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IS DEVELOPMENT OF HYPOCALCAEMIA A SURROGATE MARKER FOR EXPERIENCE OF OPERATING SURGEON IN THYROIDECTOMIES? A SINGLE CENTRE RETROSPECTIVE ANALYSIS OVER 10 YEARS AND REVIEW OF LITERATURE ON HYPOCALCAEMIA FOLLOWING TOTAL THYROIDECTOMIES

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Abstract

Introduction: Incidence of post thyroidectomy Hypocalcaemia ranges from 5.4% to 83%. We propose that the rate of change in serum calcium measurements (Calcium slope) in the first few hours after surgery is a good predictor of development of subsequent hypocalcaemia. We also analysed the incidence of hypocalcaemia over the years correlating with increasing experience of the surgeon.

Methods: Patients undergoing Thyroid Surgery from 2001-2012 under two thyroid surgeons were identified from a prospectively maintained database. Known Risk factors for hypocalcaemia were identified and recorded for each patient. Serum calcium was measured pre-operatively and post operatively at 6hrs, and 24hrs. Serum Calcium slope values (rate of fall of calcium levels) were calculated for time 0- 6hrs, and for time 0 -24hrs. Patients were divided into those who developed hypocalcaemia and those who did not, and risk factors compared between the two groups. Rates of hypocalcaemia were compared over 10 years as biannual cohorts and as 2 groups 2001 to 2006 Vs. 2007 to 2012

Results:

- From the 237 patients identified from database, 31.22% patients developed hypocalcaemia at 24hrs.
- There was a trend in fall in hypocalcaemia rates each year corresponding to the increased operative experience.
- Calcium slope levels at 6hrs are a good predictor of further hypocalcaemia.

Conclusion: There is a trend towards reduced rates of hypocalcaemia with increasing surgical experience, which may be another risk factor for hypocalcaemia. The magnitude of the early serum calcium slope may be a more useful means for identification of those at risk of developing hypocalcaemia after thyroidectomy.

Introduction

Hypocalcaemia is the single most common complication post thyroid surgery. Incidence ranges from 5.4% to 83%.[1, 2.] The rate of hypocalcaemia is very variable as there is no standard definition available. Several risk factors have been identified, but few studies have looked at effect of surgical experience on rates of hypocalcaemia. Traditionally, thyroidectomy patients remain in hospital for several days.[3]

Resource constraints have led to efforts to perform thyroidectomy on a shorter stay basis. [4] Means to identify patients at risk of hypocalcaemia is required. Routine intraoperative parathyroid hormone measurements may identify patients at risk but are expensive. [5, 6]

An alternative approach may be to determine the rate of change in serum calcium measurements in the first few hours after surgery.

Thyroidectomy for Grave's disease has higher incidence of hypocalcaemia. Refined surgical technique can lower the risk of hypocalcaemia as well. [7] Individual Surgeon experience is significantly associated with complication rates and length of stay for thyroidectomy. Sosa et al demonstrated that surgeons performing 100 or more thyroidectomies over 6-year period had the lowest complication rates when compared with surgeons performing less number of cases. The high-volume surgeons had one third fewer complications from thyroidectomy performed for benign disease and two thirds fewer from thyroidectomies performed for cancer. [8]

Hypoparathyroidism after thyroid surgery is prevented by preserving parathyroid glands in situ and by auto transplanting parathyroid tissue that cannot be preserved. The best way to preserve the blood supply to the parathyroid glands is to ligate individual branches of inferior thyroid artery as close to the gland as possible. [9]

Some studies have shown that total thyroidectomy coupled with central compartment dissection was associated with high incidence of hypocalcaemia. Inferior parathyroid glands are at risk of inadvertent removal or vascular damage during clearance of para-tracheal and pre-tracheal nodes in the central neck. [10]

The capsular dissection technique of mobilization ensures intact parathyroid glands with vascular pedicles. Thomusch et al. noted lateral ligation of inferior thyroid arteries as a strong determinant of hypocalcaemia. [11]

To our knowledge there is no direct comparison of surgeon experience and incidence of hypocalcaemia. We did this retrospective study about the incidence of hypocalcaemia after total thyroidectomies.

Adams et al. found that 36% of patients with an initial negative slope developed hypocalcaemia. These patients had a much steeper negative slope, almost twice that of normocalcaemic patients. [12]

The rate of change of serum calcium may be referred to as the calcium slope. The rate of change from 0-6 hrs from the time of surgery may be a predicting factor for the development of further hypocalcaemia. There are some published literatures regarding the usefulness of this simple measure in predicting the development of hypocalcaemia. We calculated calcium slopes for our patients and correlated the early calcium slope with subsequent development of hypocalcaemia.

