European Journal of Molecular & Clinical Medicine

ISSN 2515-8260 Volume 09, Issue 03, 2022

ORIGINAL RESEARCH

Predictors of Hypocalcaemia Following Thyroidectomy

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ABSTRACT

Background: Hypocalcaemia is a common complication following thyroid surgery, cause of which is multifactorial. The aim of this study was to identify risk factors for development of post-operative hypocalcaemia in cases of total thyroidectomy, near total thyroidectomy, and completion thyroidectomy with or without neck dissection.

Materials and Methods: From 1st November 2020 to 31st October 2021, 40 consecutive patients undergoing total thyroidectomy, near-total, sub-total or completion thyroidectomy at Govt Medical College & Hospital, Suryapet were enrolled in this prospective study, longitudinal, cohort study. The primary endpoints were the occurrence of post-operative hypocalcaemia as by defined as a nadir corrected serum calcium less than 8.0 mg/dL or symptomatic hypocalcaemia.

Results: 40 patients were analyzed. The average age was 42.53±15.86 years with 86.7% female. The most common indications for surgery were benign thyroid disease (80%). 27 patients (67.5%) experienced postoperative hypocalcaemia with 14 (35 %) requiring intravenous calcium infusion. Risk factors for postoperative hypocalcaemia included inadvertent parathyroid removal during surgery further exemplified by the fact that there is lesser incidence of post-operative hypocalcaemia in patients undergoing near total thyroidectomy.

Conclusion: Patients undergoing total thyroidectomy and in whom parathyroid could not be identified and preserved or auto transplanted may benefit from more vigilant pre-operative preparation and postoperative calcium and vitamin D supplementation.

Keywords: Thyroidectomy, Hypocalcaemia, Risk Factors, Predictors, Complications.

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INTRODUCTION

Temporary hypocalcemia has been reported to occur in 1.6% to 50% of the patients undergoing bilateral thyroid resection. Permanent hypoparathyroidism results in 0% to 13% of patients after bilateral thyroid surgery. A postoperative decrease of serum calcium is frequently observed within 2 to 5 days after a total or subtotal thyroidectomy, requiring exogenous replacement therapy to alleviate clinical symptoms. Post-operative hypocalcemia is a major concern following thyroid surgery. It often extends the duration of the hospital stay and the need for biochemical tests, when severe; it can lead to serious complications and require intravenous therapy to alleviate the clinical symptoms.[1]

Temporary hypocalcaemia has been reported to occur in 1.6 – 50 percent of the patients undergoing bilateral thyroid resection. Permanent hypoparathyroidism results in 0 – 13 percent of patients after bilateral thyroid surgery.[2]

A postoperative decrease of serum calcium is frequently observed within 2 to 5 days after a total or subtotal thyroidectomy, requiring exogenous replacement therapy to alleviate clinical symptoms.[3]

Post-operative hypocalcaemia is a major concern following thyroid surgery. It often extends the duration of the hospital stay and the need for biochemical tests, when severe, it can lead to serious complications and require intravenous therapy to alleviate the clinical symptoms.[2]
To minimize complications and allow for early discharge, we must be able to identify cohort of patients who are likely to develop symptoms of hypocalcaemia. Those at risk would not be candidates for early discharge. Additionally, patients requiring supplemental calcium, and closer monitoring to prevent symptoms, could be identified earlier.[4-10]
The purpose of this study is to evaluate calcium levels pre and post thyroidectomy and provide a statistical analysis.

- To evaluate calcium levels pre and post total thyroidectomy.
- To follow up the patients up to immediate postoperative period in patients undergoing thyroidectomy i.e. up to discharge.
- To compare the impact of age, sex, BMI, biochemical workup of the patient, surgical procedure and pathologic findings on postoperative hypocalcaemia after Total thyroidectomy or Near total thyroidectomy.
- To determine which risk factors are important for hypocalcaemia incidence.
- Statistical analysis of the gathered data.

