ORIGINAL RESEARCH

Early Predictive Factors of Hypocalcemia Following Total Thyroidectomy: A Hospital Based Study

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ABSTRACT

Background: In thyroid surgeries, hypocalcemia is a very common complication mainly because of the similar blood supply to both thyroid and parathyroids Objectives: measurement of parathormone (PTH) during total thyroidectomy can identify at risk patients of developing hypocalcaemia.

Materials and Methods: This is a Four-year prospective and cross-sectional study was conducted in three hospitals i.e Study subjects in which all thyroidectomy patients 18 years or above will be screened for development of hypocalcaemia who met inclusion criteria was taken up for study during the study period. The study is a time bound study including all thyroidectomy cases done from October 2017 to August 2021 which included a total of 62 patients.

Results: Transient biochemical hypocalcemia can occur in all forms of thyroid surgery in the immediate postoperative period. Most common time of occurrence of hypocalcemia is within first 48 hours of surgery. When thyroidectomy is done for a malignant condition, there is more risk of developing postoperative hypocalcemia in comparison to a benign condition.

Conclusion: Whether it is a benign or malignant pathology, a single PTH estimation 12 hours after surgery with a cutoff off 12.3pg/ml can best predict whether patients will go for symptomatic hypocalcemia and these patients will have to be supplemented with intravenous calcium gluconate.

Keywords: Thyroid surgeries, hypocalcemia, PTH measurement.

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INTRODUCTION

Thyroidectomy constitutes one of the most commonly done surgical procedures around the world.[1] Other than the usual complications one usually faces in any surgery like infection, hemorrhage, anesthetic accidents, due to its vital anatomical relations, thyroidectomies poses two major complications: Hypoparathyroidism and their related problems due to either unintentional gland removal or due to loss of vascularity, Injury to the RLN.[1,2]

Nowadays recent advances in anesthetic techniques and the thorough knowledge about the anatomy and physiology of the gland, we are able to perform thyroidectomies very safely compared to the past. This has also enabled us to reduce the complications of devascularising or removing the parathyroid glands. But still, the problem of hypoparathyroidism still persists especially in those patients who undergo thyroidectomies mainly for thyroid malignancies.

Inadvertent removal of the glands or loss of vascularity of the gland either by thrombosis or ligation of feeding artery have been postulated as the possible cause for this condition.[3] Primary thyroid diseases like autoimmune diseases or thyrotoxicosis may also add to the etiology. But their role is inconclusive. Out of all the above-mentioned factors, the most important one is the surgical technique and aiming at preserving the gland with its vascularity.[4]

Plasma calcium concentration is increased by parathormone by mobilizing the ion from the bone. The calcium reabsorption from the kidney is increased, but this process is offset by an increase in filtered calcium. The formation of 1, 25-dihydroxy Vit D3 is also increased. The calcium absorption from the intestine is increased, the ion from the bone is mobilized and calcium resorption from kidneys is increased. Calcitonin increases the amount of calcium in urine by inhibiting bone resorption.

Hence this study was conducted to measurement of parathormone (PTH) during total thyroidectomy can identify at risk patients of developing hypocalcaemia.

MATERIALS & METHODS

This is a Four-year prospective cross-sectional study was conducted in three hospitals i.e Study subjects in which all thyroidectomy patients 18 years or above will be screened for development of hypocalcaemia who met inclusion criteria was taken up for study during the study period. The study is a time bound study including all thyroidectomy cases done from October 2017 to August 2021 which included a total of 62 patients. Permission for the study was obtained from the College authorities prior to commencement.

Inclusion criteria:

1. Patients 18 years or above who underwent total thyroidectomy by bilateral exploration.

Exclusion criteria:

1. Second surgery after already done hemi thyroidectomy
2. Lymph node dissection concurrently
3. Oral or parenteral supplementation of calcium receiving patients
4. Those who had hypocalcaemia prior to study
5. Patients who had a parathyroid auto-transplantation done

Statistical analysis:

Diagnostic tests used were sensitivity, specificity, positive predictive value, negative predictive value and analysis of results using ROC Curves. SPSS for windows, version 17.0 was used to do analysis. Numerical parameters were compared using chi-square test. P-value < 0.05 was considered as the level of significance.

