



HYPOMAGNESEMIA PREDICTS POSTOPERATIVE BIOCHEMICAL HYPOCALCEMIA AFTER THYROIDECTOMY

Madhava Rao¹, Ranganath Reddy^{2*}, Prabhakar Reddy³

¹ Associate Professor, Department of General Surgery, Sri Lakshmi Narayana Institute of Medical Sciences, Affiliated to Bharath Institute of Higher Education and Research, Pondicherry- 605 502, India

² Assistant Professor, Department of Orthopaedics, Sri Lakshmi Narayana Institute of Medical Sciences, Affiliated to Bharath Institute of Higher Education and Research, Pondicherry- 605 502, India

³ Professor, Department of Biochemistry and Central laboratory Head, Sri Lakshmi Narayana Institute of Medical Sciences, Affiliated to Bharath Institute of Higher Education and Research, Pondicherry- 605 502, India.

ABSTRACT

Hypocalcemia is the most common complication of total thyroidectomy. It is important to identify and avoid high-risk surgical techniques to lower the rate of this complication. Additionally, by knowing risk factors of hypocalcemia, lower risk patients can be discharged earlier. In this study we aim to understand the surgical, patient-related, and disease-related and laboratory risk factors of transient hypocalcemia after total thyroidectomy to investigate the role of magnesium in biochemical and symptomatic hypocalcemia, a retrospective study was conducted. For the safety of patients, the possibility of both symptomatic and biochemical hypocalcemia should be considered together before deciding early discharge. Using intact PTH for symptomatic hypocalcemia and day-1 ionized serum calcium level for biochemical hypocalcemia will be helpful for the reliable prediction of heterogeneous nature of postoperative hypocalcemia. Proper surgical techniques and identification of the parathyroid glands is important in preventing hypocalcemia after total thyroidectomy. Additionally, for predicting hypocalcemia the relative and not absolute PTH levels should be more emphasized.

Key words: Hypomagnesemia, Relative decline of iPTH, Hypocalcemia, Symptom, Female.

INTRODUCTION

Hypomagnesemia was an independent risk factor for hypocalcemia after thyroidectomy. The decrease of serum Mg and Ca after thyroidectomy was not the common result of a decrease in PTH, but serum Mg decline was one of the important influential factors for the decrease of serum Ca after thyroidectomy. In addition, hypomagnesemia also increased the risk of symptoms; therefore, serum Ca and Mg should be routinely monitored after thyroidectomy. Magnesium plays an important role for secretion of PTH and release of PTH is impaired in magnesium deficiency [1]. Mg²⁺ is the second most abundant cation, regulating calcium (Ca) homeostasis and acting as a cofactor for more than 300 reactions responsible for metabolism and protein and nucleotide synthesis [1-2]. This study examined factors

contributing to post-thyroidectomy hypocalcemia, regulatory effects and mechanisms of Mg on Ca, interactions between Mg and Ca regulators such as parathyroid hormone (PTH), 1,25(OH)₂D, and underlying related molecular mechanisms. Wilson et al. prospectively examined the association between postoperative magnesium levels and temporary hypocalcaemia in 50 patients undergoing total thyroidectomy. They found that low magnesium was an independent predictor of postoperative hypocalcaemia after adjusting variables including postoperative serum calcium. In a retrospective study of 201 patients, Garrahy et al. found that low postoperative magnesium was an independent predictor of