Aims

- To find out whether the incidence of hypocalcaemia decreases with the increasing number of cases performed by a surgeon
- Comparison of various risk factors for hypocalcaemia following total thyroidectomy
- Assessment of early calcium slope as a means for early identification patients at risk of hypocalcaemia

Methods

Patients undergoing Thyroid Surgery from 2001-2012 under two thyroid surgeons were identified from a prospectively maintained database.

Inclusion criteria

1. Patients undergoing total thyroidectomies
2. Patient undergoing completion thyroidectomies

Exclusion criteria

1. Patients undergoing hemi thyroidectomies
2. Patients with known hypoparathyroidism or hypocalcaemia

Definitions

Hypocalcaemia is defined as a serum calcium level less than 2.15mol/dl. It is classified as transient if the levels return to normal within 6 months. Permanent hypocalcaemia is defined as hypocalcaemia persisting beyond 6 months requiring regular calcium supplements.

Postoperative serum calcium levels were plotted as a function of time and the slope was defined as an increase or decrease in serum calcium levels during 2 consecutive measurements within 48 hours after operation (within 24 hours and on the second postoperative day).

The rate of change of serum calcium may be referred to as the calcium slope.

Serum calcium slope was calculated using the formula

[Calcium at time #1- calcium at time #0] / [Time #1- time #0]

The incidence of hypocalcaemia is correlated with demographics, indication for surgery and other presumed risk factors for hypocalcaemia like presence of Graves disease, malignancy reoperation (completion thyroidectomy) were recorded for each patient.

Our total thyroidectomy patients usually get discharged after 24hrs after checking calcium levels.

Serum calcium was measured pre-operatively and post operatively at 6hrs, and 24hrs. Serum Calcium slope values were calculated for time 0- 6hrs, and for time 0 -24hrs. These results were obtained from electronic lab results database. Patients were divided into those who developed hypocalcaemia and those who did not, and risk factors compared between the two groups. Rates of hypocalcaemia were compared over the 11 years as biannual cohorts.

All the patients with symptomatic hypoparathyroidism had treatment with oral calcium and vitamin d3 supplements. They were followed up in the clinic and the supplements were gradually withdrawn.

West Suffolk Hospital is a district hospital. We do not have a dedicated endocrine centre but thyroid and parathyroid surgeries are carried out by 2 general surgeons with special interest in endocrine surgery.

All these total thyroidectomies were done by a consultant surgeon and an experienced associate specialist. Both of them are independent practitioners for the duration of the study. Few total thyroidectomies were done by trainees under their supervision. Both of surgeons were fully trained to do total thyroidectomies with adequate numbers.

The parathyroid glands were identified and preserved during surgery. Most of our total thyroidectomy patients will go home on the following morning after checking calcium levels. Patients with hypocalcaemia were treated with oral calcium and vitamin d supplements. Patients with symptomatic hypocalcaemia stayed in the hospital till their symptoms were completely controlled. All our patients were followed up in the clinics in 4 to 6 weeks. Unless they had any issues they were discharged after that follow up.

Statistics

The proportion of risk factors between the normo-calcaemic and hypocalcaemic group was compared using an online statistical tool. It calculates the z-ratio for the significance of the difference between two independent proportions, pa and pb.

For the notation used here,

- na and nb - represent the total numbers of observations in two independent samples A and B
- ka and kb - represent the numbers of observations within each sample that are of particular interest
- pa and pb - represent the proportions ka/na and kb/nb, respectively

Sample A	Sample B	
k_a = 8	k_b = 21	Sample A = Hypocalcaemia Group Sample B = Normocalcaemia Group
n_a = 74	n_b = 163	
p_a = 0.1081	p_b = 0.1288	K = Number of Male patients n = Total Number of Patients in each group
$p_a - p_b$ = -0.0207		
Reset / Calculate	z = -0.451	

Probability	
One-Tail	Two-Tail
0.326	0.652

Figure 1: Comparison of proportion of males between the 2 groups

Sample A	Sample B	
k_a = 39	k_b = 69	Sample A = Hypocalcaemia Group Sample B = Normocalcaemia Group
n_a = 74	n_b = 163	
p_a = 0.527	p_b = 0.4233	K = Number of patients with Graves disease n = Total Number of Patients in each group
$p_a - p_b$ = 0.1037		
Reset / Calculate	z = 1.486	

Probability	
One-Tail	Two-Tail
0.0686	0.1373

Figure 2: Comparison of proportion of Graves disease between the 2 groups

The difference in base line calcium levels between the hypocalcaemia and normocalcaemic groups was compared using t test. Similarly the significance of age between the 2 groups was compared using t test for 2 independent samples.

