Post-operative Transient Hypoparathyroidism: Incidence and Risk Factors

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Abstract

Background: There is limited data on the incidence and risk factors for developing postoperative hypoparathyroidism (POHP) in the South African setting. **Objectives:** This study aims to calculate the incidence of postoperative hypoparathyroidism in a South African tertiary setting, and to compare local risk factors for POHP to international published data. **Methods:** All patients who underwent a total or completion thyroidectomy at an academic referral center from January 2010 to December 2015 were included. Data reviewed included post-operative parathyroid hormone (iPTH) level , demographics, type of operation and lymphadenectomy, size of thyroid glands resected, final histology, extracapsular extension of carcinomas, number of lymph nodes resected, and the number of parathyroid excised. **Results:** Postoperatively, 29% of patients were diagnosed with hypoparathyroidism. Overall, there was no association between POHP and age or gender. In patients with Benign histology, size was significantly associated with higher rates of POHP. In patients with thyroid carcinoma, lymphadenectomy and the number of lymph nodes resected were associated with higher rates of POHP. **Conclusion:** The incidence of immediate postoperative hypoparathyroidism is within international standards. Standardized postoperative follow up is necessary, and strategies to improve POPH such as auto transplantation in locally identified high-risk subgroups should be considered.

Keywords: Postthyroidectomy, Hypocalcaemia, Hypoparathyroidism

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Introduction

Postoperative hypoparathyroidism (POHP) is a well-recognized complication of thyroid surgery. It can occur following thyroid surgery due to inadvertent devascularization of the parathyroid glands, unintentional excision of parathyroids, or if the parathyroid glands are deliberately excised as part of an oncological specimen (1). An early decrease in intact Parathyroid Hormone (iPTH) levels predicts postoperative hypocalcaemia with great specificity and hospital stays as well as an extra burden of medication and follow up for patients. Permanent hypoparathyroidism has further long term complications, such as nephrocalcinosis, renal dysfunction, basal ganglia calcifications and seizures (5,6). Internationally, the reported incidence of POHP is variable ranging from 3 to 50%(4,7), depending on the definition used(1,3). The use of multiple definitions for this complication makes it very difficult to compare incidence across different studies. The British Association of Endocrine and Thyroid Surgeons'

BAETS) most recent audit reported an incidence of transient postoperative hypocalcaemia of 24.9%(5). Previously identified predictors for POHP have included, amongst others, older age, female sex, surgery for Grave's disease, bilateral neck surgery, surgery for thyroid malignancy and size of thyroid gland (8). However, predictors for POHP also varied across different studies and in different locations, and even different studies in the same centers have produced conflicting information on predictors for POHP or hypocalcaemia (3). Limited data exists on the incidence of POHP and the factors which predict risk for this condition in South Africa. This study aims to calculate the incidence of POHP in a South African tertiary high volume setting, as well as identify the risk factors relevant to our population.

