

Ryan E. Cabance, MD¹
Emmanuel Tadeus S. Cruz, MD^{1,2}

¹Department of Otolaryngology
Head & Neck Surgery
Manila Central University - Filemon D. Tanchoco
Medical Foundation Hospital

²Department of Otolaryngology – Head & Neck Surgery
Quezon City General Hospital

Value of the 6-Hour Postoperative Ionized Calcium Slope in Predicting Post- Thyroidectomy Occurrence of Hypocalcemia

ABSTRACT

Objective: To determine the value of the 6-hour postoperative ionized Calcium (iCa) slope versus 6-hour postoperative Calcium alone in predicting the occurrence of hypocalcemia in patients who underwent thyroid surgery in a tertiary hospital in Metro Manila.

Methods:

Design: Retrospective cross-sectional study

Setting: Tertiary Private Hospital

Subjects: Pre-operative and 6-hour postoperative ionized calcium determinations were analyzed in 59 patients of the ENT-HNS Department in a tertiary hospital in Metro Manila who underwent thyroid surgery from January 2009 to December 2013.

Results: The 6-hour postoperative iCa slope (difference between the pre-operative and 6-hour postoperative iCa levels) of ≥ 0.18 mmol/L correctly predicted 57.1% of patients who eventually developed hypocalcemia, with a specificity of 81.6% and a positive predictive value of 63.2%. In contrast, the 6-hour postoperative iCa measurement identified only 23.8% (5 out of 21) patients who developed hypocalcemia.

Conclusion: The 6-hour postoperative iCa slope increased the probability of identifying patients who developed hypocalcemia from 23.8% to 57.1%. However, as a single determination, this may not suffice to take the place of serial iCa measurements after thyroid surgery.

Keywords: *ionized calcium (iCa), hypocalcemia, thyroidectomy*

Hypocalcemia is the most common complication of thyroid surgery and has a higher incidence in total and near-total thyroidectomy than other types of thyroid surgery such as total thyroid lobectomy and near-total thyroidectomy.¹ To our knowledge, there is no standard as to when the levels of ionized calcium should first be measured following thyroid surgery, nor are

Correspondence: Dr. Emmanuel Tadeus S. Cruz
Department of Otolaryngology – Head & Neck Surgery
MCU FDTMF Hospital
EDSA, Caloocan City 1400
Philippines
Phone: (632) 367 2031 local 1212 OPD 1144
Fax: (632) 367 2249
Email: orlhns_mcu@yahoo.com
Reprints will not be available from the authors.

The authors declare that this represents original material that is not being considered for publication or has not been published or accepted for publication elsewhere in full or in part, in print or electronic media; that the requirements for authorship have been met by the author, and that the author believes that the manuscript represents honest work.

Disclosures: The authors signed a disclosure that there are no financial or other (including personal) relationships, intellectual passion, political or religious beliefs, and institutional affiliations that might lead to a conflict of interest.

there accepted guidelines on when calcium supplementation should be started in the absence of symptoms of hypocalcemia regardless of ionized calcium levels. Indiscriminate calcium supplementation after thyroid surgery is unnecessary and puts patients at risk for hypercalcemia.

In our institution, a 6-hour postoperative ionized calcium determination is often requested after total thyroidectomy. However, it is only requested after a thyroid lobectomy or near-total thyroidectomy when the patient shows symptoms and signs of hypocalcemia. Calcium supplementation is started once symptoms and signs of hypocalcemia appear. In cases of asymptomatic hypocalcemia, it is often left to the discretion of the attending physician if and when supplementation will be started.