Data Summary

	A	B	Total
n	74	163	237
$-\Sigma X$	3490	8149	11639
$-\Sigma X^2$	181916	446797	628713
SS	17320.054	39396.993	57125.147
mean	47.1622	49.9939	49.1097

A = Hypocalcaemia Group
B = Normocalcaemia Group
* t test for comparison of age between 2 groups

Results$_Q$

$Mean_a - Mean_b$	t	df	P		
-2.8317	-1.3	235		one-tailed	0.0974375
				two-tailed	0.194875

t-Test Assuming Unequal Sample Variances
[Applicable only to independent samples.]$_Q$

$Mean_a - Mean_b$	t	df	P		
-2.8317	-1.31	142.81		one-tailed	0.096754
				two-tailed	0.193508

Figure 3: Comparison of significance in the difference of age between the 2 groups

Data Summary

	A	B	Total
n	163	74	237
$-\Sigma X$	381.37000	173.67995	555.05000
$-\Sigma X^2$	922.35209	408.50575	1330.8578
SS	30.0633	0.8741	30.9402
mean	2.3397	2.347	2.342

A = Hypocalcaemia Group
B = Normocalcaemia Group
* t test for comparison of baseline calcium levels between 2 groups

Results$_Q$

$Mean_a - Mean_b$	t	df	P		
-0.0073	-0.14	235		one-tailed	0.44439
				two-tailed	0.888780

t-Test Assuming Unequal Sample Variances
[Applicable only to independent samples.]$_Q$

$Mean_a - Mean_b$	t	df	P		
-0.0073	-0.2	202.26		one-tailed	0.4195225
				two-tailed	0.839045

Figure 4: Comparison of significance in the difference of baseline calcium levels between the 2 groups

The mean Ca slopes at 6 hrs between normo-calcaemia and hypocalcaemic patients was compared using Mann-Whitney test.

We also did a correlation between all (Hypocalcaemic and normo-calcaemic patients) the 6hr slopes with the 24 slopes using a Spearman Rank Correlation. Spearman's correlation coefficient, measures the strength of association between two ranked variables.

Similar correlation between all (Hypocalcaemic and normo-calcaemic patients) the 6hr slopes with calcium values at 1 month.

Results

237 were patients identified from the database. 208 out of 237 patients were females and 29 out of 237 were males. 108 out of 237 patients had surgery for Grave's disease. 59 out of 237 had total or completion thyroidectomy for thyroid cancer. 70 patients had total thyroidectomy for symptomatic multi nodular goitre out of total of 237 patients.

There were 208 total thyroidectomies and 29 completion thyroidectomies following initial lobectomy for cancer.

74 out of 237 (31.22%) patients developed hypocalcaemia at 24hrs. Patients with Graves disease had significantly higher incidence of hypocalcaemia (p<0.06). The patients who developed hypocalcaemia were younger than the normo-calcaemia group mean age 47.16yrs Vs 49.99yrs in patients with normo-calcaemia.

Patients who had total thyroidectomy for thyroid cancer had less incidence of hypocalcaemia.

Most of the patients had transient hypocalcaemia. As described in other studies the incidence of permanent hypocalcaemia in our patients is less than 1%. There is progressive fall in the percentage of patients with hypocalcaemia starting from year 2001.The percentage of patients with hypocalcaemia was

- 63.33% in 2001-2002
- 37.14% in 2003-2004
- 31.57% in 2005-2006
- 26.66% in 2007-2008
- 27.65% in 2009-2010
- 11.36% in 2011-2012

We further divided the patients in to two groups (2001 to 2006 & 2007 to 2012). The percentage of patients with hypocalcaemia in 2001 to 2006 group is around 42.72% Vs 22.06% in 2007 to 2012 group. This was statistically significant.

