Med. J. Cairo Univ., Vol. 89, No. 2, June: 635-644, 2021
www.medicaljournalofcairouniversity.net

The Timing of Parathyroid Hormone Measurement as an Early Predictor of Postoperative Hypocalcemia Post Total Thyroidectomy: A Prospective Study

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Abstract

Background: Serum intact parathyroid hormone (iPTH) level is an early marker of post-thyroidectomy hypocalcemia. However, lack of methodological standardization to define timing and cut-off points of iPTH measurement limit its clinical applicability. Here, we evaluated the relationship between two distinct postoperative time sampling and iPTH accuracy on predicting hypocalcemia.

Aim of Study: This study was aimed to evaluate the accuracy of iPTH measured after total thyroidectomy to predict postoperative hypocalcemia and to identify patients at risk of postoperative hypocalcaemia who require supplementation treatment, and those not at risk who can be safely discharged without any supplementation treatment. Moreover, combining postoperative PTH and serum calcium levels could result in an accurate prediction of the risk of postoperative hypocalcaemia.

Patients and Methods: iPTH was measured within 24h after surgery (iPTH 24h) and on the morning of the 3 rd postoperative day (iPTH 3 rd PO). Hypocalcemia was defined by levels of total calcium corrected by serum albumin ≤8.0mg/dL and/or by the presence of symptoms or signs. The most accurate iPTH cut-off point for hypocalcemia prediction was established from a ROC curve comparing both time-points.

Results: The study included 40 patients. The mean age was 46.23±9.03 years, 34 were women (85%) and all patients underwent total thyroidectomy. Hypocalcemia occurred in 8 patients (20%), of whom 5 were symptomatic. Lower levels of iPTH 24h and iPTH 3 rd PO were associated with postoperative hypocalcaemia (p<0.05). Using the ROC curve, the optimal cut-off points were 14.8pg/mL and 14pg/mL for iPTH 24h and iPTH 3rd PO, respectively. The comparison of the AUC showed no significant difference between these two points of evaluation with 98% accuracy for both time points.

Conclusions: Serum iPTH levels measured within 24h or on the 3rd morning after surgery are predictors of postoperative hypocalcemia. Notably, both time-points have the same accuracy to predict postoperative hypocalcemia (with different cutoff points).

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Key Words: *Hypoparathyroidism – Thyroidectomy – Hypocalcemia – Parathyroid hormone.*

Introduction

TOTAL thyroidectomy (TT) is currently the standard surgical procedure for the management of benign and malignant thyroid diseases. Hypocalcemia from postoperative hypoparathyroidism is the most common complication of TT. Temporary hypocalcemia occurs in 50-68% of post-TT patients, while permanent hypocalcemia occurs in 3% of post-TT patients [2]. It occurs as a result of unintentional resection, manipulation, or devascularization of the parathyroid glands during thyroidectomy leading to hypoparathyroidism. Clinical manifestations are primarily neurologic and cardiac in nature, and include perioral and acralparesthesias, muscle cramps, tetany, seizures, prolonged QT syndrome, and congestive heart failure [3].

Hypocalcemia may also be indicated by presence of the Chvostek sign or the Trousseau sign. The Chvostek sign is elicited by tapping the region of the facial nerve in the preauricular area resulting in facial contractions. The Trousseau sign is carpal spasm that may be elicited by inflation of a blood pressure cuff on the upper arm above 180mmHg [4].

In most cases the hypocalcemia is mild and presents with spontaneous resolution, however it may present in a severe form in some cases, leading to concerns in the clinical practice due to the difficulty to recognize it rapidly in those patients and to the possible delay until its manifestation [5].

Some authors believe the better way to prevent the risk of hypocalcemia is offering calcium oral supplementation accompanied or not by vitamin D to all patients submitted to total thyroidectomy. However, this approach could mean that 64% to 87% of the patients would be given unnecessary supplementation as they do not develop symptoms and their parathyroid hormone (PTH) levels return to normal within the week after surgery in 70% to 94% of the cases. Additionally, hypercalcemia occurred in 4% of the patients given calcium supplementation and vitamin D after total thyroidectomy **[6]**.

In the context of escalating health care costs, a number of initiatives have focused on various ways to facilitate timely hospital discharge without compromising patient safety. The importance of a reliable measure to predict a person's relative risk for developing clinically significant hypocalcemia following thyroidectomy should not be underestimated. Besides facilitating timely discharge in low-risk patients, classification of high-risk patients would also allow prompt prophylactic treatment [7].

Multiple studies have investigated potential predictive factors to better determine which patients are at higher risk for postoperative hypocalcemia. In the majority of studies, demographic factors including age, sex, and other comorbidities play a minimal role. Results regarding preoperative factors including 25-OH vitamin D, serum calcium, or parathyroid hormone (PTH) levels, or indications for surgery such as Graves' disease have been variable with no clear association to the development of postoperative hypocalcemia **[3]**.