The 1-hour postoperative parathyroid hormone level has shown high sensitivity and specificity in predicting patients who will develop hypocalcemia after thyroid surgery avoiding potentially dangerous clinical consequences and lessening the need for multiple calcium measurements.²⁻⁴ Unfortunately, this test is expensive and not available in our institution. Serial determinations of postoperative ionized calcium would be ideal in identifying patients with hypocalcemia but each determination poses an additional financial burden. If the test is not available, ionized calcium levels (the biologically active form) can better assess calcium homeostasis than serum calcium which, even when corrected for albumin levels has been shown to be only 53% sensitive and 85% specific in evaluating hypocalcemia.⁵

The slope or drop in calcium levels postoperatively may be predictive of hypocalcemia but multiple measurements are required in 24 hours; this slope (or difference) between pre-operative and 24-hour postoperative serum calcium levels can help differentiate between temporary or permanent hypocalcemia.⁶ Previous studies showed that 8-hour postoperative ionized calcium levels accurately detected 40% of patients who required calcium supplementation after total/near-total thyroidectomy and/or parathyroidectomy⁷ while a 12- to 18-hour slope (decrease) in serum calcium of ≥ 1.1 mg/dL predicted the occurrence of hypocalcemia in 76% of patients who underwent total thyroidectomy and reduced the number of calcium measurements from a mean of 13 tests/patient to a mean of 3 tests/patient.⁸ If the 6-hour postoperative ionized calcium slope could accurately predict patients who would develop hypocalcemia, it would be of significant value in the postoperative care of patients undergoing thyroid surgery.

This paper seeks to determine the value of the 6-hour postoperative ionized Calcium (iCa) slope, versus 6-hour postoperative Calcium alone, in predicting the occurrence of hypocalcemia in patients who underwent thyroid surgery in a tertiary hospital in Metro Manila.

METHODS

A. Research Design: Retrospective Cross Sectional

B. Sample Population

The research protocol was approved by the institution's IRB. Private and clinical division patients who underwent thyroid surgery from January 2009 to December 2013 under the service of the Department of ENT-HNS of our institution, with preoperative and 6-hour postoperative ionized calcium determinations were included. Excluded from the study were those without pre-operative and/or 6-hr postoperative iCa determinations, history of hypocalcemia / hypoparathyroidism, history of hypercalcemia / hyper-parathyroidism, diabetes, renal disease, and the use of maintenance medications such as diuretics and anti-convulsants.

C. Variables

The following variables were recorded and tabulated: preoperative ionized calcium, 6-hr postoperative ionized calcium, 6-hr postoperative iCa slope (difference between pre-operative and 6-hr postoperative iCa levels), age, sex, type of thyroid surgery (total/completion, near-total, lobectomy), histopathological findings (benign or malignant), number of parathyroid glands identified and preserved and the presence of signs and symptoms of hypocalcemia.

D. Sample Size

Using the 95% confidence level, the ideal sample size was computed to be n=40

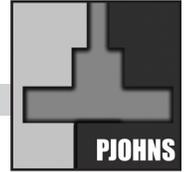
$$n = \frac{(Z_{\alpha} + Z_{\beta})^2 + (SD)^2}{E^2} \times 2$$

Where:

- Z α = 1.96 at 95% confidence level
- Z β = 1.28 at 80% power of the study
- SD = 0.098 (A Qari, 2005)
- E = 0.05 (error of 5%)

E. Statistical Analysis

The gathered data was grouped into two: the normocalcemic group (group 1) consisted of patients who did not have any postoperative calcium result below 1.10 mmol/L and did not develop any of signs or symptoms of hypocalcemia such as perioral numbness, tingling sense or paresthesia of hands and/or feet, Chvostek sign, Trousseau sign, muscle



cramps, or tetany during their hospital stay; the hypocalcemic group (group 2) composed of patients who developed the above mentioned signs or symptoms and/or had a postoperative ionized calcium level <1.10 mmol/L during their hospital stay. The signs and symptoms noted by patients in the hypocalcemic group were tallied to determine the frequency of occurrence.

The variables of the 2 groups such as the difference (slope) between preoperative and postoperative ionized calcium levels, the type of thyroid surgery, the number of parathyroid glands identified and preserved, mean age, sex and final histopath results were analyzed statistically using the T-test, Paired T-test and Mann Whitney U test, Kruskal Wallis and Bonferroni test using SPSS for Windows version 20 (IBM Corporation, NY, USA).