RESULTS

Among the 62 patients who underwent total thyroidectomy, hypo calcemic symptoms were noted in a total of 13 patients (21%). Among the 13 patients who developed symptomatic hypocalcemia, no patients (0%) in the age group less than 30 years, 5 patients (38.5%) in age group between 31-40 years, 5 patients (38.5%) in age group between 41-50 years and 3 patients (33.3%) in age group more than 50 years. Among the 62 patients who underwent total thyroidectomy, 56 patients (90.3%) were males and 6 patients (9.7%) were females.

Among the 13 patients who developed symptomatic hypocalcemia, 10 were females (76.9%) and 3 were males (23.1%). 17.9% of females developed symptomatic hypocalcemia following total thyroidectomy whereas 50% of males who underwent total thyroidectomy developed symptomatic hypocalcemia.

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Among the 13 patients who developed symptomatic hypocalcemia10 patients (76.9%) had the disease for a duration of 1-2 years, 1 patient (7.7%) had the disease for a duration between 3-5 years and 2 patients (15.4%) had the disease for a duration of between 6-10 years.

Among the 62 patients who underwent total thyroidectomy, 3 patients (4.8%) were diagnosed with Follicular carcinoma, 41 patients (66.1%) were diagnosed with MNG, 9 patients (14.5%) were diagnosed with papillary carcinoma and 9 patients (14.5%) were diagnosed with thyroiditis. [Table 1]

Among the 13 patients who developed symptomatic hypocalcemia, 3 patients (23.1%) were diagnosed with follicular carcinoma, 5 patients (38.5%) were diagnosed with MNG, 3 patients (23.1%) were diagnosed with papillary carcinoma and 2 patients (15.4%) were diagnosed with thyroiditis.

All the patients diagnosed with follicular carcinoma (100%) following total thyroidectomy developed symptomatic hypocalcemia while 12.2% among MNG, 33.3% among papillary carcinoma & 22.2% among thyroiditis developed symptomatic hypocalcemia following total thyroidectomy.

Among the 62 patients who underwent total thyroidectomy, 12 patients (19.4%) were operated for a malignant condition whereas 50 patients (80.6%) were operated for a benign condition.

Among the 13 patients who developed symptomatic hypocalcemia, 6 patients (46.2%) were diagnosed with a malignant condition and 7 patients (53.8%) were diagnosed with a benign condition.

50% of patients with a malignant pathology who underwent total thyroidectomy developed symptomatic hypocalcemia whereas 14% of patients with a benign pathology who underwent total thyroidectomy developed symptomatic hypocalcemia.

The relationship between:

1. Diagnosis and development of hypocalcemia were found to be highly significant with a p value of 0.005
2. Nature of disease and development of hypocalcemia were also found to be highly significant with a p value of 0.006
3. Duration of illness and development of hypocalcemia were found to be significant with p = 0.32, but not as much as with the diagnosis and nature of the disease.

However, the relationship between age and sex on the development of hypo calcemic symptoms were not found to be significant with a p=0.99 and p=0.190 respectively.

The serum calcium levels on admission, at 12hr and 24hrs were correlated with the development of hypocalcemia in the study subjects. It was found that Calcium measurement on admission was not found to be significant as a good predictive factor in predicting hypocalcemia with a p=0.286 whereas Calcium estimation at 12hr and 24hr were found to be highly significant in predicting hypocalcemia with p=0.000 and 0.000 respectively. [Table 2]

ROC curve plots were drawn in relation to the timing of calcium measurement and development of symptomatic hypocalcemia. The area under the curve was found to be highly significant for Calcium estimation at 12hr and 24hr with areas = 0.859 and 0.910 respectively which was highly significant. However the area under the curve drawn with calcium level estimation on admission was found to be only 0.403 which was not significant. Hence calcium level estimation on admission was not found to be a predictive factor for development of hypocalcemia. On the contrary, calcium level estimation at 12hr and 24 hours were highly predictive of patient developing symptomatic hypocalcemia in the future. [Table 3]

In order to find out the value of serum calcium measured at the said time intervals below which the patient has high possibility of developing symptomatic hypocalcemia, the values of serum calcium were extrapolated along the curve and sensitivity and specificity were noted.