Study Design

From 1st November 2020 to 31stOctober 2021, 30 consecutive patients undergoing total thyroidectomy, near-total, sub-total or completion thyroidectomy with or without neck dissection at Govt Medical College & Hospital were enrolled in this prospective study, longitudinal, cohort study.
Patients with end-stage renal disease, as determined from the medical record, were excluded. The study was approved by the Govt Medical College & Hospital, Suryapet institutional review board. Verbal and written informed consent was obtained for all participants in the study at the time of enrollment.
The preoperative evaluation comprised basic examination (disease history examination, physical examination), advanced examination (thyroid function test), imaging examination (ultrasonography, chest X-ray) and fine-needle aspiration cytology (FNAC).
Any patients with signs or symptoms of hypocalcaemia were treated with intravenous calcium gluconate replacement.Patientswere started on twice-daily oral calcium citrate 1,200 mg with vitamin D 500 IU on development of asymptomatic or symptomatic hypocalcaemia and continuedonthis supplementation at discharge until outpatient follow-up. Patients with asymptomatic hypocalcaemia were maintained on oral therapy alone.
All 30 patients were classified according to age, sex, BMI, volume of gland, thyroid status of the patient, pre-operative ALP and intra-operative identification and preservation of parathyroid. Pathologic findings for each patient were also recorded. All the cases were followed up to discharge.

Inclusion criteria:

- Patients admitted and positively diagnosed as having thyroid swellings requiring surgical management and willing for surgery.
- Patients undergoing total thyroidectomy, near-total, sub-total thyroidectomy with or without neck dissection.
- Patients undergoing Completion Thyroidectomy. Indications for completion thyroidectomy were patients who had undergone hemithyroidectomy or near-total or sub-total thyroidectomy, and presented with recurrence or whose histopathological report came as malignancy.

Exclusion criteria:

- Patients who were undergoing hemithyroidectomy or lobectomy in the current time period.
- Complications which cannot be attributed to surgery due to natural course of the disease.
- Previous neck irradiation
- Concomitant parathyroid diseases.
- End-stage renal disease.

General anesthesia was used in all cases. Thyroidectomy was undertaken through a cervical incision. In each procedure, the attending surgeon attempted to identify all parathyroid glands and assess their individual viability. Marginally viable glands were auto transplanted in the sternocleidomastoid muscle using well- established techniques. Prophylactic lymph node dissections were not performed.

Serum calcium was checked at 8 am daily post-operatively till discharge. Hypocalcaemia was defined as corrected serum calcium less than 8 mg/dL. Patients with symptomatic hypocalcaemia were those with reported paresthesia, perioral numbness, cramping and positive Chvostek's sign and Trousseau's sign. Throughout the hospitalization, patients were checked for signs and symptoms of hypocalcaemia.

Statistical Analysis

Patients who developed post-operative hypocalcaemia (asymptomatic and symptomatic) were included in group 2 and those who did not develop post-operative hypocalcaemia were in group1.

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean SD (Min-Max) and results on categorical measurements are presented in Number (%).

RESULTS

Table 1: Age distribution of patients studied

Age in years	No.ofpatients	%
21-30	16	40
31-40	3	7.5
41-50	9	22.5
51-60	6	15
61-70	3	7.5
>70	3	7.5
Total	40	100.0

Table 2: Gender distribution of patients studied

Gender	No.ofpatients	%
Female	31	77.5
Male	9	22.5
Total	40	100.0

Table 3: Distribution of height and Weight in patients studied

	No.ofpatients (n=30)	%	Mean ± SD
Height(cm)			
<150	9	22.5	

151-160	22	55	155.60±5.06
161-170	9	22.5	
Weight(kg)			
41-50	20	50	51.43±5.56
51-60	17	42.5	
61-70	3	7.5	

Table 4: BMI (kg/m2) distribution of patients studied

BMI (kg/m^2)	**No. of patients**	**%**
<18.5	4	10
18.5-25	36	90
25-30	0	0.0
>30	0	0.0
Total	40	100.0

Each patient underwent thyroid function test, preoperative evaluation of serum calcium and serum albumin and renal function tests.