Corresponding Author :- **Dr . Ranganath Reddy** Email:- drpebyreddy@yahoo.com

biochemical hypocalcaemia (2 Both studies did not adjust for PTH levels. Hammerstad et al. found that patients with Graves' who had permanent hypocalcaemia following total thyroidectomy (n=40) had a greater decline in serum magnesium (preoperatively to 48 hours post-op) [3]. This finding was limited by the relatively small sample size as only four patients developed permanent hypocalcaemia in their cohort. Cherian et al. found no association between low postoperative magnesium (<1.8 mg/dL) and postoperative hypocalcaemia in a prospective analysis of 50 patients who underwent total thyroidectomy [4]. Others have also found no association between postoperative serum magnesium and post-thyroidectomy hypocalcaemia [5-6]. On this basis, routine magnesium measurements cannot be recommended, but it would be reasonable to check and treat for hypomagnesemia in patients with severe or protracted hypocalcaemia. PTH measurements are used in many centres to predict post-operative hypocalcaemia. Studies have shown patients with low intraoperative PTH (any time from resection of the gland up to 10 minutes after resection), low postoperative PTH levels (30 minutes to 5 days after surgery), and decline of PTH between preoperative and postoperative measurements can be used to predict temporary post-thyroidectomy hypocalcaemia [7]. The utility of 4-hour iPTH and perioperative iPTH decline was studied in a prospective study of 137 patients who underwent total thyroidectomy [8]. Decline in iPTH levels (preoperative to 4 hours postoperatively) of 68.5% or more from preoperative levels was more accurate (PPV: 90.5%) compared to 4-hour iPTH (PPV: 82.5%) in predicting postoperative hypocalcaemia. In another prospective study of 106 patients, iPTH decline of 80% or more at 3 hours after surgery was found to have a PPV of 100% for postoperative hypocalcaemia [9]. In the subgroup of patients who had postsurgical PoSH, undetectable serum iPTH (compared to low but detectable) at 4 weeks after surgery was an independent predictor of permanent PoSH. In the group with undetectable PTH (n=34), 13/34 (38.2%) had permanent PoSH [10].

Post-TT hypocalcemia usually does not become evident in the first 24 hours to 48 hours. Therefore, patients are routinely hospitalized for two days after the surgery to monitor for the clinical and laboratory signs of hypocalcemia. However, this approach causes significant costs for the healthcare system and the patient and patients who are at a lower risk of developing hypocalcemia, do not benefit from a lengthy hospitalization. There is currently a trend toward discharging lower risk patients at the same day of the surgery, or even performing total thyroidectomy as an outpatient procedure. However, it is not safe to use this approach for all the patients, since patients developing hypocalcemia after being discharged experience significant distress and need to visit the emergency department. Therefore, it is important to identify risk factors that can predict the risk of developing hypocalcemia. A prospective

study of 70 patients examined the utility of iPTH at 24 hours after surgery in predicting long term parathyroid function [11]. iPTH of 5.8 pg/mL or lower had a poor PPV of 30% in predicting permanent hypoparathyroidism; however, a good negative predictive value (NPV) of 100%. Measurement of postoperative PTH levels is becoming the standard in the early detection and treatment of PoSH. Early postoperative PTH and calcium-based protocols are used to guide management with calcium and/or vitamin D supplementation and subsequent weaning in many centers. Our study aim is to explore the relationship between hypomagnesemia and biochemical hypocalcemia and symptomatic hypocalcemia in the present study.

Material and Methods:

Patients who underwent thyroidectomy (total [TTx] and completion thyroidectomy [CT]) were included in the retrospective study. And preoperative and postoperative data about calcium, magnesium and PTH was extracted from the database. Exclusion criteria were lobectomy and near TTx, or any disease which would affect the level of calcium and magnesium, or patients with preoperative hyper/hypo-calcemia/magnesiumemia. Blood was collected and tested in 6 AM in the 1st postoperative Morning postoperative calcium, magnesium and iPTH was recorded. Then normal calcemic patients without any discomfort were discharged in 1st or 2nd postoperative day. The other patients were prescribed with oral calcium and/or vitamin D supplementation on case-by-case basis. Generally, whether supply with calcium and/or vitamin D was decided by the hypocalcemic symptom or biochemical hypocalcemia.

Hypocalcemia means below the reference, reference: magnesium 0.67–1.04 mmol/L, calcium 2.1–2.7 mmol/L and Ipth 1.6–6.9 pmol/L. SxH means specific numbness, spasm, muscular cramp and Chevok's syndrome et al. led by hypocalcemia.