Owing to rapid turnover of intact parathyroid hormone (iPTH), with a half life of approximately 2-5 minutes, serum iPTH is an excellent marker of parathyroid function. This is evidenced by the fact that intraoperative iPTH determination is useful for identifying whether a hypersecreting parathyroid adenoma has been removed. However, calcium kinetics are slower. The decrease in iPTH precedes the decline in calcium, which reaches the trough level approximately 24-48 hours after surgery **[1]**.

Several researchers have now reported that intact parathyroid hormone (iPTH) levels are a significant predictor of hypocalcemia following total thyroidectomy **[8-12]**. Despite the proven efficacy of i-PTH testing in managing total thyroidectomy patients, there is still no consensus as to the when in postoperative care i-PTH testing should be done and whether serial tests or tests associated with serum calcium levels ought to be done.

The studies also differ regarding hypocalcemia definition criteria, selection of patients, protocols for management and follow-up, as well as methodological flaws such as retrospective design in many of them.

This study looked into the correlations between i-PTH serum levels measured at different times in post-thyroidectomy care and the occurrence of hypocalcemia.

Material and Methods

Patients and study design:

This study is a prospective study was conducted at Ain Shams University Hospitals & Mostafa Kamel Military Hospital, recruiting (40) patients who underwent total thyroidectomy between Septemper 2019 and August 2020 with follow-up of 1 day, 3 days, 3 weeks, 3 and 6 months postoperatively. Informed oral and written consents were taken from all patients who accepted to participate in the study. Confidentiality was assured of the personal data and medical information of all patients.

Patients:

Inclusion criteria:

- All patients who performed total thyroidectomy

Exclusion criteria:

- Completion thyroidectomy following hemithyroidectomy.
- Patients who underwent neck exploration for any reason.
- Patients who underwent parathyroid surgery for treatment of parathyroid diseases.
- Recurrent thyroid disease.
- Patients suffer from chronic diseases causing decrease calcium level in blood e.g. CKD.
- Patients who underwent parathyroid auto transplantation.
- Patients with previous diagnosis of hypoparathyroidism.

All patients were subjected to the following:

Preoperative:

Clinical history:

- Personal history: Including age, sex, weight, special habits of medical importance particularly smoking, parity.

- History of present illness: Cosmetic disfigurement, mode of onset, duration of illness, toxic manifestations.
- Past history of medical diseases: Such as diabetes, infections, malignancy, liver or renal dysfunction, parathyroid diseases, bone diseases and drug history.

Clinical examination:

- General: Body built, bone deformities, toxic signs.
- Local neck examination: For assessment of goiter size, nodular surface, relation to sternomastiod and carotid, tracheal deviation or tracheomalecia.

Investigations:

Routine preoperative investigations were requested for all patients, including complete blood picture, coagulation profile, liver and kidney function tests, fasting blood sugar. Special investigations are requested for patients with specific comorbidities as pulmonary function tests for patients with manifestations of chronic obstructive airway disease; ECG for patients above the age of 40.

Imaging:

Neck sonography with comment on both thyroid lobes size and texture, echogenicity, extension, cervical lymph nodes, parathyroid gland abnormalities if detectable, relation to great vessels of neck; multi nodular goiter will be defined as multiple nodules occupying both lobes with well define borders, iso or hyperechoic with peripheral hypoechoic halo and vascularity.

Chest X-ray to exclude cases with possible retrosternal extension or tracheal displacement.

Neck CT with contrast: Was done for patients with retrosternal extention.

Indirect laryngoscope: For assessment of vocal fold mobility.

Pathological investigations: FNAC was performed for patients with solitary thyroid nodules or patients with multinodular goiter with dominant nodules.

Biochemical assay:

- Thyroid function tests: As euthyroid will be defined as; free T3 (1.80-4.20pg/mL), free T4 (0.80-1.90ng/dL), TSH (0.4-4.0uIU/mL).
- Serum calcium (total and ionized) as normal level will be defined as (8.8-10.6mg/dL), hypocalcemia will be defined serum calcium <8.0mg/dL.
- Serum albumin; as normal level will be defined as (3.5-5.2g/dL).
- Corrected Serum Calcium; as follow=0.8 x [normal albumin (4g/dl) - patient albumin (g/dl)] + measured serum total calcium.
- Serum phosphorus; as normal level will be defined as (2.5-4.5mg/dL).
- Serum magnesium; as normal level will be defined as (1.6 to 2.6mg/dL).
- Serum 25-OH-vitamin D; as normal level will be defined as (25-80ng/mL).
- Intact parathyroid hormone; as normal level will be defined as (14.5-87.1pg/mL).

Operative technique:

All operations were performed by staff surgeons of General Surgery Department of Ain Shams University Hospitals & Mostafa Kamel Military Hospital. In all patients, every effort was taken to identify and preserve the recurrent laryngeal nerves and the four parathyroid glands.

