Original Article

PTH Gradient as a Predictor of Post Thyroidectomy Hypocalcemia

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Abstract

Background: Post thyroidectomy hypocalcemia is a common complication. Post thyroidectomy PTH estimation at varying cut offs and time have been used to predict hypocalcemia and aid in early and safe discharge. Single post thyroidectomy PTH values may be spuriously normal or high in a patient that subsequently develops unanticipated low calcium levels. This study aimed to evaluate the percentage change in preoperative and postoperative PTH (Gradient) in predicting post thyroidectomy hypocalcemia. **Methods:** Forty-one patients of thyroidectomy had PTH preoperatively, postoperatively one-hour (PTH0) and day 1 (PTH1). PTH gradient was calculated as percentage change in postoperative PTH to preoperative (PTHG0, PTHG1). Hypocalcemia was categorized into mild or severe based on corrected calcium values and presence of clinical signs and/or symptoms of hypocalcemia. **Results:** Ten (24.3%) and 11 (26.8%) patients had mild and severe hypocalcemia, respectively. PTHG0 and PTHG1 were significantly associated with risk for hypocalcemia (*P*-0.006 vs *P*-0.002). Higher PTH0 and PTH1 gradients were significantly associated with risk of hypocalcemia (PTH0 gradient OR-0.006, 95% CI 0.00–0.175, *P*-0.006; PTH1 gradient OR- 0.008, 95% CI 0.00–0.166, *P*-0.002). PTH0 gradient was the best predictor of hypocalcemia (AUC 0.855, SE-0.065, 95% CI0.710 to 0.945, *P* value <0.001) and PTH1 value was a better predictor of severe/clinical hypocalcemia (AUC 0.844, SE-0.072, 95% CI 0.697 to 0.938, *P*- value-0.001). Based on ROC, cutoffs of PTH0 gradient and PTH1 gradient for predicting hypocalcemia and severe/clinical hypocalcemia were taken as 60% and 75%, respectively (sensitivity 70%, specificity 90.5% for hypocalcemia; sensitivity 65%, specificity 90.9% for severe hypocalcemia). **Conclusion:** PTH gradient may be a better predictor of hypocalcemia and PTH1 gradient of >75% correlates with high risk of severe/clinical post thyroidectomy hypocalcemia.

Keywords: Hypocalcemia, hypoparathyroidism, PTH, PTH gradient

Introduction

Post thyroidectomy hypocalcemia, whether transient or permanent, is one of the most dreaded complications of thyroidectomy. The incidence of temporary and permanent post-surgical hypocalcemia varies from 19%–38% and 0%–3%, respectively.[1] A reliable protocol for distinguishing patients who can be safely discharged on the day of surgery from those who can benefit from in-hospital calcium monitoring can facilitate cost reductions without compromising on patient safety. Various studies have used postoperative parathyroid hormone (PTH) levels and first postoperative day PTH levels as predictor of post op hypocalcemia.[2] Institutions should have their own defined levels of these parameters which should be validated. However, PTH values may be spuriously normal or high in some patients who subsequently develop hypocalcemia. A gradient being a ration may not require repeat validation at every institute before use. The aim of present study is to evaluate the utility of percentage change in PTH value (PTH gradient) as compared to 1-hour postoperative PTH and first operative day PTH in predicting hypocalcemia, and to provide an algorithm for identifying patients at risk for hypocalcemia.

Methods

The study was conducted in the department of Endocrine Surgery, King George's Medical University, Lucknow, India

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from July 2019 to July 2020. All patients planned for total thyroidectomy (TT) with or without neck dissection were enrolled in the study. The surgeries were performed by a single surgical team. Preoperative serum PTH and 25 (OH) Vitamin D3 were measured (as a part of another ongoing sponsored study evaluating effect of preoperative calcium and vitamin D supplementation in thyroidectomy patients). Serum PTH was again evaluated at 1-hour post-thyroidectomy (PTH0) and first postoperative day (PTH1) (15.0–68.3 picogram per ml). PTH gradient (PTHG0 and PTH G1) was calculated as percentage change in PTH levels when compared to preoperative levels [(preoperative PTH–postoperative PTH)/preoperative PTH]. Serial calcium measurements were done 24-hourly, with first sample being drawn on the first postoperative day along with serum albumin. Postoperative severe/clinical hypocalcemia was defined as serum calcium of less than 8.0 mg/dL and symptoms attributable to hypocalcemia, such as paraesthesia's or numbness of the perioral region, hands or feet, or a newly positive Trousseau's sign, which required intravenous calcium infusion for resolution. Mild/biochemical hypocalcemia was defined as at least one serum calcium less than 8.5 mg/dL, requiring only oral supplementation (reference range for laboratory: 8.2–10.3 mg/dL). Patients who have undergone thyroid surgery or parathyroidectomy along with thyroidectomy and vitamin D deficiency were excluded from the study [Figure 1].

