

Critical Analysis of the Frequency and Factors Leading to Hypocalcemia after Total/ Near Total Thyroidectomy

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ABSTRACT

Objective: To critically analyze the frequency and factors leading to hypocalcemia in Total/ Near Total thyroidectomy

Methods: This descriptive case series study was conducted over period of one year by taking sample of 138 patients of simple multinodular goiter or carcinoma of thyroid who underwent total/near total thyroidectomy and patients who had serum calcium <8mg/dl postoperatively. Recurrent thyroid surgery or patients undergoing lobectomy were excluded from the study. SPSS version 21 was used for data analysis. Mean \pm SD represent the continuous variables & frequencies/ percentages represent the quantitative results. Chi-square test was applied to analyze effect modification. P value <0.05 was taken as significant. Study was approved by the ethical review committee of the SMBBMU - Larkana.

Results: The mean \pm SD age of patients was 39.86 ± 11.5 years with a range from 22 to 60 years. The mean \pm SD serum Pre-operative calcium was 9.64 ± 0.44 mg/dL. Post thyroidectomy) values of serum calcium were noted as mean \pm SD 7.68 ± 2.11 mg/dL. Sixty five percent (n =90) of all patients were females. NTT- were 67.4% (n = 93) while TT- 32.6% (n = 45). Frequency of hypocalcemia was 28.3% (n = 39). More patients after TT developed hypocalcemia (44.4%) than NTT (20.4%) P value = 0.004). Old age, female gender, surgery for thyroid cancer and patient with lower preoperative serum calcium had a higher frequency of hypocalcemia after thyroidectomy.

Practical implication

Conclusion: The frequency of post thyroidectomy hypocalcemia in this study is 28.3%.

Post thyroidectomy hypocalcemia is associated with both NTT and TT, however the frequency is more common (more than twice) after TT.

Factors like old age, female gender, patients having thyroid cancer and having lower serum calcium preoperatively are strong effect-modifiers.

Keywords: Total thyroidectomy, Near total thyroidectomy, Calcium, Hypocalcemia, Parathyroid hormone.

INTRODUCTION

To date the total thyroidectomy has been widely known and accepted surgical treatment option for benign multi-nodular thyroid goiter disease. The frequent postoperative complication of thyroid surgery, especially involving the injury to parathyroid with its vessels is hypocalcemia. Postoperative hypocalcemia is the most common complications of thyroidectomy. Postoperative hypocalcemia is a major morbidity in patients who undergo thyroidectomy.^{1,2}

It often results longer hospitalization with repeated excessive investigations, and thus significantly increases the health care costs of thyroidectomy. The frequency of cases having post-thyroidectomy hypocalcemia among reports is considerably variable in percentages, but it remains estimated between 1 to 15% during first one to two days and manifest with symptoms of mild paresthesia, tingling which may worsen to severe cramps, tetany and convulsions.^{2,3}

Based on various measurements the standard normal range of serum calcium is set to be between minimum of 2.10 to 2.6mmol/l and maximum of 8.5 to 10.5mg/dl. Many studies have documented that incidence of hypocalcemia may range between 10.6% and 50% however; some found it peaked at 83%.⁴ Generally; the level below 2mmol/l (8mg/dl) relatively lower levels than the reference range becomes symptomatic hypocalcemia.

Commonly hypoparathyroidism (which may be due to injury, loss of blood supply or inadvertent excision of this gland) leads to hypocalcemia.^{5,6} Some of other reasons of hypocalcemia include surgical stress which leads to hemodilution wherein there is abnormal loss of calcium in urine, surge of calcitonin, osteodystrophy and autoimmune fibrosis. The last mentioned factor acts by reduced blood supply to the parathyroid glands.⁷

These factors strike the importance of vigilance on serum calcium concentration especially among the patients of thyroid disorders such as toxic and retrosternal goiter, as well as thyroid cancer. It has also commonly been noted that such hypocalcemia after thyroid surgery usually remains self-limiting with few

exceptions of worse hypocalcemia.⁸ The research studies have therefore suggested that an intraoperative or early post-operative parathyroid hormone must be done in order to quickly identify and manage such a potentially life threatening complication.⁹

The current study intended to measure the burden of hypocalcemia in patients treated through total thyroidectomy. The relation of hypocalcemia with special characteristics of the disease like carcinoma thyroid, retrosternal extension of goiter were also aimed and investigated.¹⁰

Objective: To critically analyze the frequency and factors leading to hypocalcemia in Total/ Near Total thyroidectomy.