Patients were followed up rigorously at outpatient department, and begin from the end of 1st month after discharge. In terms of patients administrated with calcium and/or vitamin D were followed every month after discharge until 6 months, then 6 months thereafter. Or they were followed 1, 3, 6 month(s) after discharge until 6 months, then 6 months thereafter.

Statistical analysis:

. P value <0.05 indicated significant difference. Data analysis was performed by SPSS 11.5 version (SPSS Inc., Chicago.). If normal distributed, continuous variables were presented as the mean \pm standard deviation and compared by t-test; if not, variables were presented as median and compared by Mann Whitney U-test. Pearson Chi-square test or Fisher's exact test was used to compare frequency (percentage) for categorical variables. Logistic regression was used to determine the risk factor.

Table:1. Basic characteristics of patients enrolled

Age	41.62±11.50
Sex (male/female)	25\75
Preoperative magnesium	0.90±0.10
Postoperative magnesium	0.75±0.075
Preoperative calcium	2.23±0.12
Postoperative calcium	2.18±0.16
Preoperative iPTH	5.50±2.03
Postoperative iPTH	2.26±1.41

Table:2. Baseline comparison between biochemical hypocalcemia and eucalcemia patients

	Hypocalcemia(82)	Normocalcemia	P value
Age (>45/<45)	11\16	23\50	0.279
Sex(male/female)	6\21	23\50	0.01
Po hypomagnesemia	12\15	18\55	0.008
Po hyperphosphatemia	13\14	30\43	0.150
Po iPTH<1.6 pmol/L	10\17	35\38	0.057

Table:3. Risk factor identification of biochemical hypocalcemia

	Univariate		Multivariate		
	OR	P value	OR	95% CI	CI P value
Age (>45/<45)	1.351	0.249	2.152	1.125,4.102	0.020
Sex(male/female)	0.448	0.011	2.032	1.144,3.592	0.015
Po hypomagnesemia	2.156	0.0009			
Po yophasphatemia	1.492	0.120			
Po iPTH < 1.6 pmol/L	1.662	0.054			

Table.4 :Risk factor identification of symptomatic hypocalcemia

	Univariate		Multivariate		
	OR	P value	OR	95% CI	CI P value
Age (>45/<45)	0.770	0.492			
Sex(male/female)	1.836	0.164			
Po hypocalcemia	2.444	0.013	2.220	1.012,4.876	0.045
Po hyperphosphatemia	1.235	0.539			
Po hypomagnesemia	2.687	0.045	1.374	0.971,2.010	0.216
Po iPTH < 1.6 pmol/L	4.947	0.001	1.192	0.895,1.900	0.126

Discussion:

The study was to investigate the risk factors of hypocalcemia. Reportedly, prevalence of biochemical and symptomatic hypocalcemia was extensively various. This variability of prevalence is much associated with adopted definition of hypocalcemia, dissection technique, included extent of thyroidectomy and supplement plan of calcium and vitamin D post-thyroidectomy. As we know, the relation between calcium and magnesium metabolism is complicated. Magnesium deficiency is associated with impaired secretion and affinity of PTH. Magnesium may compete with calcium, and play a mimic effect on the parathyroid cell. The “calcium” receptor stimulates secretion of PTH in the presence of elevated level of calcium. However, when hypomagnesemia, calcemic ions are relative much more than usual, secretion of PTH is

inhibited. Rude et al. suggested that intravenous injection of magnesium solution, when hypocalcemia secondary to hypomagnesemia, secretion of PTH would increase dramatically in 1 min after administration [12].