Statistical analysis

Descriptive variables were reported as number and percent, or median and IQR. Categories of hypocalcemia were compared with other variables using Kruskal–Wallis or Fisher exact tests. The likelihood of hypocalcemia-related outcomes by postoperative PTH0, PTH1 and PTH gradient, evaluated with logistic regression models, and odds ratio (OR) was reported with 95% confidence interval (CI). Receiver operating characteristic (ROC) curves were constructed to evaluate postoperative PTH and PTH gradient as predictors of hypocalcemia-related outcomes, and the area under the curve (AUC) for each metric was reported with standard error (SE). A two-sided *P* value of <.05 was considered statistically significant. All data analyses were performed using SPSS software (v. 23). Ethical clearance has not been obtained.

Results

Patient demographic

Forty-one patients (female-37; male-4) with a median age of 39 years (IQR-27.5–45) at presentation were included in the study. Indication for surgery was a symptomatic benign multinodular goiter (85.4%) and malignancy (n = 6; 14.6%). 37 (90.3%) patients underwent TT and the rest underwent TT along with central compartment neck dissection. Twenty (48.78%) patients remained normocalcemic during the postoperative period with median corrected calcium levels of 8.35 ± 0.65 mg/dl. Ten (24.4%) patients developed mild/biochemical hypocalcemia requiring oral calcium supplementation with a median corrected calcium value of 7.65 ± 0.62 mg/dl. Eleven (26.62%) patients developed severe/clinical hypocalcemia, requiring intravenous calcium infusion for correction, with median corrected calcium value of 7.3 ± 0.74 mg/dl [Table 1].

Association of postoperative PTH and PTH gradient with hypocalcemia

Median postoperative PTH0 and PTH1, and median PTHG0 and PTHG1 differed significantly among normocalcemia and hypocalcemia patients. Median PTH0 was 42.6 pg/ml (IQR 22.2–71.6), 8.5 pg/ml (IQR 5.27–22.32), and 5.7 pg/ml (IQR 4.1–33.8) for normocalcemia, mild hypocalcemia, and severe hypocalcemia group (P < 0.001). The median PTH1 for normocalcemic, mildly hypocalcemic, and severerly hypocalcemic individuals was 41.5 pg/ml (IQR 32.5–61.6), 18.5 pg/ml (IQR 4.97–42.37), and 4.3 pg/ml (IQR 2.0–16.9), respectively (P < 0.001). The PTHG0 gradient also varied significantly across all groups; for normocalcemic individuals, it was 45.12% (IQR 16.82%–73.99%), compared with 87.25% (IQR 75.88%–91.36%) among those with mild/

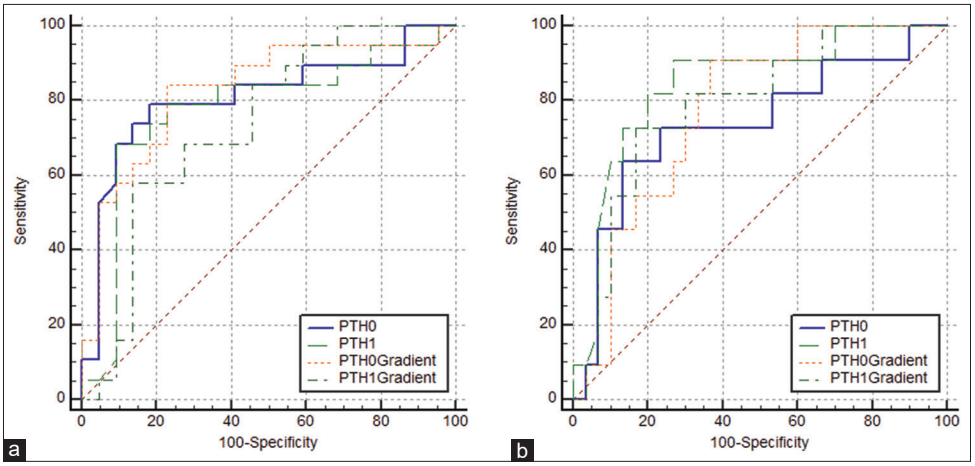

Figure 1: Comparison between (a) ROC–PTH0 versus PTH1 versus PTH0 gradient versus PTH1 gradient as predictors for hypocalcemia; (b) ROC–PTH0 versus PTH1 versus PTH0 gradient versus PTH1 gradient as predictors for severe/clinical hypocalcemia