The following results were obtained:

1. The value of serum calcium on admission, below which it can best predict the risk of hypocalcemia is 9.700 with a sensitivity of only 57.1% and specificity of 30.8% which suggests that serum calcium on admission is not a good early predictive factor for symptomatic hypocalcemia.
2. The value of serum calcium at 12hr, below which it can best predict the risk of hypocalcemia is 8.300 with a sensitivity of 89.8% and specificity of 69.2%, which suggests that serum calcium estimation at 12hris a better early predictive factor for symptomatic hypocalcemia.
3. The value of serum calcium at 24hr,below which it can best predict the risk of hypocalcemia is 6.950 with a sensitivity of 95.9% and specificity of 76.9%, which suggests that serum calcium estimation at 24hr is a good early predictive factor for symptomatic hypocalcemia.

The serum PTH levels on admission, at 12hr and 24hrs were correlated with the development of hypocalcemia in the study subjects. It was found that PTH measurement on admission was not found to be significant as a good predictive factor in predicting hypocalcemia with a p=0.118 whereas PTH estimation at 12hr and 24hr were found to be highly significant in predicting hypocalcemia with p=0.000 and 0.000 respectively. [Table 4]

ROC curve plots were drawn in relation to the timing of PTH measurement and development of symptomatic hypocalcemia. The area under the curve was found to be highly significant for PTH estimation at 12hr and 24hr with areas = 0.954 and 0.940 respectively which was highly significant. However the area under the curve drawn with PTH estimation on admission was found to be only 0.628 which was not highly significant. Hence PTH level estimation on admission was not found to be a good predictive factor for development of hypocalcemia. On the contrary, PTH level estimation at 12hr and 24 hours were highly predictive of patient developing symptomatic hypocalcemia in the future. [Table 5]

In order to find out the value of serum PTH measured at the said time intervals below which the patient has high possibility of developing symptomatic hypocalcemia, the values of serum PTH were extrapolated along the curve and sensitivity and specificity were noted. The following results were obtained:

1. The value of serum PTH on admission, below which it can best predict the risk of hypocalcemia is 23.100 with a sensitivity of only 67.3% and specificity of 53.8% which suggests that serum PTH on admission is not a good early predictive factor for symptomatic hypocalcemia.
2. That the value of serum PTH at 12hr, below which it can best predict the risk of hypocalcemia is12.100 with a sensitivity of 93.9% and specificity of 92.3%, which suggests that serum PTH estimation at 12hr is the best early predictive factor for symptomatic hypocalcemia.
3. The value of serum PTH at 24hr, below which it can best predict the risk of hypocalcemia is9.700 with a sensitivity of 87.8% and specificity of 92.3%, which suggests that serum PTH estimation at 24hr is a good early predictive factor for symptomatic hypocalcemia.

Summarizing the above findings and plotting them on a single ROC curve, the area under the curve was found to be highly significant for PTH estimation at 12hr and 24hr with areas = 0.954 and 0.940 respectively and for calcium estimation at 12hr and 24hr with areas = 0.859 and 0.910 respectively which was highly significant. [Table 6]

In case of malignant conditions of thyroid, when thyroidectomy is done, PTH estimation at 12hr and 24hr are highly significant with area under the curve 1.000 and 0.861 respectively and calcium estimation at 12hr and 24hr are also significant with area under the curve being 0.778 and 0.889 respectively.
In case of benign conditions of thyroid, when thyroidectomy is done, PTH estimation at 12hr and 24hr are highly significant with area under the curve 0.940 and 0.944 respectively and calcium estimation at 12hr and 24hr are also highly significant with area under the curve being 0.940 and 0.930 respectively.
For malignant thyroid conditions when thyroidectomy is performed, the value of serum PTH at 12hr, below which it can best predict the risk of hypocalcemia is 11.800 with a sensitivity of 100% and specificity of 100%, which suggests that serum PTH estimation at 12hr is the best early predictive factor for symptomatic hypocalcemia in malignant thyroids.
For benign thyroid conditions when thyroidectomy is performed, the value of serum PTH at 12hr, below which it can best predict the risk of hypocalcemia is 12.300 with a sensitivity of 93% and specificity of 85.7%,the value of serum PTH at 24hr, below which it can best predict the risk of hypocalcemia is 8.550 with a sensitivity of 93% and specificity of 85.7%,the value of serum Ca at 12hr, below which it can best predict the risk of hypocalcemia is 8.550 with a sensitivity of 88.4% and specificity of 85.7%andthe value of serum Ca at 24hr, below which it can best predict the risk of hypocalcemia is 6.950 with a sensitivity of 97.7% and specificity of 71.4%.