Postoperative:

a- Clinical assessment:

Patients were monitored to detect early symptoms subjective to hypocalcemia; such as (circumoral or oral numbness, paresthesia, muscular spasm up to tetany and convulsions). Also they will be screened for Chvostek sign and Trousseau sign.

b- Biochemical assessment:

Serum calcium, phosphorus, magnesium, vitamin D, albumin and parathyroid hormone assay were measured at 24 & 72 hours post-operative and (3 weeks, 3 months, 6 months in case of resistant cases).

c- Statistical analysis:

A- *Statistical analysis:*

All data were subjected to revision and validation then description and analysis on IBM-compatible PC by using SPSS (Statistical Package for the Social Science) program version 22.0.0, Microsoft Office Excel 2007, and GraphPad Prism 6.

Descriptive statistics were performed for all studied parameters in the three studied groups and were presented in the form of mean, median, standard deviation (SD), minimum, maximum, range, and percentages.

The comparison between groups regarding qualitative data was done by using Chi-square test.

The comparison between two paired groups with quantitative data and parametric distribution were done by using Paired *t*-test.

While the comparison between two groups with quantitative data and parametric distribution were done by using Independent *t*-test.

The level of significance was calculated according to the following probability (p) values:

- $p>0.05$ = Non significant (NS).
- $p<0.05$ = Significant (S).
- $p<0.001$ = Highly significant (HS).

Results

The Previous table shows that there was highly statistically significant difference found between Pre Operative and Post 24hr Regarding Ca, Corrected Ca and iPTH, and there was non statistically significant difference found between Pre Operative and Post 24hr Regarding S.albumin, 25-OH -vitamin D levels, Magnesium and Phosphorous.

The Previous table shows that there was highly statistically significant difference found between Pre Operative and Post 72hr Regarding Ca, Corrected Ca and iPTH, and there was non statistically significant difference found between Pre Operative and Post 72hr Regarding S.albumin, 25-OH -vitamin D levels, Magnesium and Phosphorous.

The Previous table shows that there was highly statistically significant difference found between Post 24hr and Post 72hr Regarding Ca, Corrected Ca and iPTH, and there was non statistically significant difference found between Post 24hr and Post 72hr Regarding S.albumin, 25-OH -vitamin D levels, Magnesium and Phosphorous.

The Previous table shows that there was Non statically significant correlation Between iPTH, Age, Weight, Height, S.albumin, 25-OH -vitamin D levels, Magnesium and Phosphorous, and there was statically significant Positive correlation Between iPTH, Ca and Corrected Ca.

The Previous table shows that there was Non statically significant correlation Between iPTH, Age, Weight, Height, S.albumin, 25-OH -vitamin D levels, Magnesium and Phosphorous, and there was statically significant Positive correlation Between iPTH, Ca and Corrected Ca.

The Previous table shows that there was non statistically significant difference found between two groups regarding S.albumin, 25-OH -vitamin D levels, Magnesium and Phosphorous, and there was highly statistically significant difference found between two groups regarding Ca, Corrected Ca and iPTH as in hypocalcemic group serum calcium ranged from 7.3mg/dl to 7.9mg/dl (mean ±SD= 7.53±0.22mg/dl), whereas iPTH varied around 7.94± 1.86pg/ml, with a lowest value of 5.1pg/ml and highest of 11.7pg/ml. normocalcemic group is considered around 8.82 mg/dl with corresponding PTH deviating around 31.33pg/ml by 6.76pg/ml.

Patients were divided into two groups, those remaining normocalcemic and those who had hypocalcemia develop requiring intervention. Patients were considered hypocalcemic as a result of meeting one of the following laboratory or clinical conditions: First, a serum-corrected calcium level below 8mg/dl; second, the development of signs and symptoms of hypocalcemia, such as perioral numbness, paresthesias of the upper extremity digits, and a positive Trousseau's sign. These patients were started on one of the following regimens on the basis of serum-corrected calcium levels: intravenous calcium, oral calcium, oral vitamin D, or a combination of the three. Patients were considered normocalcemic if they did not reach the criteria requiring intervention within admission period after surgery.

The Previous table shows that there was non statistically significant difference found between two groups regarding S.albumin, 25-OH -vitamin D levels, Magnesium and Phosphorous, and there was highly statistically significant difference found between two groups regarding Ca, Corrected Ca and iPTH.

The Previous table shows that there was highly statistically significant difference found between two groups regarding Signs and/or Symptoms.

Receiver operating characteristic curve (ROC) shows that the best cut off point of iPTH 24 hr Po to detect Hypocalcemia group was found <=14.8 with sensitivity of 100%, specificity of 93.75%, PPV of 80.0%, NPV of 100% and total accuracy of 0.98%, and Receiver operating characteristic curve (ROC) shows that the best cut off point of iPTH 72 hr Po to detect Hypocalcemia group was found <=14 with sensitivity of 100%, specificity of 90.62%, PPV of 72.7%, NPV of 100% and total accuracy of 0.98%. At 3 months duration there were 2 patients with hypocalcemia but at 6 months duration one of them regain its normal level of calcium and the other one didn't regain it. So, there was only one case of permanent hypocalcemia post total thyroidectomy after 6 months.