Table 1: Table showing comparison of risk factors between total thyroidectomy patients who did and did not develop hypocalcaemia

Risk Factor	Hypocalcaemic Group (n=74)	Normocalcaemic Group (n =163)	P
Age	47.16	49.99	0.001
Male Sex	8	21	0.32
Graves Disease	39	69	0.06
Thyroid Carcinoma	12	47	0.03(Less incidence of hypocalcaemia)
Baseline calcium (mg/dl)	2.34	2.44	0.41
Total thyroidectomy	71	136	0.91
Completion thyroidectomy	3	26	0.91

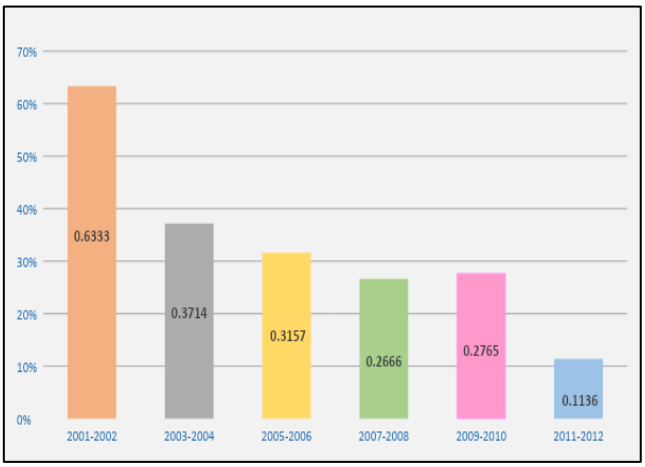

Figure 5: Graph showing incidence of hypocalcaemia yearly from 2001 to 2012

In the above graph we can notice the gradual decline in hypocalcaemia over the years.

We also divided the the patients between 2 groups 2001 to 2006 and 2007 to 2012.We can notice the significant drop in the percentage of hypocalcaemia in the later group.

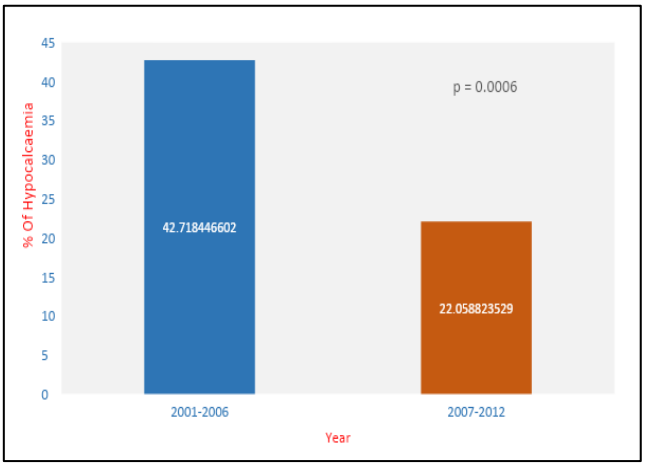

Figure 6: Graph showing incidence of hypocalcaemia in total thyroidectomy patients 2001-2005 and 2006 -2012

Calcium slope

As mentioned earlier the calcium slope is the rate of fall of calcium levels at different time points aft her surgery

Calcium slope at 6 hrs

The mean rate of fall of calcium levels in patients with normo-calcaemia 6hrs after total thyroidectomy was -0.0297.It was -0.0325 in patients who developed hypocalcaemia. This was statistically significant (P<0.0001). That means patients who developed hypocalcaemia has had a fall of .0028 mmol greater than the patients who did not develop hypocalcaemia. This fall was statistically significant

Calcium slope at 24 hrs

Similarly the mean rate of fall of calcium at 24 hrs in patients with normocalcaemia was -0.00738. It was -0.0152 in patients who developed hypocalcaemia. The fall in calcium levels was about 0.00782 mmols greater than the normo-calcaemia group at 24 hrs. This fall in calcium levels were statistically significant. The fall in calcium levels was more dramatic after 24 hrs after surgery. This was predicted by early fall at 6 hrs after surgery

Table 2: Table showing comparison of calcium slope (rate of fall of calcium) at 6hrs,and 24hrs between thyroidectomy patients who did and did not develop hypocalcaemia

	Normal 6hrs	Normal 24hrs	Hypo 6hrs	Hypo 24hrs
Sample size	163	163	75	75
Mean Slope	-0.0297	-0.00738	-0.0325	-0.0152
Standard Dev	0.116	0.026	0.028	0.016
Standard Error	0.009	0.002	0.003	0.001

This means calcium slope (the rate of fall in calcium levels) at 6 hrs is just as useful as at 24hrs at predicting subsequent hypocalcaemia and therefore can be used to identify patients at increased risk as well as identifying those at low risk who can be safely discharged early.

We did a correlation between ALL the 6hr slopes with the 24 slopes using a Spearman Rank Correlation (Spearman r=0.577) The two-tailed P value is <0.0001. This indicates that the 6 hourly slopes strongly correlate with the 24-hour slope.

We did a correlation between ALL the 6hr slopes with calcium values at 1 month using a Spearman Rank Correlation (Spearman r=0.2213). The two-tailed P value is 0.0233, which is considered significant.