Table 1: Diagnosis of patients enrolled in the study

	Frequency	**Percent**
Follicular Ca	3	4.8
MNG	41	66.1
Papillary Ca	9	14.5
Thyroiditis	9	14.5
Total	62	100.0

Table 2: Timing of serum calcium measurement

		N	Mean	Std. Deviation	95% Confidence Interval for Mean Lower Bound	95% Confidence Interval for Mean Upper Bound	t value	p
Ca on Admission	Present	13	10.246	.833	9.743	10.750	1.08	.286
	Absent	49	9.973	.807	9.742	10.205		NS
	Total	62	10.031	.813	9.824	10.237		
Ca at 12hr	Present	13	8.100	.839	7.593	8.607	4.17	.000
	Absent	49	9.361	.998	9.075	9.648		HS
	Total	62	9.097	1.091	8.820	9.374		
Ca at 24hr	Present	13	6.554	1.131	5.870	7.237	5.63	.000
	Absent	49	8.845	1.345	8.459	9.231		HS
	Total	62	8.365	1.599	7.958	8.771		

Table 3: Area under the ROC curve

Test Result Variable(s)	**Area**	**Std. Error(a)**	**p**	**Asymptotic 95% Confidence Interval**	
				Lower Bound	**Upper Bound**
Ca on Admission	.403	.087	.284	.233	.573
Ca at 12hr	.859	.064	.000	.734	.984
Ca at 24hr	.910	.049	.000	.813	1.006

Table 4: Timing of serum PTH measurement

		N	Mean	Std. Deviation	95% Confidence Interval for Mean		t value	p
					Lower Bound	Upper Bound		
PTH on Admission	Present	13	23.854	3.384	21.809	25.899	1.58	.118
	Absent	49	25.918	4.354	24.668	27.169		NS
	Total	62	25.485	4.230	24.411	26.560		
PTH at 12hr	Present	13	11.192	1.305	10.403	11.981	5.82	.000
	Absent	49	21.863	6.533	19.987	23.740		HS
	Total	62	19.626	7.287	17.775	21.476		
PTH at 24hr	Present	13	7.938	1.295	7.156	8.721	5.23	.000
	Absent	49	20.327	8.466	17.895	22.758		HS
	Total	62	17.729	9.087	15.421	20.037		

Table 5: Area under the ROC curve

Test Result Variable(s)	Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
PTH on Admission	.628	.079	.159	.474	.782
PTH at 12hr	.954	.027	.000	.901	1.006
PTH at 24hr	.940	.028	.000	.885	.996

Table 6: Area under the ROC curve

Test Result Variable(s)	Area	Std. Error(a)	P	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
PTH on Admission	.628	.079	.159	.474	.782
PTH at 12hr	.954	.027	.000	.901	1.006
PTH at 24hr	.940	.028	.000	.885	.996
Ca at 12hr	.859	.064	.000	.734	.984
Ca at 24hr	.910	.049	.000	.813	1.006

DISCUSSION

The patients were then observed for the development of symptoms of hypocalcemia in form of a positive Chvostek sign, Trousseaus sign, carpopedal spasm or convulsions and the time at which the estimation of serum calcium and parathormone levels could best predict the risk of developing hypocalcemia was studied.