Table (1): Distribution of the studied cases according to Demographic Data.

Demographic data	No.= 40
Age:	
Mean ± SD	46.23±9.03
Range	28-63
Sex:	
Male	6 (15.0%)
Female	34 (85.0%)
Weight:	
Mean ± SD	78.55±6.89
Range	67-93
Height:	
Mean ± SD	163.28±5.99
Range	155-178
Comorbidity:	
HTN	4 (50.0%)
DM	2 (25.0%)
DM & HTN	1 (12.5%)
Asthmatic	1 (12.5%)

Table (2): Comparison between Pre operative and Post 24hr Regarding Ca, Corrected Ca, S.albumin, iPTH, 25-OH -vitamin D levels, Magnesium and Phosphorous.

	Pre operative	24hr post operative	Test value*	*p*-value	Sig.
Ca:					
Mean ± SD	9.3±0.51	8.56±0.61	6.054	0.000	HS
Range	8.5-10.4	7.3-9.7			
Corrected Ca:					
Mean ± SD	9.37±0.52	8.6±0.63	6.407	0.000	HS
Range	8.5-10.4	7.3-9.7			
S.albumin:					
Mean ± SD	4.02±0.27	4.08±0.23	–1.059-	0.296	NS
Range	3.5-4.5	3.6-4.5			
iPTH:					
Mean ± SD	39.98±10.72	26.66±11.26	8.087	0.000	HS
Range	21.7-60.1	5.1-39.5			
25-OH-vitamin D levels:					
Mean ± SD	25.10±4.33	24.82±4.68	1.365	0.180	NS
Range	18.1-35.6	17.9-36.5			
Magnesium:					
Mean ± SD	1.92±0.14	1.89±0.10	1.171	0.249	NS
Range	1.6-2.3	1.7-2			
Phosphorous:					
Mean ± SD	3.59±0.38	3.72±0.27	–1.870	0.069	NS
Range	2.9-4.4	3.5-4.5			

p-value >0.05: Non significant (NS).
p-value <0.05: Significant (S).
p-value <0.01: Highly significant (HS)*: Paired *t*-test

Table (3): Comparison between Pre operative and Post 72hr Regarding Ca, Corrected Ca, S.albumin, iPTH, 25-OH -vitamin D, Magnesium and Phosphorous.

	Pre operative	72hr post operative	Test value*	*p*-value	Sig.
Ca:					
Mean ± SD	9.3±0.51	8.72±0.63	4.651	0.000	HS
Range	8.5-10.4	7.22-9.7			
Corrected Ca:					
Mean ± SD	9.37±0.52	8.77±0.62	5.044	0.000	HS
Range	8.5-10.4	7.3-9.7			
S.albumin:					
Mean ± SD	4.02±0.27	4.06±0.21	–0.598	0.553	NS
Range	3.5-4.5	3.7-4.4			
iPTH:					
Mean ± SD	39.98±10.72	26.82±11.28	7.924	0.000	HS
Range	21.7-60.1	5.2-39.7			
25-OH -vitamin D levels:					
Mean ± SD	25.10±4.33	24.98±4.24	0.224	0.824	NS
Range	18.1-35.6	19.4-36.1			
Magnesium:					
Mean ± SD	1.92±0.14	1.87±0.11	1.081	0.286	NS
Range	1.6-2.3	1.7-2			
Phosphorous:					
Mean ± SD	3.59±0.38	3.70±0.17	–1.919	0.062	NS
Range	2.9-4.4	3.6-4.3			

p-value >0.05: Non significant (NS).
p-value <0.05: Significant (S).
p-value <0.01: Highly significant (HS)*: Paired *t*-test

Table (4): Comparison between Post 24hr and Post 72hr Regarding Ca, Corrected Ca, S.albumin, iPTH, 25-OH -vitamin D levels, Magnesium and Phosphorous.

	24hr post operative	72hr post operative	Test value	*p*-value	Sig.
Ca:					
Mean ± SD	8.56±0.61	8.72±0.63	–4.209	0.000	HS
Range	7.3-9.7	7.22-9.7			
Corrected Ca:					
Mean ± SD	8.6±0.63	8.77±0.62	–4.830	0.000	HS
Range	7.3-9.7	7.3-9.7			
S.albumin:					
Mean ± SD	4.08±0.23	4.06±0.21	0.802	0.427	NS
Range	3.6-4.5	3.7-4.4			
iPTH:					
Mean ± SD	26.66±11.26	26.82±11.28	–1.357	0.182	NS
Range	5.1-39.5	5.2-39.7			
25-OH -vitamin D levels:					
Mean ± SD	24.82±4.68	24.98±4.24	–0.345	0.732	NS
Range	17.9-36.5	19.4-36.1			
Magnesium:					
Mean ± SD	1.89±0.10	1.87±0.11	–0.010	0.992	NS
Range	1.7-2	1.7-2			
Phosphorous:					
Mean ± SD	3.72±0.27	3.70±0.17	0.252	0.802	NS
Range	3.5-4.5	3.6-4.3			

p-value >0.05: Non significant (NS).
p-value <0.05: Significant (S).
p-value <0.01: Highly significant (HS)*: Paired *t*-test

Table (5): Correlation between iPTH and Corrected Ca Post 24hr with Age, Weight, Height, S.albumin, 25-OH -vitamin D levels, Magnesium and Phosphorous.