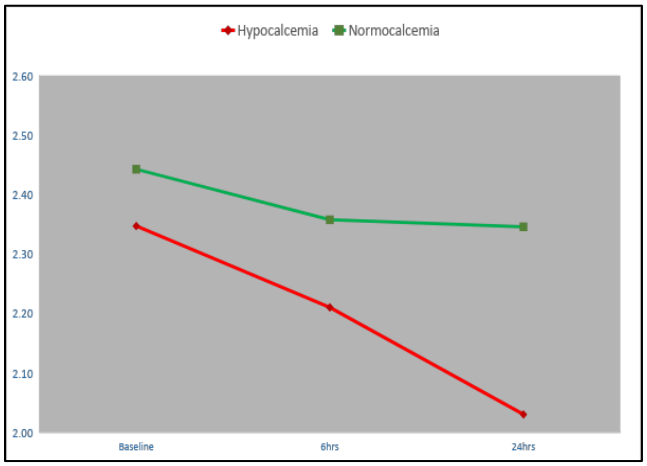

Figure 7: Graph showing calcium levels between patients with & without hypocalcaemia at different time points

In a nutshell the rate of fall of calcium levels was more in the hypocalcaemia group when compared with normo-calcaemia group. Patients who became hypocalcaemic had a much sharper fall in serum calcium levels over the first 6 hours post-operatively. There was a significant linear correlation between slope over the first 6 hours and serum adjusted calcium value at 24hours.Patients who became hypocalcaemic at 24 hours had a more negative serum calcium slope over the first 6 post-operative hour

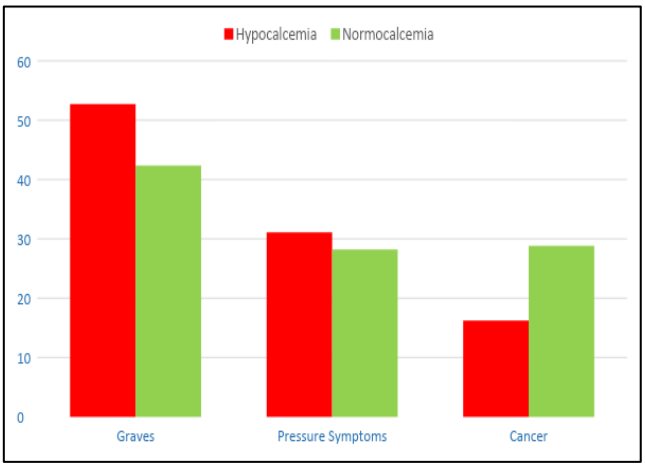

Figure 8: Graph showing incidence of hypocalcaemia in patients who had thyroidectomy for various indications.

We can notice from the above graph that maximum number of hypocalcaemia patients has had surgery for Graves disease. The patients who had thyroidectomy for cancer had less incidence of hypocalcaemia. Those who had thyroidectomy for pressure symptoms (mostly symptomatic multi nodular goitre) has had almost equal incidence of hypocalcaemia when compared with patients who did not develop hypocalcaemia

Discussion and review of literature

Need for standard definition for hypocalcaemia post thyroidectomy

The reported incidence of hypocalcaemia is widely variable. This may be as a result of highly variable definitions used for defining hypocalcaemia.

Jessie Wu et on reviewing 19 articles published since 2008 about post operative hypocalcaemia noted transient hypocalcaemia rate of 5 to 71%. The rate of permanent hypocalcaemia ranged from 0 to 3-5%. The biochemical definition of hypocalcaemia ranged from 1.8mmol/l to 2.1mmo/l. The definition of transient hypocalcaemia ranged from post operative hypocalcaemia that resolved in less than 6 months and up to 12 months in some studies.

26% of publications failed to give any definitions for hypocalcaemia, transient and permanent hypoparathyroidism. Corrected calcium, total calcium and

ionized calcium have all been included in the definitions in different studies. This review stresses the importance of having a standard definition for hypocalcaemia, transient and permanent hypocalcaemia.

In our study we used a definition of corrected calcium levels less than 2.15 for hypocalcaemia. It is defined as transient if it settles before 6 months and as permanent if it lasts beyond 6 months[49].

Risk factors for development of hypocalcaemia after total thyroidectomy

The most common problem encountered after total thyroidectomy is hypocalcaemia. It can be temporary or permanent. Temporary hypocalcaemia can be biochemical or symptomatic hypocalcaemia which usually develops 24 to 48 hours after the thyroidectomy [13].