METHODS

This descriptive study was conducted at Department of surgery, after approval from the ethical Review Committee (SMBBMU/OFF ERC/55 Dated: 31/3/2016). During 2 years, study period one hundred and thirty-eight (138) patients were included after carefully following the inclusion criteria, in surgical departments CMCH-SMBB Medical University Larkana. [Inclusion criteria: Patients with simple Multinodular goiter and patient with carcinoma of thyroid. Exclusion criteria: Patients who had serum calcium less than 8mg/dl were excluded, recurrent thyroid surgery, patient undergoing lobectomy].

Patients were recruited after their written and informed consent, having multinodular goiter and carcinoma of thyroid planned for total/near total thyroidectomy.

Preoperative assessment of patient was done on History, Clinical examination and laboratory investigation (serum calcium, serum parathyroid hormone and serum calcitonin levels), including investigations for fitness for G/A.

Patients underwent total and near total thyroidectomy. Patients were checked during first 24 hours for any sign and symptom of hypocalcemia. Symptoms of hypocalcemia like tingling, numbness and twitching of muscles and signs for hypocalcemia like chevostok sign and trousseau sign were recorded. Low calcium was treated accordingly with IV or oral treatment after receiving post-operative levels of serum calcium, and serum

parathyroid hormone and serum calcitonin levels. Patients were discharged on oral calcium supplements and advised follow ups in OPD.

Serological workup was done before surgery. After twenty four hours/ a day of thyroid resection serum calcium was repeated to compare pre and post thyroidectomy levels.

Data were analyzed by using SPSS 21 version. Mean and standard deviations were calculated for quantitative variables such as Age, size of swelling, serum calcium etc. Chi square test were applied where applicable.

Ratios and proportions were calculated for qualitative variables such as sex, occupation, marital status etc. Chi square test were applied where applicable. P value 0.05% will be considered as significant.

RESULTS

Total 138 selected patients were included in the study. The mean ± SD serum Pre-operative calcium was 9.64 ± 0.44 mg/dL. Its minimum value was 8.50 while maximum value was 10.50 mg/dL. On the other hand, postoperative (Post thyroidectomy) mean values of calcium was noted as mean 2.11 mg/dL± SD 7.68 ± with a minimum and maximum values of 2.40 & 9.55 respectively. There was almost uniform presentation in all age groups from 21

through 60 years of age. Each of the four groups had nearly a quarter of total sampled participants.

Female gender was found to be more affected of multinodular goiter. Nearly two thirds of all patients 65.2% (n =90) were female & male patients were 34.8% (n = 48).

More than two third majority of patients i-e; 68.8% (n = 95) were from rural areas while only 31.2% (n = 43) were from urban living areas. Patients presenting with goiter and selected in this series for surgical treatment had most common diagnosis of simple multinodular goiter 79% (n = 109) while other 29% (n = 21) had thyroid cancer. Two types of procedures were performed as per protocol of the study on these subjects. These procedures were Near Total Thyroidectomy NTT- 67.4% (n = 93) and Total Thyroidectomy TT- 32.6% (n = 45).

The outcome variable and objective (i-e; frequency of hypocalcemia in Total/ Near Total thyroidectomy) of this study was found to be positive in slightly more than a quarter of all patients i-e; 28.3% (n = 39 out of 138).

It was statistically found that there was significant difference in Pre-operative and Post-operative serum calcium levels among all patients. (t statistic = 10.864; p value < 0.001). Similar results were also noted when procedures (NTT versus TT) were compared for the level of difference of serum calcium. (p value < 0.001). Table: 1

Table 1: Co-relation of pre- and post-operative serum calcium with the type of surgical procedure

Paired Samples Test		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% C. I. of the Difference				
Procedure performed					Lower	Upper			
NTT	Pre op: & Post op: Serum calcium	1.52118	1.72776	17916	1.16535	1.87701	8.491	92	.000
T T	Pre op: & Post op: Serum calcium	2.86911	2.55012	38015	2.10297	3.63525	7.547	44	.000

Postoperative tetany was observed among twenty-seven patients (18.5%) which was two third proportion in hands one hand in sites other hands.