It approved conversely; hypomagnesemia could inhibit secretion. Cherian et al. reported that lower magnesium level among patients with abnormal postoperative than those with normal PTH in a series of 50 patients, yet it was not significant (p = 0.22) [13]. While, postoperative in eumagnesemia patients was lower than that in hypomagnesemia patients significantly in the present study. Clinically, limited literature had investigated the role of hypomagnesemia after thyroidectomy. Wilson et al. reported that hypomagnesemia indeed had a significant relation with hypocalcemia in a prospective study in a series of 50 patients with total thyroidectomy

[14] and Hammerstad et al. suggested that decreasing degree of magnesium level in 48 h after operation may predict development of permanent hypoparathyroidism combined with preoperative serum calcium and postoperative PTH [15]. In our present study, we also found that the significant relation between hypomagnesemia and hypocalcemia. Being different from the Cherian's research, in which the prevalence of hypomagnesemia/post-thyroidectomy was about 24% and 70% respectively, only 23.36% patients developed hypomagnesemia after surgery, and no patient had hypomagnesemia [13]. The obvious statistic gap may attribute to the totally different environment and dietary habit. In addition, gender (female) was proved to be an independent risk factor for hypocalcemia in the present study. Likely, Wilson et al. also reported that there was a trend to lower calcium levels in female patients, though not positively related in multivariate analysis [14]. Different level of magnesium between genders may be the main reason.

Syedmoradi et al. reported that hypomagnesemia was much prevalent in women than man, $p < 0.05$ in cross-sectional study with 1558 subjects in Iranian urban area [14]. Relative parathyroid insufficiency seems to be the principal mechanism of post thyroidectomy hypocalcemia, even in patients with normal postoperative PTH concentrations [15]. Seo et al. proved that the absolute postoperative values and the relative decline $>70\%$ in PTH values in 1h after surgery was reliable predictive factors for hypocalcemia [16]. A consensus was nearly reached that it would be more reasonable to take the baseline function of parathyroid into consideration, rather than the absolute number. Additionally, there lacks an illustration of continuing change of magnesium, calcium and iPTH, blood only was collected in the 1st morning after surgery [17]. We believe it would be interesting to observe the change of electrolyte and iPTH in days after surgery. And we will investigate whether correction of hypomagnesemia could alleviate hypocalcemia, including symptoms in further prospective studies. Symptoms and biochemical data prospectively. Besides, all of less than total thyroidectomy is excluded from the final analysis. And all of operations were performed by one surgeon. Additionally, data integrity is well in our study, every

REFERENCE:

1. Anast CS, Winnacker JL, Forte LR, et al. Impaired release of parathyroid hormone in magnesium deficiency. *J Clin Endocrinol Metab* 42, 1976, 707-17.
2. Garrahy A, Murphy MS, Sheahan P, et al. Impact of postoperative magnesium levels on early hypocalcemia and permanent hypoparathyroidism after thyroidectomy. *Head Neck* 38, 2016, 613-9.
3. Hammerstad SS, Norheim I, Paulsen T, et al. Excessive decrease in serum magnesium after total thyroidectomy for Graves' disease is related to development of permanent hypocalcemia. *World J Surg* 37, 2013, 369-75.
4. Cherian AJ, Gowri M, Ramakant P, et al. The role of magnesium in post-thyroidectomy hypocalcemia. *World J Surg* 40, 2016, 881-8.
5. Cavicchi O, Piccin O, Caliceti U, et al. Accuracy of PTH assay and corrected calcium in early prediction of hypoparathyroidism after thyroid surgery. *Otolaryngol Head Neck Surg* 138, 2008, 594-600.

patient had perioperative data about electrolyte and iPTH [18-20].

Conclusion:

Risk factors for the occurrence of PoSH may be classified as modifiable or treatable (such as Vitamin D deficiency or hypomagnesemia) or non-modifiable (such as postoperative PTH level or Graves' disease). A more accurate understanding of risk attributable to individual risk factors would help in a better prediction of risk of PoSH and this can be factored into the discussions regarding the risks and benefits of surgery. When the risk is considered high, it may be possible and appropriate to modify approach or extent of surgery in 'high risk' patients or use some of the novel preventative measures such as fluorescent imaging for parathyroid identification or preservation.