Age at operation

Both young and old age has been related to the risk of developing hypocalcaemia after total thyroidectiomy.

Erbil *et al.*[14] and Dedivitis *et al.*[15] observed that elderly patients have significant risk factor for post-operative hypocalcaemia. [14] Ageing is said to be associated with decreased intestinal calcium absorption, decreased renal 1α hydroxylase, decreased dermal synthesis of vitamin D. These contribute to susceptibility to hypocalcaemia after total thyroidectomy.

Our study does not concur with these findings. Our patients with hypocalcaemia were younger mean age 47.16yrs Vs 49.99yrs in patients with normo-calcaemia.

Bhattacharyya et al reported that younger age was statistically associated with an increased incidence of hypocalcaemia[16]

Identification and preservation of parathyroid glands

Lesser the number of parathyroid saved, the more the chances of developing post total thyroidectomy hypocalcaemia. Some authors have suggested that at least 3 parathyroids are to be saved while others opined that 2 functional glands are enough to prevent post total thyroidectomy hypocalcaemia. [17,18] We do not have the data to comment on this finding.

The preservation of parathyroid tissue is mandatory to obviate the terrible consequences of permanent hypoparathyroidsm. Parathyroid glands should remain in situ with an intact blood supply[19]. Parathyroid auto transplantation can be considered when parathyroid glands are resected or devascularised. If incidental excision or devascularization of the parathyroid glands is noted, parathyroid autotransplantation may reduce the occurrence of permanent hypocalcaemia among patients with postoperative hypocalcemia[17]

In bilateral thyroid surgery, peripheral ligation of the inferior thyroid artery at the thyroid capsule should be favoured over central ligation[11]

Bergamaschi and et al found that thyroidectomy with node dissection and completion thyroidectomy are risk factors for permanent Hypoparathyroidism.[20]

Inferior parathyroid glands are at risk of inadvertent removal or vascular damage during clearance of para tracheal and pre-tracheal nodes in the central neck[21]

In our study completion thyroidectomy was not associated with increased risk hypocalcaemia but our numbers are not high enough.

Experience of the surgeon and incidence of hypocalcaemia

The risk of complications following total thyroidectomy is also related to the experience of the operating surgeon and the number of operations performed in that particular hospital.

Our hospital is not a high volume centre. Total number of thyroid operations average at around 50 per year. Half of these will be total thyroidectomies. There is a trend towards lowered incidence of hypocalcaemia

In our study we noticed that the incidence of hypocalcaemia has been dropping over the period of 10 years. It is significantly less in 2007 to 2012 when compared with 2001 to 2006 (Almost 45% Vs 25%)

In a multivariate analysis involving more than 7200 thyroidectomies by Thomusch O et al centres with volumes of more than 150 cases per year had better extent of resection and lower incidence of complications including hypocalcaemia[23]

In a cross sectional analysis of patients who had undergone thyroidectomies between 1991 and 1996 in Maryland Sosa JA etal found that the highest-volume surgeons (who had performed more than 100 cases in 4 year period) performed the greatest proportion of total thyroidectomies. After adjusting for case mix and hospital volume, highest-volume surgeons had the shortest length of stay and the lowest complication rate. Length of stay and complications were more determined by surgeon experience than hospital volume, which had no consistent association with outcomes[8].

Junior surgeons will need adequate supervision to minimise the chances of complications. Emre AU et al reported that the complications of thyroid surgery done by the residents are similar to that of the consultants when they are adequately supervised. Therefore trainees can

perform thyroid surgery safely under adequate supervision by an experienced surgeon[24]. Reeves Ts et al compared the outcome of Six hundred and fifty patients undergoing total thyroidectomy by two surgeons over a 5-year period in the endocrine surgical unit at Royal North Shore Hospital, St Leonards, Australia, with 120 patients undergoing total thyroidectomy by seven provincial surgeons who were former trainees in the unit. Each of the seven surgeons in provincial practice performed only between 2 and 16 thyroidectomies annually. The percentage of total thyroidectomies for benign and malignant disease was identical for both the endocrine surgical unit and provincial center groups (44%). There was no difference in the incidence of recurrent laryngeal nerve palsy, permanent hypoparathyroidism, or postoperative bleeding between the two groups[42].

Total thyroidectomy for Thyroid cancer

Apart from the neck dissection thyroidectomy for cancer itself is an independent risk factor for development of hypocalcaemia. Malignancy tends to be treated with a more aggressive approach to thyroid surgery, thereby leading to incidental parathyroidectomy and hypocalcemia[22]

The altered anatomy of patients with massive thyroid cancer could increase the likelihood of parathyroid tissue removal during total thyroidectomy.