Various other studies report incidence of hypocalcemia from 5-20%. Among this permanent hypocalcemia was reported in 0-3.8% and transient hypocalcemia in 0.9-25.9%. There have been various reasons postulated to the development of post-surgical hypocalcemia which includes the nature of trauma in preoperative period, tying of the inferior thyroid artery, thyrotoxic osteodystrophy and release of thyrocalcitonin during the surgical period, a low level of calcium prior to surgery, and the spasm occurring to the blood supply during the time we mobilize the gland.[5,6]It was found that more severe the disease in terms of its aggressiveness, more risk of developing hypocalcemia in the post-operative period.

A significant association was also found between the nature of the disease for which the patient was operated upon and the risk of development of hypocalcemia which when analyzed showed a p = 0.006 which suggests the fact that when thyroidectomy is being done for a malignant condition, there is more risk of developing hypocalcemia in the postoperative period. No association was found between age and sex on the development of postoperative hypocalcemia.

Among serum calcium estimation, the best time at which we can early detect the risk of hypocalcemia was it being done at 24 hours post-surgery which gave a sensitivity of 95.9% and specificity of 76.9% for a serum calcium value of 6.950 mg/dl. The serum calcium estimation done at 12hr had a sensitivity of 89.8% and specificity of 69.2% for a serum calcium value of 8.300 mg/dl which was also significant, but not as much as at 24hr calcium estimation which is evident from the sensitivity and specificity values. Estimating the serum calcium levels on admission showed a sensitivity of 57.1% and specificity of 30.8% at a serum calcium value of 9.700mg/dl which had no use in predicting postoperative hypocalcemia.[7-9]

Whereas in serum PTH estimation, the best time at which we can early detect the risk of hypocalcemia was it being done at 12 hours post-surgery which gave a sensitivity of 93.9% and specificity of 92.3% for a serum PTH value of 12.100 pg/ml. The serum PTH estimation done at 24hr had a sensitivity of 87.8% and specificity of 92.3% for a serum PTH value of 9.700 pg/ml which was also significant, but not as much as at 12hr PTH estimation which is evident from the sensitivity and specificity values. Estimating the serum PTH levels on admission showed a sensitivity of 67.3% and specificity of 53.8% at a serum PTH value of 23.100 pg/ml which had no use in predicting postoperative hypocalcemia.

Summarizing the above findings of serum PTH estimation, in a resource limited setup, if minimum resources needed to be used, a single PTH estimation at 12hour which showed a value equal to or less than 12.100 pg/ml had the best chance of predicting the risk of postoperative hypocalcemia at the earliest stage.

If the nature of the disease, whether benign or malignant, was also taken into account, for malignant pathology, the best predictor of developing hypocalcemia would be a single PTH estimation at 12 hour with a value less than or equal to 11.800 pg/ml which had a sensitivity of 100% as well as specificity of 100% and in case of benign condition, the single best predictor would be a single PTH estimation at 12 hour with a value less than or equal to 12.300 pg/ml which has a sensitivity of 93% and specificity of 85.7%.

A similar study done by Adolfo Pisano et al showed that serum calcium level showed the highest sensitivity and specificity after 24hrs (93.9% and 100%) for a value of <7.97 mg/dl and serum PTH level showed the highest sensitivity and specificity in predicting hypocalcemia after 6hrs (84.8% and 93.7%) which is in close relation to the results of the present study.[10]

Another study done by Cord Sturgeon et al concluded that a PTH value of < 10pg/ml on postoperative day 1 is a strong predictor of developing hypocalcemia.[11]

A similar study done by Felipe Augusto Brasilerio Vanderlei et al showed that selection of PTH at 1 hour with cut off values as 12.1 ng/l divided patients without and with symptoms with a sensitivity of 93.7% and specificity of 91.6% which almost correlates with the result of this present study.[12]

CONCLUSION

It was concluded that Transient biochemical hypocalcemia can occur in all forms of thyroid surgery in the immediate postoperative period. Most common time of occurrence of hypocalcemia is within first 48 hours of surgery. When thyroidectomy is done for a malignant condition, there is more risk of developing postoperative hypocalcemia in comparison to a benign condition. Pt will have to be given iv calcium gluconate in view of symptomatic hypoglycemia post which can be better predicted by 12 hours post surgery S. PTH estimation with a cutoff of 12.3 pg/ml.

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