Post 24 hr	iPTH		Corrected Ca	
	r	*p*-value	*r*	*p*-value
iPTH			0.735**	0.000
Corrected Ca	0.735**	0.000		
Age	–0.099	0.543	–0.111	0.494
Weight	0.163	0.315	0.126	0.439
Height	0.048	0.770	0.130	0.425
Ca	0.707**	0.000	0.978**	0.000
S.albumin	–0.048	0.767	–0.054	0.739
25-OH -vitamin D levels	0.094	0.563	–0.087	0.594
Magnesium	0.115	0.481	0.076	0.642
Phosphorous	0.035	0.830	0.179	0.268

Table (6): Correlation between iPTH and Corrected Ca Post 72 hr with Age, Weight, Height, S.albumin, 25-OH -vitamin D levels, Magnesium and Phosphorous.

Post 72 hr	iPTH		Corrected Ca	
	r	*p*-value	*r*	*p*-value
iPTH			0.694**	0.000
Corrected Ca	0.694**	0.000		
Age	–0.089	0.584	–0.141	0.385
Weight	0.133	0.413	0.166	0.307
Height	0.042	0.798	0.062	0.703
Ca	0.636**	0.000	0.973 **	0.000
S.albumin	–0.204	0.207	0.020	0.904
25-OH -vitamin D levels	–0.134	0.411	–0.213	0.187
Magnesium	0.557	0.598	0.288	0.072
Phosphorous	–0.027	0.870	–0.010	0.952

Table (7): Comparison between Non Hypocalcemia (no.=32) and Hypocalcemia (no .=8) regarding Ca, Corrected Ca, S.albumin, iPTH, 25-OH -vitamin D levels, Magnesium and Phosphorous Post 24hr.

Post 24hr	Non Hypocalcemia No.= 32	Hypocalcemia No.= 8	Test value•	*p*-value	Sig.
Ca:					
Mean ± SD	8.82±0.34	7.53±0.22	10.211	0.000	HS
Range	8.42-9.7	7.3-7.9			
Corrected Ca:					
Mean ± SD	8.87±0.34	7.54±0.21	10.496	0.000	HS
Range	8.5-9.7	7.3-7.9			
S.albumin:					
Mean ± SD	4.09±0.25	4.04±0.09	0.579	0.566	NS
Range	3.6-4.5	3.9-4.2			
iPTH:					
Mean ± SD	31.33±6.76	7.94±1.86	9.620	0.000	HS
Range	18.3-39.5	5.1-11.7			
25-OH -vitamin D levels:					
Mean ± SD	24.78±5.06	24.98±2.90	–0.107	0.916	NS
Range	17.9-36.5	21.6-29.8			
Magnesium:					
Mean ± SD	1.90±0.09	1.86±0.12	0.886	0.381	NS
Range	1.7-2	1.7-2			
Phosphorous:					
Mean ± SD	3.72±0.27	3.70±0.29	0.202	0.841	NS
Range	3.5-4.5	3.5-4.3			

p-value >0.05: Non significant (NS). *: Chi-square test.
p-value <0.05: Significant (S). •: Independent *t*-test.
p-value <0.01: Highly significant (HS).

Table (8): Comparison between Non Hypocalcemia (no.=32) and Hypocalcemia (no.=8) regarding Ca, Corrected Ca, S.albumin, iPTH, 25-OH -vitamin D levels, Magnesium and Phosphorous Post 72hr.

Post 72hr	Non Hypocalcemia No.= 32	Hypocalcemia No.= 8	Test value•	*p*-value	Sig.
Ca:					
Mean ± SD	8.98±0.34	7.66±0.27	10.213	0.000	HS
Range	8.34-9.7	7.22-7.9			
Corrected Ca:					
Mean ± SD	9.04±0.32	7.69±0.22	11.285	0.000	HS
Range	8.5-9.7	7.3-7.9			
S.albumin:					
Mean ± SD	4.06±0.22	4.04±0.14	0.264	0.794	NS
Range	3.7-4.4	3.8-4.2			
iPTH:					
Mean ± SD	31.57±6.56	7.81±1.4	10.093	0.000	HS
Range	19.4-39.7	5.2-9.9			
25-OH -vitamin D levels:					
Mean ± SD	24.74±4.52	25.98±2.88	–0.735	0.467	NS
Range	19.4-36.1	22.4-31.3			
Magnesium:					
Mean ± SD	1.90±0.09	1.76±0.10	0.775	0.254	NS
Range	1.7-2	1.7-1.99			
Phosphorous:					
Mean ± SD	3.69±0.15	3.75±0.21	–0.888	0.380	NS
Range	3.6-4.3	3.6-4.2			

p-value >0.05: Non significant (NS). *: Chi-square test.
p-value <0.05: Significant (S). •: Independent *t*-test.
p-value <0.01: Highly significant (HS).