RESULTS

A total of 59 out of 76 patients who underwent thyroid surgery in our department between January 2009 and December 2013 were included in this study. Seventeen patients were excluded because of the absence of either a pre-operative or 6-hr postoperative iCa result. There were 55 (93.2%) females and 4 (6.8%) males with ages ranging from 20 to 82 years old with an average age of 41.96 years. All were euthyroid and normocalcemic at the time of surgery. There was no significant difference in the sex and age distribution among the patients between the two groups. (Table 1)

Table 1. Age and Sex of Patients grouped according to presence of postoperative hypocalcemia

	# of patients (%) (n=59)	# Normocalcemic (%) (n=38)	# Hypocalcemic (%) (n=21)	<i>p-value*</i>
Female	55 (93.2%)	35 (92.1%)	20 (95.2%)	1.00 (NS)
Male	4 (6.8%)	3 (7.9%)	1 (4.8%)	
Age in yrs \pm SD	41.96 \pm 13.92	41.55 \pm 13.85	42.71 \pm 14.34	0.76 (NS)

**p-values* >0.05 - Not significant; *p-values* ≤ 0.05 -Significant

There was no significant difference between the pre-operative iCa levels of the normocalcemic and hypocalcemic groups ($p=0.07$). However, a significant difference was noted in the 6-hr postoperative iCa levels of the 2 groups ($p=0.00$) with the hypocalcemic group having lower iCa levels. Comparing the 6-hr postoperative iCa slope, there was a significant difference ($p=0.006$) between the 2 groups with the hypocalcemic group having a larger drop (mean=0.18) in iCa levels. (Table 2)

Table 2. Comparison of pre- and post-operative iCa levels between Normocalcemic and Hypocalcemic groups

N=59	Normocalcemic (n=38)	Hypocalcemic (n=21)	<i>p-value</i>
Pre-op mean (n=38)	1.37	1.27	0.07 (NS)
Postop mean (n=21)	1.26	1.09	0.00 (S)
Mean slope \pm SD (median)	0.10 \pm 0.30 (0.10)	0.18 \pm 0.09 (0.19)	0.006 (S)

**p-values* >0.05 - Not significant; *p-values* ≤ 0.05 -Significant

Thirty-six out of 38 patients in the normocalcemic group had a drop in their iCa levels 6-hrs postoperatively while the remaining 2 had an increase in their postoperative iCa levels. All patients in the normocalcemic group had 6-hr postoperative iCa levels within normal range.

Only 5 patients in the hypocalcemic group had iCa levels less than 1.10 mmol/L at 6-hrs postoperatively. None of the 21 patients were symptomatic at 6-hrs postop. At 18-hrs postop, 1 patient developed symptoms of hypocalcemia despite a normal iCa level. At 24 hours postop, 5 patients had below normal iCa levels and signs and symptoms of hypocalcemia; and 1 patient developed signs/symptoms but had normal iCa levels. Table 3 summarizes the findings in the hypoglycemic group. Calcium supplementation was started for all the patients once clinical signs and symptoms were observed. Supplementation for patients with only biochemical hypocalcemia was given according to the discretion of the attending physician.

Table 3. Presence of Biochemical and/or Clinical Hypocalcemia among patients in the Hypocalcemic Group (n=21)

Hours Postop	iCa < 1.10 mmol/L NO signs/symptoms	iCa < 1.10 mmol/L WITH signs/symptoms	iCa ≥ 1.10 mmol/L WITH signs/symptoms
6 hrs	5	0	0
18 hrs	0	0	1
24 hrs	5	5	1
36 hrs	0	1	0
48 hrs	2	0	1
TOTAL	12	6	3

The mean 6-hr postoperative iCa slope (difference between the pre-operative and 6-hr postoperative iCa levels) of 0.18mmol/L of the hypocalcemic group correctly identified 12 out of the 21 patients who developed hypocalcemia while the other 9 patients had a slope of

<0.18mmol/L. The sensitivity was 57.1% and specificity of 81.6% with a positive predictive value of 63.2%. (Table 4)