Table 5: Thyroid Status distribution of patients studied

ThyroidStatus	**No.ofpatients**	**%**
Euthyroid	36	90
Hyperthyroid	4	10
Total	30	100.0

Operative Approach

All operations were performed by staff surgeons or senior residents. The surgical type included total thyroidectomy with or without bilateral or unilateral neck dissection, near-total thyroidectomy, sub-total thyroidectomy.

Table 5: Various surgeries included in the study

Operation	**No.ofpatients**	**%**
Total Thyroidectomy	28	70
NearTotalThyroidectomy	4	10
TotalThyroidectomywithBilateralMRND	3	7.5
TotalThyroidectomywithUnilateralMRND	3	7.5
CompletionThyroidectomy	2	5
Total	40	100.0

The mean (±SD) age for all patients was 42.53±15.86 years. The female/male ratio was 6.5/1 (n= 28/4). The mean (±SD) height and weight for all patients were 155.60±5.06 cm and 51.43±5.56 kg respectively. The means (±SD) for serum albumin, creatinine, hemoglobin, white blood count and alkaline phosphatase, were 4.12±0.39 g/dL, 0.83±0.16 mg/dL, 11.80±1.21 g/dL, 7373.33±2529.13 cells/cumm, and 69.67±22.80 U/L respectively. The postoperative serum calcium level was lower than the preoperative serum calcium level (7.50±0.97 mg/dL vs 8.96±0.72 mg/dL, P <0.001).

Total thyroidectomy was done in 28 (70%) patients, near-total thyroidectomy was done in 4 (10%) patients, Total Thyroidectomy with Bilateral MRND was done in 2 (6.7%) patients, Total Thyroidectomy with Unilateral MRND was done in 3 (7.5 %) patients and completion thyroidectomy was done in 2 (5%).

Majority of patients (38 i.e. 95%) were euthyroid clinically and biochemically before operation, 2(5%) patient was hyperthyroid before surgery.
Parathyroid was preserved or auto-transplanted in 28 (70%) and 2 (5%) patients respectively. Incidental parathyroidectomy was done in 10 (25%) patients.
There was no operative mortality. There was no incidence of transient vocal cord paralysis. Of all the thyroidectomies, the tissue diagnosis was found to be benign in 36 (90%) patients and malignant in 4 (10%) patients.

Table 6: Parathyroid gland identification and preservation vs. incidental parathyroidectomy

Parathyroid	**No. ofpatients**	**%**
No	10	2.5
Yes	28	70
Autotransplanted	2	0.5
Total	40	100.0

Evaluation of patients according to postoperative hypocalcaemia
18 (45%) patients did not develop post-operative hypocalcaemia. 12 (30%) patients developed hypocalcaemia out of which 10 (25%) patients had asymptomatic hypocalcaemia and 10 (25%) had symptomatic hypocalcaemia.

Table 7: Post-op Hypocalcaemia in patients studied

Post-opHypocalcaemia	**No.ofpatients**	**%**
No	18	45
Asymptomatic	10	25
Symptomatic	12	30
Total	40	100.0

Majority of patients developed hypocalcaemia, asymptomatic or symptomatic, on post-operative day 1 (30%), followed by post-operative day 2 and 3.

Table 8: Post-op day of development of Hypocalcaemia

Post-op day ofdevelopmentofHypocalcaemia	**No. of patients**	**%**
1	13	32.5
2	5	12.5
3	5	12.5
5	1	2.5
NA	16	40
Total	40	100.

Table 9: Comparison of clinical variables of patients studied in relation to incidence of Hypocalcaemia

Variables	**Post-op development ofHypocalcaemia**		**Total**	**P value**
	No	**Yes**		
Ageinyears	40.08±14.9	44.17±16.68	42.53±15.86	0.499
Height(cm)	156.25±3.89	155.17±5.78	155.60±5.06	0.575
Weight(kg)	52.42±5.20	50.78±5.84	51.43±5.56	0.438
BMI(kg/m^2)	21.39±1.53	21.04±2.03	21.18±1.83	0.613

There was no significant difference in pre-operative hemoglobin, albumin, white blood count, serum creatinine, alkaline phosphatase and thyroid gland volume in group 1 and group 2.