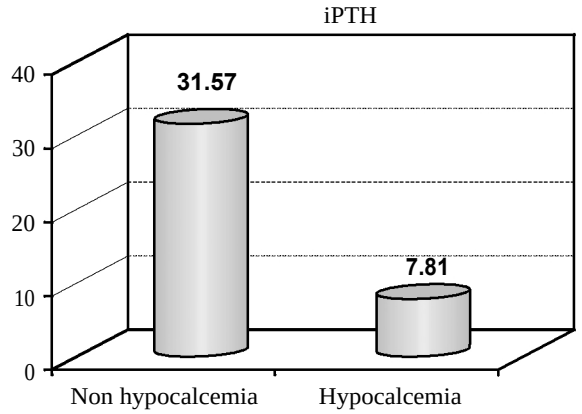


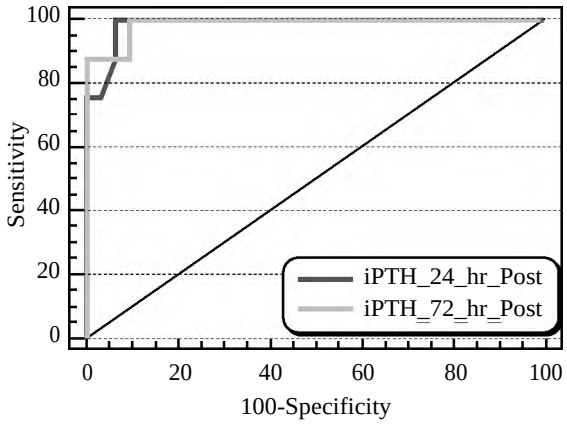
Fig. (1): Shows the difference between (non Hypocalcemia group and Hypocalcemia group) regarding iPTH.

Table (9): Comparison between Non Hypocalcemia (no.=32) and Hypocalcemia (no.=8) regarding Signs and/or Symptoms.

Signs and/or Symptoms	No Hypocalcemia		Hypo-calcemia		Test value*	*p*-value	Sig.
	No.	%	No.	%			
No	32	100.0	3	37.5	22.857	0.000	HS
Yes	0	0.0	5	62.5			

p-value >0.05: Non significant (NS). *: Chi-square test.
p-value <0.05: Significant (S). •: Independent *t*-test.
p-value <0.01: Highly significant (HS).

Table (10): ROC curve (NonHypocalcemia and Hypocalcemia) group regarding iPTH 24 hr Post and iPTH 72 hr Post total thyroidectomy.



	Cut of point	AUC	Sen-sitivity	Spe-cificity	+PV	–PV
iPTH 24 hr Post	<=14.8*	0.98	100.0	93.75	80.0	100.0
iPTH 72 hr Post	<=14*	0.98	100.0	90.62	72.7	100.0

Discussion

Postoperative hypocalcemia is a common and important complication of thyroid surgery. The identification of those patients at higher risk for this event could optimize their clinical management reducing expenses, hospital length of stay and unnecessary exams, as well as avoiding discomfort to the patient due to overtreatment **[13]**.

Serum calcium levels 24 hours after surgery is not considered a very reliable predictor for the need of calcium therapy at discharge **[14]**. The assessment of serum calcium begins to have clinical significance and starts to be predictive of a safe discharge only at 48 hours after surgery. This value, when altered, seems to be associated with symptomatic hypocalcaemia and the need for post-discharge therapy **[15]**. In recent years, the identification of new early predictors of serum calcium levels 48 hours after surgery has become an important research topic. Even if currently there is not an unanimous consensus on the use iPTH in routinely clinical settings (and in particular on its cut-off value and on its sampling timing) this test seems to be a promising solution to this predictive need **[16,17]**.

Our study indicates that postoperative iPTH measurements, either within 24h after surgery or within 72h after surgery postoperative day, are strong predictors of postoperative hypocalcemia. Interestingly, the performance of the two time-points was comparable, but the best cut-off points were different (14.8 and 14, respectively), an aspect that is critical in the clinical application of these data. Our data could have important clinical implications.

First, our results indicate that measuring iPTH 24h or on 3rd day after the surgery has the same accuracy to predict postoperative hypocalcemia. Therefore, in the postoperative follow-up, one of these time-points can be chosen to evaluate parathyroid function taking into account the logistics of the hospital and the patient him self.

Second, besides the prospective design, we also did not use the iPTH level as an indication for treatment, and therefore we were able to determine the best cut-off point and its real value as a predictor of postoperative hypocalcemia without the interference of treatment. Serum PTH level is regarded as one of the most sensitive in vivo biomarkers of vitamin D activity **[18]**.