In our study we did not get this finding. In fact the patients who had thyroidectomy for cancer had less incidence of hypocalcaemia. This may be related to doing straight forward cases with advanced cases being referred to high volume centres.

Reoperation

Reoperation may increase risk of iatrogenic injury to the parathyroid glands by ten times [11]. The incidence of transient hypocalcaemia ranges from 3% to 44.1%, and permanent, from 0 to 11%[17-19]. Inflammation, bleeding, friability of tissues and adhesion structures are factors that hinder the identification of parathyroid glands and pose a higher risk of injury to the parathyroid vascular pedicle[40,41].

In our series we did not have the numbers to demonstrate significant difference in the incidence of hypocalcaemia in reoperation cases. The reoperations were mostly completion thyroidectomies were done for thyroid cancers detected in lobectomies.

Total thyroidectomy for Graves disease

Hypocalcaemia in Graves disease is multifactorial. The Graves disease patients are susceptible to hypocalcaemia for the following reasons.

Patients who had undergone total thyroidectomy for Graves disease has got increased incidence of post-operative hypocalcaemia. In our study 39 out of 108 patients with Graves disease developed hypocalcaemia. This finding correlates with the evidence available in the literature.[11] Graves' disease has been associated with both transient and permanent hypocalcaemia. This may be due to increased bone turnover and difficult operations owing to increased vascularity of the thyroid gland in Graves disease[25.] The increased bone turn over is related to the following observations in animal models.

In 1891 when von Recklinghausen described the "worm eaten" appearance of the long bones of a young woman who died from hyperthyroidism. Following findings were found in the animal research.

- Thyroid hormone directly stimulates bone resorption in organ culture. This action may be mediated by a nuclear triiodothyronine (T3) receptor which has been found in rat and human osteoblast cell lines[50,51]
- Thyroid-stimulating hormone (TSH) may also appear to have a direct effect on bone formation and bone resorption, mediated via the TSH receptor on osteoblast and osteoclast precursors[52]

In patients with Graves disease preoperative treatment with beta-blockers showed a borderline association with vitamin D treatment at discharge and a significant association with vitamin D treatment at 6 weeks after surgery. Patients with lower preoperative serum calcium levels had an increased risk of needing postoperative treatment with i. v. calcium.[43]

In Graves' disease, raised preoperative markers of bone turnover in patients with vitamin D deficiency or insufficiency[14], and higher preoperative alkaline phosphatase and thyroid-binding inhibitory immunoglobulin levels[26] were associated with transient hypocalcaemia.

Longer duration of Graves disease is reported to be associated with increased risk of hypocalcaemia after thyroidectomy[14]. Rapid control of Graves disease has been reported as a risk factor for hypocalcaemia as well[25].

In a recent meta-analysis published in BJS, higher pre op TSH and high levels of pre op thyroid auto antibodies are not associated with risk of hypocalcaemia[45].

Post op complications

In a Swedish Multicenter Study of 1,157 patients operated by P. Hallgrimsson et al reoperation for bleeding was associated with increased risk of hypocalcaemia. Postoperative bleeding could be a marker for a more difficult operation but also for inferior preoperative treatment. It is also possible that reoperation per se

confers a risk of inadvertent damage to the parathyroid glands[43]

Post operative wound infection has been reported to be associated with development of hypocalcaemia[43,46.]

Female sex

Thyroid diseases requiring surgery are much more common in females. Female sex itself is a predictor of hypocalcaemia after total thyroidectomies. In our study we had very few male patients to get any statistical significance.

Lower vitamin D levels in women is one of the many proposed causes for this effect [26]

In an observational study of 223 patients done by Yamashita H et al, the most significant finding was a lower serum 25 (OH) D concentration in the women than in men [26]. This might account for the increased incidence of hypocalcaemia in females after total thyroidectomy.

Vitamin D deficiency

The relationship between the development of hypocalcaemia after thyroidectomy and vitamin D deficiency is controversial. There are few studies suggesting the increased risk of hypocalcaemia in vitamin D deficiency. [27]

This finding supports routine vitamin D measurement, particularly in high-risk groups such as those with dark skin, malabsorption, the elderly and obese individuals[28]. However these tests are not cheap to run routinely.