Table 10: Comparison of study variables of patients studied in relation to incidence of Hypocalcaemia

Variables	Post-opdevelopment of Hypocalcaemia		Total	P value
	No	Yes		
Volume of thegland	0.14±0.21	0.13±0.13	0.13±0.16	0.816
Albumin(g/dL)	4.12±0.32	4.13±0.44	4.12±0.39	0.940
Hemoglobin(g/dl)	11.90±1.03	11.74±1.34	11.80±1.21	0.727
Total Count(cells/cumm)	8008.33±2528.55	6950.00±2510.04	7373.33±2529.13	0.269
SerumCreatinine(mg/dl)	0.87±0.16	0.81±0.17	0.83±0.16	0.375
ALP(U/L)	68.25±23.29	70.61±23.10	69.67±22.8	0.787

Student t test

Thyroid surgery was done for benign condition in 32 (80%) patients and for malignant conditions in 8 (20%) patients; there was found to be no difference statistically between development of post-operative hypocalcaemia and tissue diagnosis.

Table 11: Tissue Diagnosis of patients studied in relation to incidence of Hypocalcaemia

Tissue Diagnosis	Post-op development ofHypocalcaemia		Total
	No	Yes	
Benign	14(82.35%)	16(69.5%)	30(75%)
Malignant	3(7.5%)	7(30.5%)	10(25%)
Total	17(100%)	23(100%)	40(100%)

Majority of patients (39 i.e. 97.5%) in the study were euthyroid before surgery; no difference was found statistically between patients with hyperthyroidism and post- operative hypocalcaemia. Preservation of parathyroid was done in 28 (70%) patients and there was found to be lesser incidence of post-operative hypocalcaemia in these patients.

Table 12: Parathyroid gland preservation of patients studied in relation to incidence of Hypocalcaemia

Parathyroid	Post-op development of Hypocalcaemia		Total
	No	Yes	
No	4(23.5%)	9(39.1%)	13(32.5%)
Yes	13(76.4%)	14(60.9%)	27(67.5%)
Total	17(100%)	23(100%)	40(100%)

Various procedures performed and the incidence of post-operative hypocalcaemia. There was found to be lesser incidence of post-operative hypocalcaemia in patients undergoing near total thyroidectomy. However, there was no statistically significant increase in incidence of

post-operative hypocalcaemia in patients who underwent total thyroidectomy with neck dissection.

Table 13: Incidence of post-operative hypocalcaemia in relation to surgical procedure

Procedure	Post-opHypocalcaemia(no. of cases)	Post-op NO hypokalemia (no. of cases)	Total	P value
Totalthyroidectomy	17	11	28	0.5
Total thyroidectomywith B/LMRND	4	0	4	0.23
Total thyroidectomywith U/LMRND	1	2	3	0.76
Near totalthyroidectomy	0	4	4	0.02
CompletionThyroidectomy	1	0	1	0.4
Total	23	17		

Post-operative hospital stay was significantly longer in group 3 (mean ± SD 6.50±2.60days) than in group 1 (mean ± SD 4.00±0.74 days) with P = 0.003.

DISCUSSION

Postoperative hypocalcaemia is a major concern after thyroid operation. It often lengthens the duration of hospitalization and the need for biochemical tests, and it significantly increases the overall cost of a thyroidectomy. When severe, it can lead to serious complications and requires IV therapy to alleviate clinical symptoms and prevent serious complications. In this study, postoperative asymptomatic and symptomatic hypocalcaemia were observed in 26.7% and 33.3% of patients, respectively, in our series. The most severe symptoms—cardiac arrhythmias, spasm, and stridor—were not seen in our series.