The role of iPTH as a predictor for postoperative hypocalcemia has been addressed by several studies. The studies differ regarding selection of patients, duration of follow-up, definitions of outcomes as well as methodological flaws like retrospective design, use of surrogate endpoints and lack of standardized criteria to interpret the iPTH (not all the studies used a receiver operator characteristics to define the cut-off of iPTH) **[19-22]**.

In a prospective study, including 103 patients, Chia et al., showed that Patients who undergo TT with 8-hour postoperative PTH levels greater than or equal to 15pg/mL (1.6pmol/L) are at low risk for developing postoperative hypocalcemia, whereas those with PTH levels less than 15pg/mL (1.6pmol/L) have a high risk of developing hypocalcemia **[23]**. In another prospective study, including 101 patients, Filho et al., showed that the optimal cut-off points were 19.55pg/mL and 14.35pg/mL for iPTH 4h and iPTH 1st PO, respectively **[5]**.

In a prospective study, including 200 patients, Barczyn´ski et al., showed that a cutoff of 10pg/mL for iPT H 4h after surgery is most accurate to predict calcium levels under 8.0mg/dL **[24]**. On the other hand, in another prospective study that included 1504 patients, Raffaelli et al., observed that even patients with iPTH above 10pg/mL 4h after surgery could present postoperative hypocalcemia (18% of this group of patients) **[13]**.

Payne et al., 2003 tested PTH levels at 6, 12, and 20h after their surgery: Merging PTH and serum calcium measurement at 6h would fairly establish subjects not at risk for hypocalcemia.

Such arrangement was 100% specific, identified 68% of normocalcemic patients enduring for secure early discharge, determining a reduced hospital stay and budget. Lombardi et al., similarly found that PTH at 4-6h to be a precise predictor of hypocalcemia **[25,26]**. As demonstrated by Ritter et al., in a retrospective analysis of 1054 consecutive thyroidectomies, the majority of 189 patients with low postoperative iPTH (<10pg/ml) recovered the parathyroid function within the initial months after surgery **[27]**.

Grodski and Serpell evaluated 24 studies where the blood serum calcium determinations were tested as an internal dominate. There was critical disparity in study protocol among all papers considered by the Authors. Quick PTH was adopt in most studies and standard PTH was apply in other group. The timing of hormone sampling differs from trial to trial: In some analysis the sample was extract directly after thyroid gland excision and the authors tempt to use this early information to decide for parathyroid auto transplantation. Authors concluded that when a 75-80% PTH decline is experienced, auto transplant is advised. Other protocols used serial measurement taken just after skin closure, at 5, 10, 20min to 1, 2, 4, up to 24 and 48h **[28]**.

A systematic review and meta-analysis by Musholt, Clerici **[29]** demonstrated that postoperative PTH measured 10 minutes after removal of the thyroid gland is highly predictive of postoperative hypocalcaemia and there is no need for additional observation. They also supported that when using the percentage change, a 75% change in PTH concentration results in the maximum summation of sensitivity and specificity and when using the absolute level, the result of 7pg/ml offers the maximum summation of sensitivity and specificity.

In our study, we showed that the measurements of iPTH at two different time-points (24h and 72h following the surgery) are excellent predictors for postoperative hypocalcemia with the best cut off point of iPTH 24hr Po to detect Hypocalcemia group <=14.8 with sensitivity of 100%, specificity of 93.75%, PPV of 80.0%, NPV of 100% and total accuracy of 0.98%, and that the best cut off point of iPTH 72hr Po to detect Hypocalcemia group was found <=14 with sensitivity of 100%, specificity of 90.62%, PPV of 72.7%, NPV of 100% and total accuracy of 0.98%.

Vitamin D plays a critical role in calcium metabolism. It is stored in fat cells and is converted to 25-hydroxyvitamin D in the liver, followed by conversionto 1,25-dihydroxyvitamin D in the kidney. This activated form of vitamin D then increases calcium absorption in the intestine. We hypothesized that those patients with higher serum levels of vitamin D (and indirectlyin fatty tissue) may be able to mobilize these reserves inconditions of an acute decrease in PTH levels or hypocalcemia. However, this hypothesis was not supported by our data, as there was no correlation between preoperative levels of 1,25-dihydroxyvitamin D and postoperative calcium levels.

This result was similar to a prospective observational study on 134 patients by Lee et al., 2015 which found that The incidence of laboratory or symptomatic hypocalcemia did not differ according to vitamin D deficiency. Only incidental parathyroidectomy was associated with symptomatic hypocalcemia **[30]**.

A literature review confirmed that there is no consistent use of, rationale for, or seeming need to declare definitions of "transient" and "permanent" hypoparathyroidism. The definition of permanent hypoparathyroidism varies in terms of calcium level, need for supplementation (calcium and/or active vitamin D), and duration of hypoparathyroidism. Some studies defined permanent hypoparathyroidism as hypocalcemia with ongoing requirement for supplements, i.e., calcium and vitamin D, or calcium and/or vitamin D.The duration of ongoing requirement for supplements also varied from >6 months to 12 months.