Methods

All patients who underwent a total thyroidectomy or completion thyroid lobectomy from January 2010 to December 2015 at the Groote Schuur Surgical Breast and Endocrine Oncology Unit were included in this study. Data was reviewed retrospectively from a prospectively maintained database. All operations were done by a standard trans cervical open approach, and used a harmonic dissector to facilitate hemostasis. This is an academic training unit, with primary operating surgeons of varying experience, from senior subspecialist to trainee surgeon, supervised during surgery. The data reviewed included post-operative parathyroid hormone level, age, gender, weight and dimensions of thyroid specimen resected, extent of surgery and if lymphadenectomy was done, type of lymphadenectomy, presence of extracapsular extension of carcinoma, number of lymph nodes present in the specimen, presence and number of parathyroids in the specimen and final histological diagnosis of thyroid pathology. Central lymphadenectomy refers to resection of the nodes in level 6 of the neck, and lateral lymphadenectomy implies resection of nodes from level 2a, 3 and 4 of the neck.Following a total or completion thyroidectomy, the unit protocol requires serum iPTH to be drawn 6-12 hours postoperatively. Patients were defined as having POHP if the postoperative serum iPTH level was less than 1.6 pmol/l (lower limit of normal in the assay used in our laboratory). The records of these patients were then assessed for surgical and patient risk factors which have been shown in international cohorts to be associated with POHP. The pathology reports were analyzed for information about the size and weight of the resected thyroid specimens, presence of parathyroids and number of lymph nodes resected. Volume was calculated by multiplying anterior-posterior, craniocaudal and transverse measurements of the resected specimens. All histological subtypes of carcinoma were grouped under 'malignant', while all other diagnoses were grouped into the 'benign' group. Descriptive statistics were performed on the patients, followed by Wilcoxon signed rank tests to explore the relationship between volume and weight and the outcome of postoperative hypoparathyroidism. Fishers' exact, Pearson chi-squared and 2 sample proportion tests were used to explore relationships between the outcome and gender, cancer and lymphadenectomy while taking into account the numbers in the sample. Significance level was set at alpha $\leq$ 0.05. Pearson's correlation was used to investigate the linear relationship between weight and volume of the thyroid tissue removed.

Results

The records of 203 patients were captured for this study. Papillary thyroid cancer (31%) and multi-nodular goiter (29%) were the most common histological diagnoses (Table1). The patients had a mean age of 47.6 years and 85% were female. Percentage distribution of histological results for malignant and benign patients are shown in table 1. Papillary thyroid cancer was the most common malignant histological diagnosis, while multinodular goiter (MNG) was the most common benign diagnosis. Only one thyroid cyst was seen along with one case of Hurthle cell adenoma. Lymphoma and papillary microcarcinoma were rare cancers in this series.

Table 1:Distribution of Histological Results

Total number of patients	203
Histology results	
Total malignancies	**93(45.8%)**
Papillary Thyroid Cancer	63 (31.03%)
Follicular Thyroid Cancer	15 (7.39%)
Medullary Thyroid Cancer	7 (3.45%)
Hurthle Cell Carcinoma	5 (2.46%)
Lymphoma	1(0.49%)
Papillary microcarcinoma	1 (0.49%)
Poorly Differentiated Carcinoma	1 (0.49%)
Total Benign Diagnoses	**110 (54.2%)**
Multinodular Goitre	59 (29.06%)
Hashimoto's thyroiditis	12 (5.91%)
Normal completion thyroidectomies	12 (5.91%)
Graves' Disease	7 (3.45%)
Thyroiditis	7 (3.45%)
Follicular adenoma	5 (2.46%)
Nodular hyperplasia	3 (1.48%)
Toxic Multinodular Goitre	3 (1.48%)
Hurthle cell adenoma	1 (0.49%)
Thyroid cyst	1 (0.49%)

Overall 59 patients (29.1%) developed immediate postoperative hypoparathyroidism. Their characteristics are described in Table 2.

Table 2: Relationship Between Gender, Age, Parathyroid in Specimen and Cancer Status of Patients

Characteristics	Post-operative PTH			
	normal post op iPTH 144 (70.9%)	low post op iPTH 59 (29.1%)	Total N = 203	P value
Gender				
Male	24 (17%)	10 (17%)	34	
Female	120 (83%)	49 (84%)	169	0.961
Age mean (SD)	47.8 (14)	46.9 (13.8)	202	0.6773
No parathyroid tissue present in specimen	129	47		0.059
Cancer				
No	82 (57%)	28 (48%)	110	0.3885
Yes	62 (43%)	31 (53%)	93	0.3874

iPTH, intact Parathyroid Hormone; SD, Standard Deviation.

Gender did not significantly affect the outcome in this group. Age was not significantly associated with increased risk of POHP, and whether or not the underlying diagnosis was benign or malignant did not play a role either. Numbers of thyroidectomies for Grave's disease were too small to assess. Parathyroids were only inadvertently removed in 27 cases (13%). The presence of parathyroids in the specimen was not significantly associated with low post-operative iPTH. The chance of parathyroids being present in the specimen was also not significantly increased if the operation was done for a malignancy.