Some recent studies did not find any correlation between development of hypocalcaemia and pre-operative vitamin D levels. As per Griffin TP et al there was no correlation between vitamin D levels and risk of postoperative hypocalcemia[47]. Similarly Lin Y et al did not find any increase in the rates of biochemical or symptomatic hypocalcaemia in patients with vitamin D deficiency.[48]

Serum calcium slope

The rate of change of calcium levels from base line to different time points is called calcium slope. Previous studies have shown that the rate of change of serum calcium over the first 24 hours following thyroid surgery can be used to identify patients at risk of hypocalcaemia[29,30]. Adams et al performed a retrospective review of their experience in patients undergoing thyroid or parathyroid surgery[30]. In the thyroid surgery group, they also observed that patients with an initial positive slope never developed hypocalcaemia. However, only 27% of patients had an initial positive slope. They also noted that 36% of patients with an initial negative slope developed hypocalcaemia. These patients had a much steeper negative slope, almost twice that of normo-calcaemia patients[30].

These results indicate that an initial up sloping postoperative calcium curve based on two early postoperative calcium measurements is strongly predictive of a stable postoperative calcium level, and a steeply down sloping initial calcium curve is worrisome for eventual hypocalcaemia.

We had similar findings in our study. Patients who had hypocalcaemia had significant greater fall in calcium levels in in the first 6 hours after surgery when compared to patients with normo-calcaemia. Similarly significantly greater fall in calcium levels were noted at 24 hours after total thyroidectomy as well. The rate of fall of calcium levels were more in the hypocalcaemia group when compared with normo-calcaemia group. Patients who became hypocalcaemic had a much sharper fall in serum calcium levels over the first 6 hours post-operatively. There was a significant linear correlation between slope over the first 6 hours and serum adjusted calcium value at 24hours. Patients who became hypocalcaemic at 24 hours had a more negative serum calcium slope over the first 6 post-operative hours. Walsh SR et al in their study concluded that serum calcium slope may be useful in identifying patients suitable for early discharge following thyroid surgery[39].

Graf At et al in their retrospective study concluded that the combination of the early calcium slope and single early measurement of intact parathyroid hormone represents the safest method of assessing risk and identifying those patients who can be discharged on the day of surgery[45].

Lower intra operative and lower pre-operative calcium levels have also been reported to be associated with transient hypocalcaemia after total thyroidectomies[44].

Thus doing calcium levels in the early post-operative period and noticing the fall of calcium levels is a good predictor for development of subsequent hypocalcaemia. This can facilitate early discharge.

Other ways of predicting development of hypocalcaemia

Intra operative para thyroid hormone level measurement can predict the development of hypocalcaemia[31]

Reduced intra operative PTH levels can predict the need for parathyroid gland auto transplantation[36]

Some patients with a normal intraoperative PTH level may subsequently develop transient hypocalcaemia[32]

In patients with a normal postoperative PTH concentration, post-thyroidectomy hypocalcaemia is usually self-limiting[31,32] probably caused by vitamin D deficiency, haemodilution and secondary hyperparathyroidism.

Some patients remain normo-calcaemic despite low postoperative PTH levels possibly owing to medications that increase renal calcium reabsorption[33,34]

As per Barczyński M et al PTH measurements at various time points showed that a single PTH measurement 4 hours after surgery may be more accurate than earlier measurements in predicting transient hypocalcaemia[35]

Study by Hermann M et al noted that a PTH level of 6·0 pg/ml or less at 3 h following surgery had a sensitivity and PPV of 100 and 15 per cent respectively for predicting permanent hypocalcaemia.

In patients with transient hypocalcaemia after surgery, a PTH concentration of 12 pg/ml or less[37] and undetectable PTH at 1 month [38] were associated with the development of permanent hypocalcaemia.

Limitations of the study

The data was collected retrospectively from the electronic records. There was some missing data. More complicated cases like retrosternal thyroid got referred to tertiary centres. We did not have the data about the specific identification and preservation of the parathyroid glands in all the patients. Few of our patients also had central neck dissections. The numbers were very limited to make any comparisons. The rates of hypocalcaemia may also be higher because of disproportionate numbers of Graves disease patients.

Future study

Prospective study with all available data and the status of identification of parathyroid glands, auto transplantation of accidentally removed parathyroid glands and measurement of parathormone levels will be interesting. It would also be interesting to see whether the incidence of hypocalcaemia rates plateaus in few years' time with increasing experience of the surgeons over the years.

Conclusion

There is a trend towards reduced rates of hypocalcaemia with increasing surgical experience, which may be another risk factor for hypocalcaemia. It is an indirect marker of operating surgeon's experience. The magnitude of the early serum calcium slope may be a more useful means for identification of those at risk of developing hypocalcaemia. Surgery for hyperthyroidism is an independent risk factor for development of hypocalcaemia.

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