Although hypocalcaemia is a source of significant morbidity and cost after total thyroidectomy, this study demonstrated that early postoperative PTH can accurately predict patients not at risk of hypocalcaemia. It is especially important in our practice, where patients sometimes travel several hundred kilometres for their surgery, to ensure that symptomatic hypocalcaemia does not occur after discharge. The ability to accurately predict patients not at risk of hypocalcaemia allows us to safely institute early discharge for many of our patients. By using the iPTH result to tailor oral calcium and vitamin D supplementation, we are able to better manage post-thyroidectomy hypocalcemia.

We believe that the prospective design and the protocol that did not include the iPTH levels as a criterion for treatment are strengths.

In conclusion, this prospective cohort study demonstrates that iPTH 24h or on the 3 rd day after surgery are good predictors of postoperative hypocalcemia. Notably, both time-points have the same accuracy to predict postoperative hypocalcemia (with different cut-off points).

These findings might have important implications in the follow-up of those who underwent thyroidectomy enabling earlier and safer discharge for patients. Hence, patients with iPTH above 14.8pg/ml 24h after surgery or 14pg/ml on the 3rd day after surgery can be safely discharged from hospital without supplemental calcium and/or vita min D.

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توقيت قياس هرمون الغدة الجاردرقية للتنبؤ الدقيق بنقص نسبة الكالسيوم بالدم ما بعد الاستئصال الكامل للغدة الدرقية

الخلفية: يعد قياس مستوى هرمون الغدة الجاردرقية (iPTH) هو علامة مبكرة لنقص كالسيوم الدم بعد استئصال الغدة الدرقية. ومع ذلك، فإن عدم وجود توحيد منهجي لتحديد التوقيت ونقاط التوقف المثلى لقياس الهرمون (iPTH) يحد من قابليته للتطبيق السريري.

هنا، قمنا بتقييم العلاقة بين اثنتين من توقيتات قياس الهرمون وتحديد مدى دقة كلاً منها في التنبؤ بنقص كالسيوم الدم. لقد هدفنا إلى تقييم مدى دقة قياس (iPTH) بعد استئصال الغدة الدرقية بالكامل للتنبؤ بنقص كالسيوم الدم بعد الجراحة وتحديد المرضى المعرضين لخطر الإصابة به بعد الجراحة والذين يحتاجون إلى علاج مكمل، وأولئك غير المعرضين للخطر والذين يمكن خروجهم بأمان دون أي علاج مكمل.

الطريقة: تم قياس iPTH في غضون ساعة بعد الجراحة (iPTH 24Hr)، وفي صباح اليوم الثالث بعد الجراحة (iPTH 3rd PO)، وتم تحديد نقص كالسيوم الدم من خلال مستويات لكالسيوم الكلي المصححة بواسطة الألبيومين 8.0 مجم / ديسيلتر و ، أو من خلال وجود الأعراض، وتم الوصول لنقطة قطع (iPTH) الأكثر دقة للتنبؤ بنقص كالسيوم الدم من منحنى ROC لمقارنة النقطتين الزمنيتين.

النتائج: شملت الدراسة أربعين مريضاً حيث كان متوسط العمر 46.23 ± 9.03 سنة، 34 منهم من النساء (85%) وخضع جميع المرضى لاستئصال الغدة الدرقية الكلي.

حدث نقص كالسيوم الدم في ثمانية مرضى (20%)، منهم خمسة مرضى لديهم أعراض، وارتبطت المستويات المنخفضة من (iPTH 24Hr) و (iPTH 3rd PO) بنقص نسبة كالسيوم الدم بعد الجراحة ($p < 0.05$).

وباستخدام منحنى ROC، كانت نقاط القطع 14.8 بيكو غرام / مل و 14 بيكو غرام / مل لـ قياس iPTH في غضون 24 ساعة و 3rd PO iPTH، على التوالي وأظهرت مقارنة AUCH عدم وجود فرق كبير بين هاتين النقطتين في التقييم بدقة 98% لكلاً النقطتين الزمنيتين.

الاستنتاجات: مستويات هرمون الغدة الجاردرقية (iPTH) التي تقاس في غضون 24 ساعة أو في اليوم الثالث بعد الجراحة تنبىء بدقة بنقص كالسيوم الدم بعد الجراحة. والجدير بالذكر أن كلاً النقطتين الزمنيتين لهما نفس الدقة للتنبؤ بنقص كالسيوم الدم بعد العملية الجراحية (مع نقاط قطع مختلفة).

تشير هذه النتائج إلى أن انخفاض مستوى هرمون الغدة الدرقية السليم في المصل بعد استئصال الغدة الدرقية هو مؤشر مبكر لنقص الكالسيوم في الدم مقارنة بمستويات الكالسيوم في الدم وحدها، ويعتبر قياس الهرمون (iPTH 24Hr) بعد استئصال الغدة الدرقية مؤشراً موثوقاً على نقص كلس الدم ويمكن أن يسمح بخروج مبكراً من لمرضى من المستشفى.