biochemical hypocalcemia, and 89.08% (IQR 80.26%–93.68%) for severe/clinical hypocalcemia individuals ($P < 0.001$). Similarly, PTHG1 gradient for normocalcemic individuals was 47.50% (IQR 20%–64.25%) compared with 73.44% (IQR 54.25%–90%) among those with mild/biochemical hypocalcemia, and 92% (IQR 82%–97%) for severe/clinical hypocalcemia individuals (*P*-0.001).

Lower levels of both PTH0 and PTH1 were positively associated with higher risk of hypocalcemia on logistic regression; however, this association was not statistically significant (PTH0 OR-1.003, 95% CI 0.969–1.039, *P*-0.85; PTH1 OR-1.024, 95% CI 0.988–1.062, *P*-0.21). Higher change in the PTHG0 and PTHG1 was significantly associated with higher risk of hypocalcemia (PTHG0 OR-0.006, 95% CI 0.00–0.175, *P*-0.006; PTHG1 OR-0.008, 95% CI 0.00–0.166, *P*-0.002). Similar results were obtained when PTH levels and gradients were compared for severe/clinical hypocalcemia [Table 2].

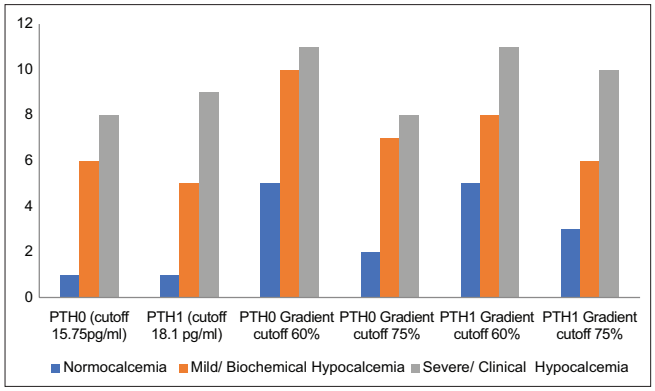

Figure 2: Graph representing hypocalcemia at various PTH and PTH gradient cutoff values

Receiver operator characteristic curve analysis

On ROC analysis, PTH0, PTH1, PTHG0, and PTHG1 were significant predictors of hypocalcemia and severe/clinical hypocalcemia. On comparison of ROC curves, PTHG0 had advantage over other values as a predictor of hypocalcemia (AUC 0.855, SE-0.065, 95% CI 0.710 to 0.945, *P* value <0.001), whereas PTHG1 value had advantage over other values as predictor of severe/clinical hypocalcemia (AUC 0.844, SE-0.072, 95% CI 0.697 to 0.938, *P*- value-0.001); however, the difference between the ROC curves was not statistically significant [Table 3 and Figure 1].

Based on ROC analysis, cutoffs for PTH0 and PTH1 were taken as 15.75 pg/ml (sensitivity 95%, specificity 67%) and 18.1 pg/ml (sensitivity 95%, specificity 67%) for predicting

