental parathyroidectomy; IPE: incidental parathyroidectomy. SD: 1 standard deviation.

Legends for Figures

Fig. 1. Serum calcium levels (mmol/litre) for incidental parathyroidectomy (IPE) vs. no incidental parathyroidectomy (No IPE) patients. The curves joining the means were used to calculate the area under the curve (AUC) for group comparison. Preoperative values were displayed at time 0

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