The study through stratified analysis found that with the increasing age, the frequency of post-thyroidectomy hypocalcemia increased which was 28.6% among patients of 21-30 years age and slightly increased 34.4% among patients of age 51-60 years. However; the finding was not associated with statistical significance. (P value = 0.740).

Likewise; it was noted that frequency of post-thyroidectomy hypocalcemia was more in female patients (33.33%) almost double than the males (18.75%). The finding was associated with statistical significance. (P value = 0.059)

It was also worth-noting that patients who were diagnosed as having thyroid cancer had much higher ~ more than twice frequency of post-thyroidectomy hypocalcemia (48.3%) compared to the simple multinodular goiter patients (22.9%) and the result was statistically very significant P value = 0.008. Table-2

Table 2: Cross-Tabulation of Diagnosis/ Type of Lesion Wwth Frequency Of Post-Thyroidectomy Hypocalcemia (n = 138).

Diagnosis/ Type of lesion	Post-thyroidectomy Hypocalcemia		Total	P value
	Yes	No		
Simple Multinodular Goiter	25 22.9%	84 77.1%	109 100%	0.008
Thyroid Cancer	14 48.3%	15 51.7%	29 100%	
Total	39 28.3%	99 71.7%	138 100%	

Similarly; it was noted that the patients treated with Total thyroidectomy developed higher frequency of post-thyroidectomy hypocalcemia (44.4%) than those treated through Near Total thyroidectomy (20.4%) P value = 0.004.

Lower serum calcium pre-operatively affected the outcomes accordingly and these patients had higher frequency of post-operative hypocalcemia (36.4%) than those having better pre-

operative serum calcium (24.4%) however; the result was statistically non-significant (P value = 0.138)

Significant association of post-thyroidectomy hypocalcemia with occurrence of post-operative tetany (P value = 0.035) while there was a significant association of type of procedure performed with level of post-thyroidectomy hypocalcemia. Accordingly; lower levels of serum calcium were detected with total thyroidectomy compared to subtotal thyroidectomy (P value = 0.010).

DISCUSSION

The current study is first of its kind in the region of upper Sindh where the thyroid disorders are relatively common and present with as variety of lesion ranging from benign to malignant. Two different techniques (Total/ Near Total thyroidectomy) of thyroid resection were assessed with relation to occurrence of postoperative hypocalcemia.

The current study has evaluated these much-debated techniques with respect to incidence of hypocalcemia after total thyroidectomy and near total thyroidectomy in the local population to remove the dearth of local evidence.

The current study found that frequency of hypocalcemia following thyroidectomy was 28.3% (n = 39). When compared between the two techniques it was significantly found that more than twice was incidence rate of hypocalcemia with TT (i-e; 44.4%) compared to that with NTT (i-e; 20.4%; p value = 0.004). Other contemporary studies have reported a similar rate. ¹¹ Lale A, et al. ¹² found that the frequency of hypocalcemia was 28.4% (in which about 1.7% cases had permanent hypocalcemia). Eismontas V, et al., reported a relatively much higher rates of post-thyroidectomy hypocalcemia which was 64.2%.¹³ A relatively lower rates were documented by a recent study (Al Qubaisi M, et al.) wherein; hypocalcemia following TT was 10.35%.¹⁴ Likewise; Unalp HR and coworkers found that NTT was associated with relatively much lower incidence with a much lesser severity of post-operative hypocalcemia compared the TT for a benign multinodular goiter. ¹⁵

Post-thyroidectomy; the transient hypocalcemia takes duration of six months to resolve completely (Incidence range = 0.3% to 49%). Although temporary, it is may prove to be very fatal.¹⁶ While; if persists beyond six months then it is termed as Permanent hypocalcemia (Incidence = 0% to 13%).¹⁷ A medical audit conducted by the British Association of Endocrine and Thyroid Surgeons found that at least of a quarter of all patients developed postop hypocalcemia. Among these patients 27.4% were transient while 12.1% had a permanent hypocalcemia. Otherwise; some studies reported the rate of transient hypocalcemia was 19-38% and the rate of permanent hypocalcemia after surgery was 0-3% after surgery.¹⁸