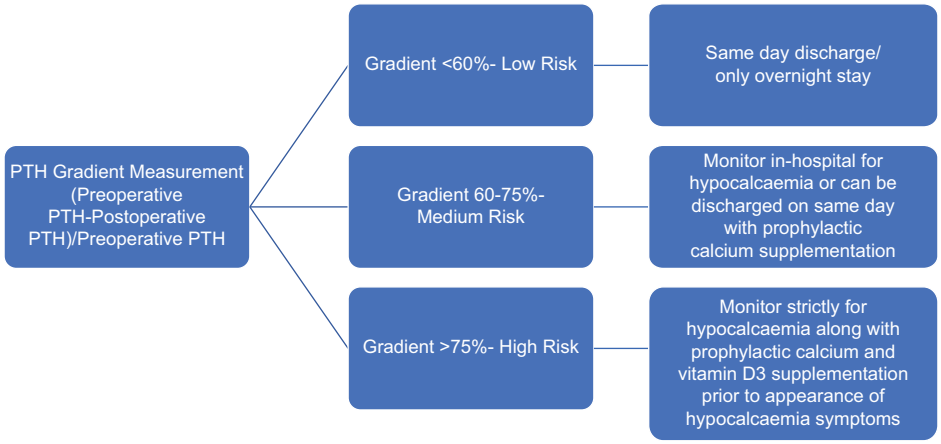

Figure 3: Proposed risk stratification system

Table 1: Patient demographics

Characteristics	Overall	Normocalcemic	Mild/biochemical hypocalcemia	Severe/clinical Hypocalcemia	*P*
Total	41	20	10	11	
Corrected Calcium mg/dl (Median)	8.1±0.73 (6.70-9.96)	8.35±0.65 (7.05-9.96)	7.65±0.62 (7.04-8.17)	7.3±0.74 (6.7-8.01)	0.01
Preoperative (IQR) PTH pg/ml	85.5 (51.35-85.5)	89.3 (65.1-111.17)	72.7 (51.3-115.17)	69.6 (42.4-90.0)	0.25
Postoperative PTH (PTH0) (IQR) pg/ml	22 (5.85-50.05)	42.6 (22.2-71.6)	8.5 (5.27-22.32)	5.7 (4.1-33.8)	<0.001
First postoperative day PTH (PTH1) (IQR) pg/ml	25.5 (4.75-52.4)	41.5 (32.5-61.6)	18.5 (4.97-42.37)	4.3 (2.0-16.9)	<0.001
PTH 0 gradient (IQR)	75.38% (43.15%-89.25%)	45.12% (16.82%73.99%)	87.25% (75.88%-91.36%)	89.08% (80.26%-93.68%)	<0.001
PTH 1 gradient (IQR)	62.43% (37.74%-89.25%)	47.50% (20%-64.25%)	73.44% (54.25%-90%)	92% (82%-97%)	0.001
Average Hospital Stay (days)	3 (2-8)	3 (2-4)	4 (3-5)	6 (3-8)	0.002

Table 2: Logistic regression analysis PTH0 versus PTH1 versus PTH0 gradient versus PTH1 gradient as predictor of hypocalcemia

Outcome	PTH0		PTH1		PTH0 Gradient		PTH1 Gradient	
	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*
Hypocalcemia	1.003 (0.969-1.039)	0.85	1.024 (0.988-1.062)	0.19	0.006 (0.00-0.175)	0.006	0.008 (0.00-0.166)	0.002
Severe/clinical hypocalcemia	0.974 (0.933-1.016)	0.21	1.088 (0.994-1.191)	0.06	0.007 (0.00-0.706)	0.035	0.005 (0.00-0.302)	0.012

Table 3: Receiver operator characteristic analysis PTH0 versus PTH1 versus PTH0 gradient versus PTH1 gradient as predictor of hypocalcemia

Variable	AUC	S.E	95% CI	*P*
Hypocalcemia				
PTH0	0.819	0.071	0.668-0.922	<0.001
PTH0 Gradient	0.855	0.065	0.710-0.945	<0.001
PTH1	0.821	0.073	0.670-0.923	<0.001
PTH1 Gradient	0.817	0.068	0.684-0.949	0.001
Severe/clinical hypocalcemia				
PTH0	0.736	0.099	0.576-0.861	0.022
PTH0 Gradient	0.776	0.075	0.619-0.891	0.007
PTH1	0.844	0.072	0.697-0.938	0.001
PTH1 Gradient	0.818	0.076	0.670-0.967	0.002

hypocalcemia. Based on these cutoffs, 95% patients with normocalcemia, 40% patients with mild/biochemical hypocalcemia, and 27.28% patients with severe/clinical hypocalcemia had PTH0 values above 15.75 pg/ml; and 95% patients with normocalcemia, 50% patients with mild/biochemical hypocalcemia, and 18.18% patients with severe/clinical hypocalcemia had PTH1 values above 18.1 pg/ml.