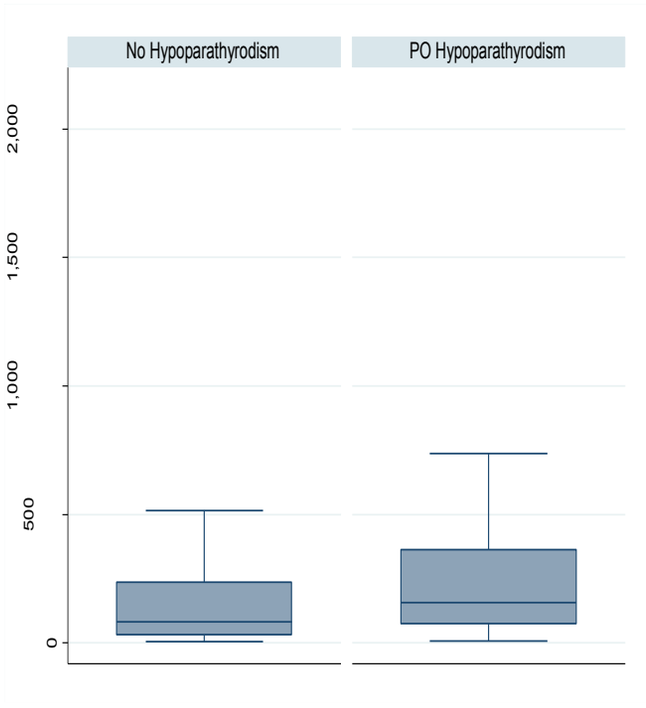

Figure 1 A box plot of the volume of thyroid specimen resected in patients with and without Post-operative hyperparathyroidism

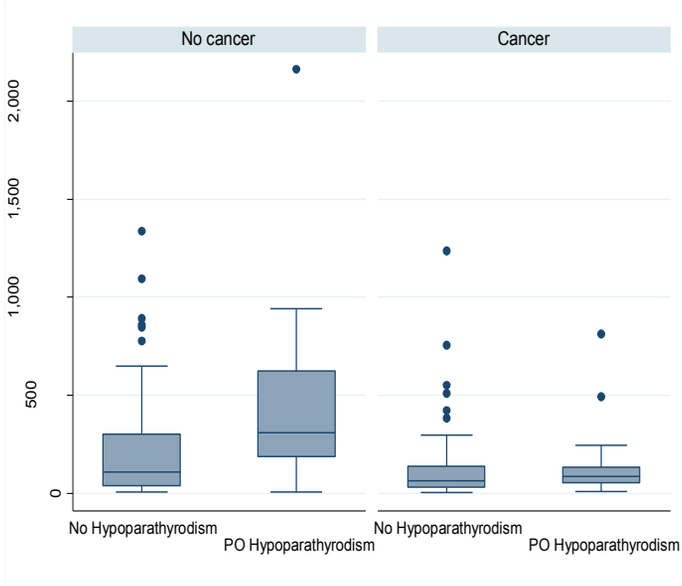

Figure 2 Box plots of the weight of thyroid specimen in patients with and without cancer by postoperative hypoparathyroidism status

There was a significant relationship between volume and POHP in patients who had surgery for benign thyroid disease, with a significant increase of POHP in those with a thyroid volume greater than 200cm3. There was no volume correlation in patients who underwent surgery for malignancy.