Edeaf O, and coworkers¹⁸ and many other researchers have overall found that serum level of preoperative calcium is a strong predictor of postoperative hypocalcemia among patients of thyroidectomy. Other factors include; perioperative parathyroid hormone, preoperative vitamin D3 and postoperative magnesium. Preoperatively having Grave's disease or removal of large part of thyroid gland and female sex are also significant factors affecting postoperative hypocalcemia. The current study has not evaluated these factors in detail in this series of patients.

In the current study we noted that mean pre-operative serum calcium level was 9.64 ± 0.44 mg/dL (Minimum 8.50; maximum 10.50 mg/dL). Further; postoperative serum calcium level was 7.68 ± 2.11 mg/dL (Minimum 2.40; maximum 9.55 mg/dL). Other studies have reported higher values (without any significant difference) i-e; preoperative and postoperative values of serum calcium 9.3 ± 0.4 mg/dL and 8.4 ± 0.6 mg/dL, respectively ($p < 0.001$).^{11,14}

In current study the mean \pm SD age of patients was 39.86 ± 11.5 years with a range from 22 to 60 years. Age was a non-significant effect modifier such that with the increasing age, the frequency of post-thyroidectomy hypocalcemia increased from 28.6% in 21-30 years age to 34.4% in 51-60 years age (P value = 0.740). Malik MZ, et al., reported mimicking results wherein; mean age of thyroidectomy patients was 38.673 ± 8.63 .²⁰ A study by Unalp HR and coworkers found that the mean \pm SD age was 47.9 ± 12 years (range, 20-77 years).¹⁵ They further found that higher the age significantly more was the frequency of hypocalcemia (p value < 0.001).

Colak T, et al.,²² in a study (comparing the safety and efficacy of total thyroidectomy with subtotal thyroidectomy) reported that mean age was 43 years \pm 12 among the former while among later group mean age was 46 years \pm 10.9 years. Another study documented mean age of the patients was 46.2 (18-87) ($m = 46$) years.¹³³ Even larger age was documented by Eismontas V et al. i-e; mean age \pm SD age was 57.2 ± 13.4 years.¹³ These and other studies agreed that elder age patients had higher frequency of postoperative hypocalcemia (odds ratio 1.05, 95% CI 1.01-1.09, p value < 0.001).¹¹⁻¹³

The current series of TT and NTT most of the patients were female, i-e. female to male ratio was almost 2:1. Gender affected the frequency of post thyroidectomy hypocalcemia. Female patients were twice more affected from hypocalcemia compared to male patients with statistical significance. (P value = 0.059) Like the current study; Lale A, et al.¹² found that the frequency of hypocalcemia was more in the female gender significantly (p value = 0.002) Unlap et al., also reported female to male ratio of 6.1:1.¹⁵ Other studies like Malik MZ et al., and Eismontas V et al., and other also found similar results of higher female affectivity with statistical significance (odds ratio 5.94, 95% CI 1.13-31.26, P value = 0.035).^{13, 20} However; some contradiction was noted by some studies like; a comparative study by Colak T et al.²² found no significant difference in the sex and duration of goiter between the two groups (P value = 0.74 and P value = 0.59, respectively).

In the current study; some 21% patients had thyroid cancer and most of them had papillary carcinoma and only two had follicular carcinoma. In some cases, the cancer was diagnosed incidentally. Likewise; Colak T, et al.,²² in a study (comparing the safety and efficacy of total thyroidectomy with subtotal

thyroidectomy) reported that thyroid cancer was found in 7.4% cases. Duclos A, et al, also documented prevalence of thyroid malignancy rate of 22.6% malignant.¹⁹ We in current study found that cancer diagnosed patients had more than twice incidence of post-thyroidectomy hypocalcemia (48.3%) then benign goiter patients (22.9%; p value = 0.008). these findings are supported by the Lale A, et al. (2018)²² and other studies which reported that malignant thyroid pathology (p value = 0.006) was associated with upto 2.21 times higher risk of hypocalcemia.¹⁵