Out of the 38 patients in the normocalcemic group, 9 (23.7%) underwent total thyroidectomy, 13 (34.2%) near total thyroidectomy and 16 (42.1%) thyroid lobectomies. Of the 21 patients in the hypocalcemic group 11 (55%) underwent total thyroidectomy, 5

Table 4. Comparison of pre- and post-operative iCa levels between the Normocalcemic and Hypocalcemic groups

6-hr Postop iCa Slope (mmol/L)	Normocalcemic # of patients (n=38)	Hypocalcemic # of patients (n=21)	Total
≥0.18	7	12	19
<0.18	31	9	40
Sensitivity = 57.1%			
Specificity = 81.6%			
Positive Predictive Value = 63.2%			
Negative Predictive Value = 77.5%			

(23.8%) near total thyroidectomy and 5 (23.8%) total lobectomy. The 6-hr postoperative iCa slope between the 2 groups according to the type of thyroid surgery done showed no significant difference. However, in both groups, the patients who underwent total/completion thyroidectomy had a significantly larger drop in iCa 6-hours postoperatively when compared to near-total thyroidectomy and lobectomy within the same group. (Table 5)

Comparison of the 6-hr iCa slope in the patients with hypocalcemia showed no significant difference between those with malignant and benign tumors. (Table 6)

A minimum of 2 parathyroid glands were identified and preserved in all of the cases. There was no significant difference in the slope of the 2 groups according to the number of parathyroid glands preserved. Hypocalcemia developed in 14 out of 21 (29.8%) patients despite having 4 parathyroid glands preserved. (Table 7)

Among the 21 patients in the hypocalcemic group, 9 (42.9%) developed signs and symptoms of hypocalcemia during their hospital stay. The most common complaint was tingling / numbness in the

Table 5. Comparison of the mean 6-hr postoperative iCa slope between and within normocalcemic and hypocalcemic groups according type of thyroid surgery.

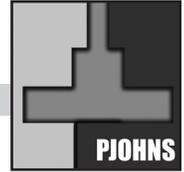
N=59	Normocalcemic (%) (n=38)			Hypocalcemic (%) (n=21)			p-value*
	Pre-op mean	Postop mean	Mean slope ± SD (median)	Pre-op mean	Postop mean	Mean slope ± SD (median)	
Thyroid Lobectomy ± isthmusectomy (n=21)	16 (42.1%)			5 (23.8%)			0.74 (NS)
	1.32	1.25	0.07 ± 0.15 (0.09)	1.19	1.08	0.11 ± 0.06 (0.1)	
Near Total Thyroidectomy (n=18)	13 (34.2%)			5 (23.8%)			0.17 (NS)
	1.29	1.29	0.003 ± 0.32 (0.09)	1.20	1.05	0.14 ± 0.07 (0.13)	
Total Thyroidectomy (n=20)	9 (23.7%)			11 (52.4%)			0.38 (NS)
	1.54	1.23	0.31 ± 0.42 (0.18)	1.35	1.12	0.23 ± 0.08 (0.22)	
p-value*	0.03 (S)			0.01 (S)			

* p-values >0.05- Not significant; p-values ≤0.05-Significant

Table 6. Comparison of the mean 6-hr postoperative iCa slope benign and malignant findings in the Hypocalcemic Group.

Hypocalcemic Group (n=21)	Malignant			Benign			p-value*
	Pre-op mean	Postop mean	Mean slope ± SD	Pre-op mean	Postop mean	Mean slope ± SD	
	6 (28.6%)			15 (71.4%)			0.95 (NS)
	1.29	1.11	0.18 ± 0.09	1.27	1.09	0.18 ± 0.09	

* p-values >0.05- Not significant; p-values ≤0.05-Significant

**Table 7.** Comparison of the mean 6-hr postoperative iCa slope between normocalcemic and hypocalcemic groups according to the # of parathyroid glands preserved.