Intact PTH level checked at 1 hour after surgery was useful in prediction of symptomatic hypocalcemia. Serum ionized calcium measured on the morning after surgery was a reliable predictor for biochemical hypocalcemia. Using both iPTH and postoperative iCa^{++} levels will increase the diagnostic accuracy for the early and reliable prediction of postoperative hypocalcemia. Hypomagnesemia is not a rare complication successive to thyroidectomy. To be independent risk factor for biochemical hypocalcemia in the study, other than the variable sex. And relative decline of iPTH, outweighed absolute value of iPTH and magnesium, was identified to be risk factor of symptomatic hypocalcemia.

Acknowledgments

Authors of this study wish to thank the Dean, Sri Lakshmi Narayana Institute of Medical Sciences, Puducherry, 605 502, India for providing research laboratory.

Funding Statement

This research received no specific grant from any funding agency

Conflicts Of Interest

The authors declare no conflict of interest.

6. Wu SD, Gao L, *et al.* Is routine calcium supplementation necessary in patients undergoing total thyroidectomy plus neck dissection? *Surg Today* 41, 2011, 183-8.
7. Edafe O, Antakia R, Laskar N, *et al.* Systematic review and meta-analysis of predictors of post-thyroidectomy hypocalcaemia. *Br J Surg* 101, 2014, 307-20.
8. Lecerf P, Orry D, Perrodeau E, *et al.* Parathyroid hormone decline 4 hours after total thyroidectomy accurately predicts hypocalcemia. *Surgery* 152, 2012, 863-8.
9. Schlottmann F, Arbulú AL, Sadava EE, *et al.* Algorithm for early discharge after total thyroidectomy using PTH to predict hypocalcemia: prospective study. *Langenbecks Arch Surg* 400, 2015, 831-6.
10. Sitges-Serra A, Ruiz S, Girvent M, *et al.* Outcome of protracted hypoparathyroidism after total thyroidectomy. *Br J Surg* 97, 2010, 1687-95.
11. Julian MT, Balibrea JM, Granada ML, *et al.* Intact parathyroid hormone measurement at 24 hours after thyroid surgery as predictor of parathyroid function at long term. *Am J Surg* 206, 2013, 783-9.
12. Sasson AR, Pingpank JF Jr, Wetherington RW, Hanlon AL, Ridge JA, *et al.* Incidental parathyroidectomy during thyroid surgery does not cause transient symptomatic hypocalcemia. *Archives of otolaryngology-head & neck surgery*.
13. Cherian AJ, *et al.* The role of magnesium in post-thyroidectomy Hypocalcemia. *World J Surg.* 40, 2016, 881-8.
14. Syedmoradi L, Ghasemi A, Zahediasl S, Azizi F, *et al.* Prevalence of hypo- and hypermagnesemia in an Iranian urban population. *Ann Hum Biol.* 38, 2011, 150-5.
15. Raffaelli M, *et al.* Post-thyroidectomy hypocalcemia is related to parathyroid dysfunction even in patients with normal parathyroid hormone concentration early after surgery. *Surgery.* 159, 2016, 78-84.
16. Seo ST, *et al.* Transient and permanent hypocalcemia after total thyroidectomy: early predictive factors and long-term follow-up results. *Surgery.* 158, 2015, 1492-9.
17. Sitges-Serra A, *et al.* Outcome of protracted hypoparathyroidism after total thyroidectomy. *The British journal of surgery.* 97, 2010, 1687-95.
18. Abboud B, *et al.* Careful examination of thyroid specimen intraoperatively to reduce incidence of inadvertent parathyroidectomy during thyroid surgery. *Archives of otolaryngology-head & neck surgery.* 133, 2007, 1105-10.
19. Page C, Strunski V, *et al.* Parathyroid risk in total thyroidectomy for bilateral, benign, multinodular goitre: report of 351 surgical cases. *J Laryngol Otol.* 121, 2007, 237-41.
20. Sakorafas GH, *et al.* Incidental parathyroidectomy during thyroid surgery: an underappreciated complication of thyroidectomy. *World J Surg.* 29, 2005, 1539-43.