The shortest length of stay in hospital was 1 day and the longest length of stay in hospital was 9 days with a median of 1 day. Although the current study has not compared the hospital stay, mode of thyroidectomy and resulting postoperative hypocalcemia yet; it was keenly observed that the postoperative hypocalcemia lengthens the duration of hospitalization among patients as has been found by other studies as well (>2 days; p value < 0.001) compared to normocalcemia patients.^{15, 22}

Symptoms of hypocalcemia usually manifest when the serum calcium level is below 8.0 mg/dL (2.0 mmol/L).²³ In the current series it was noted that only one fifth i-e; 19.5% ($n = 27$) of all patients had symptoms of hypocalcemia i-e; tetany. Majority of tetany symptoms was detected in hands. But; it can be fairly understood that some patients who had postoperative hypocalcemia were asymptomatic. Other contemporary studies have reported that as much as 58.8% showed symptoms of hypocalcemia. Initially mild paresthesia and tingling may ensue. These may be followed by more symptoms like severe cramps and tetany. Severe and sudden cases can also lead to seizures, laryngospasm or even the congestive heart failure and arrhythmias. However; post thyroidectomy, symptomatology may also depend upon the degree and rapidity of hypocalcemia onset.

Researcher have been arguing over the utility and usefulness of prophylactic approach of vitamin D and calcium supplementation. Some comment that it significantly decreased the rate of laboratory and symptomatic hypocalcemia while others think that it might lead to hypercalcemia or parathyroid hormone inhibition which the earlier rule out thoroughly. They favor that routine supplementation is less expensive than performing laboratory tests in the course of treatment of hypocalcemia.¹⁹

Studies investigating the favorable effect of preoperative vitamin D and calcium supplementation among thyroidectomy patients came up with different results. One study by Malik MZ, et al.,²⁰ found that 6.5% in treatment group developed hypocalcemia compared to 26.1% patients in control group (p value = 0.011) while their mean preoperative calcium levels were matching i-e; 9.482 ± 0.49 and 9.678 ± 0.54 mg/dl respective group. On the other Antakia A and coworkers completely rejected this finding and found no benefit of preemptive calcium or vitamin D3 supplementation to prevent post thyroidectomy hypocalcemia.²¹

We overall think that still there is need to more extensive and larger sampled studies to reach to decisive point and suggest usefull evidence supporting the prophylactic calcium and vitamin D therapy for patients of thyroidectomy.

The role of parathyroid hormone and its most vulnerability to excision during thyroidectomy is also quite important factor in determining the post thyroidectomy hypocalcemia. Therefore; certain studies concluded that low preoperative calcium levels are not rightly associated with postoperative hypocalcemia, keeping the fact abreast that the sensitivity of this parameter is also very low (29-58%).²²⁻²³ Additionally, a study failed to show any association between preoperative calcium levels and postop hypocalcemia.²⁴ This simultaneously raises the importance of hypoparathyroidism management.²⁵ The evaluation of parathyroid was beyond the scope of this study.

A positive outcome of this study was that there were no any deaths related to the surgery or other serious complications except the incidence of transient vocal cord paralysis which was near to 5%.

Despite of having certain limitations of study design and the sample size being relatively smaller and a single centre, the study

has come up with significant piece of evidence upon post thyroidectomy hypocalcemia occurrence. The results of the study may carefully be inferred as its generalizability is limited.

CONCLUSION

The current study concludes that:

- The frequency of hypocalcemia in this study was 28.3% which is comparable to other studies.
- Post operatively alteration in serum calcium level occurs with NTT but it is more with TT (more than twice)
- Elder age, female gender were more with thyroid cancer.
- Patient having lower serum calcium pre-operatively were strongly associated with occurrence of postoperative hypocalcemia.

Suggestions: Prophylactic administration of vitamin D and calcium supplementation to prevent post thyroidectomy hypocalcemia can be evaluated in prospective studies using larger sample size.

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Conflict of interest: None

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