N=59	Normocalcemic (%) (n=38)			Hypocalcemic (%) (n=21)			p-value*
	Pre-op mean	Postop mean	Mean slope ± SD	Pre-op mean	Postop mean	Mean slope ± SD	
0 (n=0)	0			0			N/A
1 (n=0)	0			0			N/A
2 (n=4)	3 (75%)			1 (25%)			0.18 (NS)
	1.33	1.37	0.13 ± 0.04	1.29	1.11	0.22 ± 0	
3 (n=8)	2 (25%)			6 (75%)			0.10 (NS)
	1.37	1.22	0.07 ± 0.05	1.27	1.09	0.21 ± 0.08	
4 (n=47)	33 (70.2%)			14 (29.8%)			0.08 (NS)
	1.37	1.22	0.10 ± 0.33	1.27	1.09	0.16 ± 0.09	

* p-values >0.05- Not significant; p-values ≤0.05-Significant

Table 8. Frequency of Signs and Symptoms of Hypocalcemia

Signs / Symptoms	Frequency
Tingling / numbness upper extremities	7
Tingling / numbness lower extremities	1
Circumoral numbness	3
Positive Trousseau	4
Positive Chvostek's	1

upper extremities which was reported by 7 patients. The most common sign was a positive Trousseau sign which was elicited in 4 patients. All the 21 patients in the hypocalcemic group were asymptomatic at 6-hours postop. The initial appearance of signs and symptoms occurred at an earliest of approximately 18 hours to a latest of 48 hours postoperatively with some lasting up to 72 hours despite calcium supplementation. One patient required oral calcium supplementation up to 2 weeks postoperatively. (Table 8)

DISCUSSION

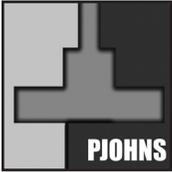
Calcium plays a major role in many physiologic processes such as contraction of skeletal, cardiac and smooth muscles; blood clotting; and nerve impulse transmission. Neurons are sensitive to changes in calcium ion concentrations and elevation of calcium ion concentration above normal (hypercalcemia) causes depression of the nervous system while decreases in calcium concentration (hypocalcemia) cause the nervous system to become more excitable.⁹ Parathyroid hormone plays a major role in controlling extracellular calcium and phosphate concentrations by various mechanisms. Hypofunction, ischemia or injury of the parathyroid glands causes hypocalcemia which may lead to tetany if not corrected. Removal of 3 of the 4 normal glands causes temporary

hypoparathyroidism. But even a small amount of parathyroid tissue is capable of hypertrophying to perform the function of all the glands.⁴

Hypocalcemia, although often transient, is the most common cause of morbidity following thyroid surgery. In this study, hypocalcemia occurred in 35.6% (21 out of 59) of patients. The incidence of hypocalcemia in patients who underwent total thyroidectomy was 55%, higher than the results of other studies^{10,11} and may be attributed to the different levels of expertise of the surgeons.

Based on the 6-hr postoperative iCa measurement, only 5 (23.8%) patients were identified as hypocalcemic. Sixteen patients who were normocalcemic at 6-hrs postop eventually developed hypocalcemia during their hospital stay. Three out of the 17 patients who were excluded had a normal 6-hr postop iCa result and eventually developed hypocalcemia during the course of their hospitalization. In contrast, when the pre-operative and 6-hour postoperative iCa difference (slope) was determined, 12 out of the 21 (57.1%) patients were correctly predicted to develop hypocalcemia.

A significant difference was seen between the iCa slopes of the normocalcemic and hypocalcemic groups with the hypocalcemic group having a larger drop in iCa levels at 6-hours postop. This study showed that the mean 6-hr postoperative slope of iCa (≥ 0.18 mmol/L) correctly predicted 57.1% (12 out of 21) of patients who developed hypocalcemia with a positive predictive value of 63.2%. This is in contrast to the study of Bentrem *et al.* that showed that 8-hr postoperative iCa levels identified 40% of patients who would need supplementation. This study, however, utilized lower biochemical criteria (iCa < 1.0 mmol/L).⁷ The results of this study are lower than the 76% (42 out of 55) correctly predicted cases of hypocalcemia following total thyroidectomy in the study of Tredici, *et al.* that utilized the 12- to 18-hour postoperative serum calcium slope.⁸



It is also worth mentioning that 3 out of the 21 (14.3%) patients in the hypocalcemic group developed signs and symptoms of hypocalcemia but their iCa levels were normal. This occurrence may be explained by a rapid decline in iCa levels following thyroid surgery without necessarily falling below normal levels.¹²

The type of thyroid surgery, age, sex, histopathologic findings and the number of parathyroid glands preserved were not found to be associated with the occurrence of hypocalcemia. However, patients who underwent total thyroidectomy had a significantly larger drop in iCa levels at 6 hours after the surgery.