Although initial analysis indicated no significant difference between malignant and benign patients' risk of developing POHP, it was postulated that the disease processes should be considered separately to the additional surgeries for malignancies, and may have different risk factors. They were analyzed separately

Table 3: Distribution of Study Characteristics According to Post-operative Hypoparathyroidism Status

Variable	Cancer status							
	Benign patients				Malignancy patients			
	Post-operative hypothyroidism				Post-operative hypothyroidism			
	No n(82)	Yes n(28)	Total n=110	P values	No n(62)	Yes n(31)	Total n=93	P values
Gender								
Male	10 (12.20%)	1 (3.57%)	11		14 (22.60%)	9 (29.03%)	23	
Female	72 (87.80%)	27 (96.43%)	99	0.284	48 (77.40%)	22 (70.97%)	70	0.497
Age median (IQR)	48.5 (37-57)	51.5 (38.5-57)	110	0.8088	52 (38-61)	45 (37-58)	92	0.4933
Tissue Weight (gr) median (IQR)	62 (24-169)	150 (134-296)	25	**0.0030**	27.5 (11.7-72)	38.5 (24.1-109.5)	20	0.1340
Tissue Volume (cm^3) median (IQR)	109.9 (37-303)	309 (188-624)	105	**0.0013**	64 (28.8-139.6)	85.35 (53.25-133.15)	83	0.2598
Nodes median (IQR)	0 (0-0)	0 (0-0)	89	0.2654	0 (0-5)	1 (13-37)	86	**0.0060**
Procedure								
Completion lobectomy	20 (24.39%)	4 (14.28%)	24	0.2634	15 (24.19%)	4 (12.90%)	19	
Total Thyroidectomy	59 (71.95%)	20 (71.42%)	79	0.9571	47 (75.80%)	27 (87.10%)	74	0.278
Missing	3 (3.67)	4 (14.28%)	7	**0.0472**	-	-	-	
Lymphadenectomy								
No	81 (98.80%)	24 (85.70%)	105		35 (56.45%)	7 (22.58%)	42	
Yes	1 (1.20%)	4 (14.30%)	5	**0.015**	27 (43.55%)	24 (77.42%)	51	**0.002**
Types of lymphadenectomy								
Central and lateral	1 (1.20%)	-	1	-	12 (19.40%)	16 (51.61%)	28	**0.0014**
Central	-	4 (14.30%)	4	-	15 (24.20%)	8 (25.80%)	23	0.8661
Extra-capsular								
No	-	-	-	-	33 (53.23%)	16 (51.61%)	49	0.8827
Yes	-	-	-	-	10 (16.13%)	9 (29.03%)	19	0.1458

Table 3 shows the distribution of study characteristics stratified by POHP and cancer status. 110 had benign diagnoses and 93 had malignant histology. For benign patients, weight, volume, were significantly associated. The median weight of the resected thyroid specimens of 62gr was lower for patients with no POHP compared to those with positive operative hypothyroidism (150gr) (p=0.00030). The median volume of resected specimens was statistically different (p= 0.0012) between patients without POHP (109.9 (IQR 37-303) and those who were found to be having POHP 309 (IQR 188-624).

For patients with malignant histology, the number of lymph nodes resected, lymphadenectomy, and extent of lymphadenectomy showed statistically significant differences with regard to POHP status. The relationship between lymphadenectomy and POHP was statistically significant (p= 0.002). 16 patients who underwent both central and lateral lymphadenectomy developed POHP (51.61%), a statistically significant difference (p= 0.0014).

A diagnosis of malignancy alone was not a predictor for postoperative hypoparathyroidism (p = 0.3874), but malignancy patients undergoing lymphadenectomy had a significantly higher proportion of postoperative hypoparathyroidism (p = 0.0179). This suggests that the risk factor is in fact undergoing a lymph node dissection, rather than the malignancy itself. The patients with a greater number of nodes removed were also more likely to develop POHP (p = 0.0060).