Temporary hypocalcaemia has been reported to occur in 1.6-50% of the patients after bilateral thyroidectomy. Permanent hypoparathyroidism results in 0-13 % of patients after bilateral thyroid surgery.[1]

Various factors account for these differences in the literature, such as the definition of hypocalcaemia, the type of disease, and the surgical technique. Among potential factors causing this decrease in serum calcium, there are post-operative hemodilution and calcitonin release.[1]

A moderate, asymptomatic hypocalcaemia is usually observed within 12 hours following unilateral or bilateral thyroidectomy, is associated with serum phosphorus decrease, and recovers spontaneously within 24 hours in most patients. Perioperative hemodilution may be responsible for this decrease. This hypocalcaemia is self-limited, usually asymptomatic, and does not require supplementation.1 In our study, there was continued hypocalcaemia, asymptomatic or symptomatic, post-operatively for more than 48 hours from development of hypocalcaemia.

Elevation of serum calcitonin (calcitonin leak), secondary to manipulation of the thyroid, was suspected to participate in this calcium decrease, but this was not confirmed in further studies.[1]

Preoperative hyperthyroid status is associated with decreased gastrointestinal calcium absorption and increased osteoclast activity, with increased bone resorption to maintain serum calcium levels.[1] Wingert and colleagues found that risk for transient hypocalcaemia after thyroid operation for Graves' disease is 20 times higher than in other groups. However, in this study no difference was found statistically between patients with hyperthyroidism and post-operative hypocalcaemia.

The serum calcium generally reaches its nadir within 48 hours of surgery.[1] In this study post-operative hypocalcaemia developed 1.89±1.13 day after surgery.

The risk of hypocalcaemia in hyperthyroid patients is correlated more closely with the pre-treatment serum levels of free thyroxine and with markers of bone turnover rate, such as serum alkaline phosphatase levels.[1] However, in this study no statistically significant difference was found between serum alkaline phosphatase and development of post-operative hypocalcaemia.

It is clear that impaired parathyroid function is the major contributing factor for clinically relevant hypocalcaemia. Proper surgical technique is of utmost importance in preserving viable parathyroid glands and several factors have been associated with impaired post-operative function. There is a risk of iatrogenic injury to the parathyroids, with biopsy of all the glands necessarily involves the risk of parathyroid gland injury. Susceptibility of parathyroid glands to injury during neck dissection mainly resides in their widely variable anatomical position, their relationship with the thyroid gland, and intheir very delicate vascular supply. A higher incidence of postoperative hypocalcaemia is seen after total thyroidectomy versus subtotal thyroidectomy. Other factors associated include central neck dissection, reoperative cases, surgery for substernal goiter, surgery for carcinoma and surgery for Grave's disease.1 In the present study, there was found to be lesser incidence of post-operative hypocalcaemia in patients undergoing near-total thyroidectomy than patients who underwent total thyroidectomy with or without neck dissection. This, emphasizes the need for parathyroid preservation in case of bilateral thyroidectomy.

Despite the efforts of the surgeon, inadvertent parathyroid removal during thyroidectomy has been reported in 9-15 % of the cases, even in experienced centers according to recent reports. Identifying and dissecting the parathyroid glands during thyroidectomy does not guarantee viability.[1] In this study identification and preservation of parathyroid was done in 28 (70%) patients and there was found to be lesser incidence of post-operative hypocalcaemia in these patients.

In the absence of any reliable predictors of clinically relevant hypocalcaemia after bilateral thyroid resection, prolonged hospitalization to monitor calcium levels has been considered the standard of care. Conversely current health-care practices encourage shorter hospitalization to reduce costs. For this reason there has been a great deal of interest in identifying peri-operative factors that can predict the development of post- thyroidectomy hypocalcaemia, allowing for early treatment of patients at risk and safe early discharge of patients not at risk.

In this study, the postoperative serum calcium level was statistically lower than the preoperative serum calcium level irrespective of whether the patient developed hypocalcaemia or not.

A prospective study done by Haluk Recai Unalp et. al., published in 2008, in Turkey, included 143 consecutive patients undergoing surgical therapy for non-toxic multinodular goiter. Patients were randomly assigned to surgical procedures. Patients in group 1 (n = 75) performed Total Thyroidectomy, and patients in group 2 (n = 68) performed near total thyroidectomy. The difference between serum calcium levels and percentage decrease in serum calcium levels before and after thyroidectomy were calculated. Total Thyroidectomy had a 33-fold increased risk for hypocalcaemia.