The most common sign of hypocalcemia was numbness of the upper extremities and the most common sign was a positive Trousseau sign. All cases of hypocalcemia in this study were transient with the earliest onset at 18 hours postoperatively. None of the patients required calcium supplementation for more than 2 weeks after surgery.

Additional studies on postoperative iCa determinations may identify which may be the most beneficial as a single determination in predicting the development of hypocalcemia when serial determinations are not feasible.

REFERENCES

1. Qari FA. Estimation of ionized calcium levels after thyroidectomy at King Abdul Aziz university hospital (Jeddah). *Kuwait Med J.* 2005 Sep; 37 (3): 169-172. [Editor: Duplicate Publication of Qari FA. Estimation of ionized calcium levels after thyroidectomy at King Abdul Aziz university hospital (Jeddah). *Pak J Med Sci.* 2004 Oct-Dec; 20 (4): 325-330.]
2. Le TN, Kerr PD, Sutherland DE, Lambert P. Validation of 1-hour post-thyroidectomy parathyroid hormone level in predicting hypocalcemia. *J Otolaryngol Head Neck Surg.* 2014 Jan 29; 43(1):5.
3. Venderlei F, Vieira J, Hojajj FC, Cervantes O, Kunii I, Ohe MN, et al. Parathyroid hormone: an early predictor of symptomatic hypocalcemia after total thyroidectomy. *Arq Bras Endocrinol Metabol.* 2012 Apr; 56 (3): 168-172.
4. Lam A, Kerr PD. Parathyroid hormone: an early predictor of post-thyroidectomy hypocalcaemia. *Laryngoscope.* 2003 Dec; 113 (12), 2196-2200.
5. Byrnes MC, Huynh K, Helmer SD, Stevens C, Dort JM, Smith RS. A comparison of corrected serum calcium levels to ionized calcium levels among critically ill surgical patients. *Am J Surg.* 2005 Mar; 189 (3): 310-314.
6. Pfeleiderer A, Ahmad N, Draper MR, Vrostsou K, Smith WK. The timing of calcium measurements in helping to predict temporary and permanent hypocalcemia in patients having completion and total thyroidectomies. *Ann R Col Surg Engl.* 2009 Mar; 91(2): 140-146.
7. Bentrem DJ, Rademaker A, Angelos P. Evaluation of serum calcium levels in predicting hypoparathyroidism after total / near-total thyroidectomy or parathyroidectomy. *Am Surg.* 2001 Mar; 67 (3): 251-252.
8. Tredici P, Grosso E, Gibelli B, Massaro MA, Arrigoni C, Tradati N. Identification of patients at high risk for hypocalcemia after total thyroidectomy. *Acta Otorhinolaryngol Ital.* 2011 Jun; 31(3): 144-148.
9. Hall JE, Guyton AC. Guyton and Hall Textbook of Medical Physiology. 12th ed. Philadelphia. Saunders Elsevier. 2010 Jun. 1388-1391.
10. Asari R, Passler C, Kaczirek K, Scheuba C, Niederle B. Hypoparathyroidism after total thyroidectomy: a prospective study. *Arch Surg.* 2008 Feb; 143 (2): 132-137.
11. Leahu A, Carroni V, G.B. Calcium level, a predictive factor of hypocalcemia following total thyroidectomy. *Jurnalul de Chirurgie, Iasi.* 2009; 5 (2): 148-152.
12. Kim JH, Chung MK, Son YI. Reliable early prediction for different types of post-thyroidectomy hypocalcemia. *Clin Exp Otorhinolaryngol.* 2011 Jun; 4 (2): 95-100.