Discussion

It is commonly accepted that thyroid surgery is complex and should be performed in a high volume unit (9). Even within a high volume center with experienced surgeons, POHP is common. In order to improve patient outcomes, it is necessary to measure the incidence of this problem and then identify the risk factors to evaluate whether practice can be modified to decrease the complication rate. In our tertiary referral unit, 29% of patients undergoing total or completion thyroidectomy in the past five years were diagnosed with postoperative hypoparathyroidism. We defined postoperative hypoparathyroidism as serum iPTH of less than 1.6 pmol/l, measured within 6 - 12 hours postoperatively. Other units have used different

definitions, making comparison of incidences challenging (3). Some units measure only postoperative calcium, and plot a trend of serum calcium to predict whether or not the patient will develop symptomatic hypocalcaemia. Some units measure both iPTH and serum calcium. A 2008 review showed that an early low postoperative PTH correlates closely with postoperative hypocalcaemia (10), allowing us to perform a single blood test to determine if postoperative hypoparathyroidism is present. Our incidence of postoperative hypoparathyroidism (29%) falls well within quoted ranges (11) and is close to the BAETS quoted incidence of postoperative hypocalcaemia. Despite using different markers, this provides the same information. This result indicates that we are working to international standards (5)

In benign disease, only the weight and volume (closely related) of the specimen was a significant risk factor for development of postoperative hypoparathyroidism. It is easy to understand how a larger volume of tissue in a limited space makes an operation more technically challenging. Parathyroids are small glands, difficult to identify, with an average weight of around only 60 mg(12). The risk factors we have identified may also have to do with the distribution of disease we operate on in our unit. Autoimmune thyroid disease was identified as a risk factor for postoperative hypoparathyroidism by the American College of Endocrinology(8). However, only 3.45% of our thyroidectomies done over five years were for Grave's Disease, meaning that the numbers are too small to allow comment on the significance of this as a risk factor.

In patients with thyroid cancer, lymph node dissection was a risk factor for postoperative hypoparathyroidism. The need for a neck dissection reflects a more advanced stage cancer. However, the presence of extracapsular extension or excised parathyroids on histology is not significant for POHP. This implies that it is the inadvertent removal of parathyroid tissue during the lymphadenectomy specimen that is the problem rather than deliberate removal of parathyroid glands invaded by the malignant thyroid tissue. This indicates that if better identification of parathyroid tissue intraoperatively were to occur, parathyroid tissue could be preserved in-situ or auto-transplanted, and the incidence of POHP decreased. There are multiple devices either commercially available or under development to address this issue, but they are not yet feasible for widespread use.

The identification of key risk groups in our practice: patients with malignancy, who undergo neck dissection and those who have a large multinodular goiter, allows us to target these groups for specific parathyroid preserving strategies. Alternate strategies of parathyroid tissue identification and preservation should be considered and investigated. Newer technologies such as immunofluorescence are being explored, but are far from widespread use (13). In high risk patients a low threshold for auto transplantation of ischemic parathyroids should be considered. The best techniques for auto transplantation should be standardized and widely taught. The data was not suitable for a regression analysis and this may have limited our ability to identify risk factors. There were few male patients in this study and this may have limited our ability to detect a difference by sex. The investigation of an effect of age may have been limited by the study containing very few patients at the extremes of age. The majority were middle aged. A major shortcoming of this study was the inability to document the incidence of temporary versus permanent hypoparathyroidism in our patients. During the study period, follow up of these patients was not standardized and not all done through the surgical service. Many patients did not have regular repeat iPTH levels and where these were done, we were not always able to retrospectively access the result. Also, the documentation of length of hospital stay and long term adverse outcomes was not available. Improvements in these aspects of the post-operative care pathway as well as more consistent measurement of Vitamin D levels which has been noted to be a cause of postoperative hypocalcaemia(8), are some of the interventions that will flow from the conclusion of this research.

Conclusion

The incidence of postoperative hypoparathyroidism after total thyroidectomy in our unit is 29%. The main risk factors for POHP in our context are large size of the thyroid gland and lymphadenectomy (and specifically the extent of the lymphadenectomy). While the incidence of this complication is within international standards, the adverse clinical impact may be greater in our setting as many patients are not able to access

adequate follow up including appropriate investigations and treatment of POHP and its complications. Every effort should be made to minimise the incidence of POHP.

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