A retrospective study done by Bassam Abboud et al. done in 2001 in Lebanon, of 265 patients who underwent unilateral (n=50) or bilateral (n=215) thyroidectomy between 1996 and 2000 was done to determine incidence and risk factors for hypocalcaemia. Free thyroxine and thyrotropin levels were obtained before operation in 254 patients, together with preoperative and postoperative calcium and phosphorus levels. All patients were examined for age, gender, extent of thyroidectomy, initial versus reoperative neck operation, pathologic

characteristics of resected thyroid tissue, substernal thyroid extension, and parathyroid resection and auto transplantation. The study concluded that bilateral thyroidectomy, elevated free thyroxine level, and parathyroid auto transplantation are independent risk factors for post thyroidectomy hypocalcaemia.

A study done by Yesim Erbil et al. in 2009, Turkey, two hundred consecutive patients with nontoxic multinodular goiter treated by Total Thyroidectomy and Near Total Thyroidectomy were included prospectively in the present study. Group 1 (n = 49) consisted of patients with a postoperative serum calcium level less than 8 mg/dL, and group 2 (n = 151) had a postoperative serum calcium level greater than 8 mg/dL. Patients were evaluated according to age, preoperative serum 25-hydroxy vitamin D (25-OHD) levels, postoperative serum calcium levels, incidental parathyroidectomy, and the type of thyroidectomy. The study showed age and Total thyroidectomy to be significantly associated with postoperative hypocalcemia.

A study done by Chung-yau Lo et al. in Hong-Kong presented at 19th Annual meeting of the American Association of Endocrine Surgeons 1998, included 271 patients from January 1995 to October 1997, parathyroid auto transplantation was performed routinely for devascularized or inadvertently removed glands in 98 (36%) of patients undergoing thyroidectomy. Potential risk factors and the impact of parathyroid auto transplantation on postoperative hypocalcaemia were studied. The study showed that patients with postoperative hypocalcaemia after parathyroid auto transplantation have virtually no risk of having permanent hypoparathyroidism. Transient hypocalcaemia however was more in patients who underwent parathyroid auto transplantation.

A study done by M.P. Prim et al. in Madrid presented at the Annual Meeting of the American Academy of Otolaryngology–Head and Neck Surgery 1999, included 321 who underwent bilateral thyroidectomy. Recurrent laryngeal nerve paralysis,hypocalcaemia, serohematoma, wound infection, and postoperative hemorrhage were evaluated. Multivariate analysis was used to identify the relationships between the variables included in the study. Permanent hypocalcaemia occurred in 2.2% of the patients, whereas unilateral paralysis of the RLN developed in 0.9%. Hypocalcaemia was related to sex and surgical procedure ($P < 0.03$), thus concluding that patients showed increased incidence of post-operative hypocalcaemia in female patients and in those who underwent total thyroidectomy compared to those who had subtotal or unilateral thyroidectomy.

CONCLUSION

In our study, it was found that incidence of hypocalcaemia following total thyroidectomy was found to be higher. Factors contributing to this were found to be variation in surgical technique as the surgeries were done by different surgeons in a teaching institute, incidence was higher in patients who underwent neck dissection along with total thyroidectomy, and increase in incidence was seen in surgeries wherein parathyroid glands were not identified on table.

There was found to be significant increase in post-operative hospital stay in patients who developed hypocalcaemia.

A postoperative calcium level should be obtained 24 hours after thyroidectomy and calcium therapy be begun in hypocalcaemic patients with one or more of these factors even if they are asymptomatic to ensure safety and attempt a more appropriate hospitalization time. Routine parathyroid auto transplantation or preservation during thyroid operation to minimize the risk of hypocalcaemia.

Acknowledgment

The author is thankful to Department of General Surgery for providing all the facilities to carry out this work.

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