On the basis of ROC analysis, cutoffs of PTHG0 and PTHG1 for predicting hypocalcemia and severe/clinical hypocalcemia were taken as 60% and 75%, respectively (sensitivity 70%, specificity 90.5% for hypocalcemia and sensitivity 65%, specificity 90.9% for severe/clinical hypocalcemia). Based on these cutoffs, 100% patients with mild/biochemical hypocalcemia and 100% patients with severe/clinical hypocalcemia had PTHG0 more than 60% and 75%, respectively. Similarly, 80% patients with mild/biochemical hypocalcemia and 91% patients with severe/clinical hypocalcemia had PTHG1 above 60% and 75%, respectively [Figure 2].

Discussion

The role of postoperative single PTH threshold in predicting hypocalcemia has been extensively studied across literature. There has been contradictory evidence for the use of single PTH threshold, and the correct timing for measurement of such threshold. Single threshold of PTH in the immediate postoperative period or on the first postoperative day has been shown to have a sensitivity of more than 85% and a specificity reaching 100%.[1,3-5] Other studies, however, report that single threshold PTH may not be a reliable indicator of post thyroidectomy hypocalcemia with an accuracy approaching only 80%, due to factors like heterogeneity in the timing of sample withdrawal and temporary stunning of parathyroid gland.[6,7] In the present study, we report that both PTH levels and PTH gradient can be used to predict the risk of developing hypocalcemia post thyroidectomy. Between 1-hour postoperative PTH and first postoperative day PTH, PTH1 has a slight advantage in predicting hypocalcemia as compared to PTH0. On logistic regression, PTH gradients (both PTHG0 and PTHG1) were more predictive of hypocalcemia as compared to PTH0 and PTH1 values. On ROC analysis, PTH values were more sensitive and PTH gradients were more specific for predicting hypocalcemia. Based on the above observations, we propose low risk as PTH gradient less than 60%, medium risk as PTH gradient between 60% and 75%, and high risk as PTH gradient more than 75% for the risk of developing hypocalcemia [Figure 3].

The utility of percentage change in PTH (PTH gradient) as compared to the preoperative value has also been explored, with different studies reporting different cutoff values. Lecerf *et al*.[8] suggested a cutoff of 68.5%, which had a sensitivity of 97.4% and specificity of 95.9% in predicting hypocalcemia. Khadem *et al*.[9] compared single PTH threshold with PTH gradient and suggested that PTH gradient was more predictive of hypocalcemia. Other similar studies have suggested optimal cutoff between 60% and 80% of PTH gradient for predicting hypocalcemia.[7,10] In the present study, higher PTH gradient (PTHG0 and PTHG1) was significantly correlated with higher risk of hypocalcemia. PTH gradient of more than 75% was associated with high risk of developing clinical hypocalcemia. In resource-limited setting, where PTH assays cannot be done in the immediate postoperative setting, PTH assay on the first postoperative day can be used, which shows similar sensitivity and specificity in our study.

In the present study, we have also analyzed the difference between PTH0 versus PTH1 and PTHG0 versus PTHG1. The AUC shows similar results for hypocalcemia and severe hypocalcemia when all four parameters were compared; the PTHG0 showed an advantage in predicting hypocalcemia as compared to other values, and PTH1 value had advantage over other values as predictor of severe/clinical hypocalcemia. Based on our results and suggested risk stratification categories, we propose that patients in the low risk category (<60% gradient) can be safely discharged on the same day or next day post thyroidectomy. Patients in the medium risk category (60%–75% gradient) can be monitored in-hospital for

hypocalcemia or can be discharged on same day with calcium supplementation. Patients in the high-risk category (>75% gradient) should be monitored strictly for hypocalcemia along with prophylactic calcium and vitamin D3 supplementation prior to appearance of hypocalcemia symptoms. The proposed system is summarized in Figure 3.

There are certain limitations to this study. The sample size is relatively small to draw conclusion regarding the superiority of one modality over the other. With statistical differences being small, it is difficult to generalize the conclusions. Further prospective studies are required to establish role of PTH gradient over single threshold PTH value alone. Further evaluation is also required for establishing a protocol for prophylactic post thyroidectomy calcium supplementation.

Conclusion

PTH gradient may have a potential advantage over single threshold PTH value alone in predicting post thyroidectomy hypocalcemia. Based on the observations on the current study, a risk stratification system can be established, with patients having a gradient of >75% at high risk of hypocalcemia. However, further prospective studies with larger sample size need to be carried out to draw conclusive evidence for the same.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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