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General Surgery

HYPOMAGNESEMIA PREDICTS POSTOPERATIVEBIOCHEMICAL HYPOCALCEMIA AFTER THYROIDECTOMY

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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.

KEYWORDS : 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). Mg^{2+} 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 anindependent 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 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 centres. Our study aim is to explore the relationship betweenhypomagnesemia and biochemical hypocalcemia and symptomatic hypocalcemia in the present study.

MATERIALAND 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/magnesemia. 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 ± 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

RESULTS:

Table.1: Basic characteristics of patients enrolled

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

Table. 3: Risk factor identification of biochemical hypocalcemia

Table.4 : Risk factor identification of symptomatic hypocalcemia

DISCUSSION:

The study was to investigatethe risk factors of hypocalcemia. Reportedly, prevalence of biochemical and symptomatichy pocalcemia was extensively various. This variability ofprevalence is much associated with adopted definition ofhypocalcemia, dissection technique, included extent ofthyroidectomy and supplement plan of calcium andvitamin D post-thyroidectomy. As we know, the relation between calcium and magnesiummetabolism is complicated. Magnesium deficiency isassociated with impaired secretion and affinity of PTH. Magnesium may compete with calcium, and play a mimiceffect on the parathyroid cell. The "calcium" receptorstimulates secretion of PTH in the presence of elevatedlevel of calcium. However, when hypomagnesemia, calcemicions are relative much more than usual, secretion ofPTH is inhibited. Rude et al. suggested that intravenousinjection of magnesium solution, when hypocalcemi asecondary to hypomagnesemia, secretion of PTH wouldincrease dramatically in 1 min after administration (12).

It approved conversely, hypomagnesemia could inhibitPTH secretion. Cherian et al. reported that lower magnesiumlevel among patients with abnormal postoperativePTH than those with normal PTH in a series of 50 patients, yet it was not significant (p = 0.22) (13). While,postoperativeiPTH in eumagnesemia patients was lowerthan that in hypomagnesemia patients significantly in thepresent study.Clinically, limited literature had investigated the roleof hypomagnesemia after thyroidectomy. Wilson et al.reported that hypomagnesemia indeed had a significantrelation with hypocalcemia in a prospective study in aseries of 50 patients with total thyroidectomy (14) and Hammerstad et al. suggested that decreasing degree ofmagnesium level in 48 h after operation may predict developmentof permanent hypoparathyroidism combinedwith preoperative serum calcium and postoperative PTH (15). In our present study, we also found that the significantrelation between hypomagnesemia and hypocalcemia. Being different from theCherian's research, in which the prevalence of hypomagnesemiapre/post-thyroidectomy was about 24% and70% respectively, only 23.36% patients developed hypomagnesemiaafter surgery, and no patient had hypomagnesemia (13). The obvious statistic gap may attribute tothe totally different environment and dietary habit. In addition, gender (female) was proved to be an independentrisk factor for hypocalcemia in the present study.Likely, Wilson et al. also reported that there was a trend tolower calcium levels in female patients, thoughnot positively related in multivariate analysis (14). Differentlevel of magnesium between genders may be the main reason.

Syedmoradi et al. reported that hypomagnesemia was much prevalent in women than man , p < 0.05in cross-sectional study with 1558 subjects in Iranian urbanarea (14).Relative parathyroid insufficiency seems to be the principalmechanism of postthyroidectomy hypocalcemia, evenin patients with normal postoperative PTH concentrations (15). Seo et al. proved that the absolute postoperativevalues and the relative decline >70% in PTH values in 1 hafter surgery was reliable predictive factors for hypocalcemia (16). A consensus was nearly reached that it would bemore reasonable to take the baseline function of parathyroidinto consideration, rather than the absolute number. Additionally, there lacks an illustration of continuingchange of magnesium, calcium and iPTH, blood onlywas collected in the 1st morning after surgery (17). We believeit would be interesting to observe the change of electrolyteand iPTH in days after surgery. And we will investigatewhether correction of hypomagnesemia could alleviatehypocalcemia, including symptoms in further prospectivestudies. Symptoms and biochemical dataprospectively. Besides, all of less than toal thyroidectomy.is excluded from the final analysis. And all of operationswere performed by one surgeon. Additionally, data integrityis well in our study, every patient had perioperativedata 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 tothyroidectomy. To be independent risk factor forbiochemical hypocalcemia in the study, other than thevariable sex. And relative decline of iPTH, outweighed absolutevalue of iPTH and magnesium, was identified to berisk factor of symptomatic hypocalcemia.

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 ypophasphatemia	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 hypocalsemia	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

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