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4-Hour postoperative PTH level predicts hypocalcemia after thyroidectomy in children☆,☆☆

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ABSTRACT

Background: Hypocalcemia occurs frequently after a total thyroidectomy in pediatric patients. Four hour postoperative PTH monitoring predicts the need for calcium supplementation in the adult thyroidectomy population. We evaluated the role of the 4 h postoperative PTH level in determining the need for calcium supplementation after thyroidectomy in the pediatric population.

Methods: This is a retrospective review of children undergoing total thyroidectomy by a single pediatric surgeon from July 2011 through July 2018. Intact PTH obtained four hours postoperatively determined the need for calcium supplementation for patients beginning in November 2014 onward. Serum total calcium levels were monitored concurrently with serum intact PTH levels. Serum calcium levels were followed in our Multispecialty Pediatric Endocrine Surgery clinic within the month following thyroidectomy.

Results: From July 2011 through July 2018, there were a total of 56 total thyroidectomies at our institution. Prior to November 2014, all pediatric total thyroidectomies received calcium supplementation per our institutional protocol. Based on ionized calcium levels, 26.3% (5/19) of children developed hypocalcemia. From November 2014 to July 2018, 37 pediatric patients required total thyroidectomies. 29.7% (11/37) had low 4-h postoperative PTH levels. 72.7% (8/11) patients with low 4-h postoperative PTH levels had corresponding postoperative day 1 total calcium levels less than 8.5 or ionized calcium levels less than 1.12, and five children (45.5%) developed symptomatic hypocalcemia. 70% (26/37) of children had normal 4-h postop PTH levels, with only 5 (19%) ever developing hypocalcemia. No patients with a normal postop PTH level developed symptomatic hypocalcemia or required IV calcium repletion. A single 4-h postoperative PTH <10 pg/dl for identifying hypocalcemia has a sensitivity of 81% and specificity of 91%, with AUC 0.81.

Conclusion: The 4-h postoperative serum PTH level can help determine the need for calcium supplementation in pediatric patients undergoing total thyroidectomy, thereby reducing unnecessary calcium supplementation and serial lab draws to monitor for postoperative hypocalcemia.

Level of evidence: Level II.

Thyroid cancer, the most common childhood endocrine cancer [1], comprises 2%–10% of all cancers in children, with 1% in prepubertal children and 7% in adolescents [2]. The presentation is typically more aggressive in children with higher rates of extrathyroidal extension, nodal disease, and distant metastases [3,4]. Hypocalcemia constitutes the most common complication following total thyroidectomy, occurring more commonly in children than adults. While definitions of hypocalcemia have not been standardized in the pediatric population, temporary hypocalcemia has been reported in 9%–52% of total thyroidectomies, with permanent hypocalcemia being much more rare (0%–6.7%) [5–8]. Risk factors for hypocalcemia include total thyroidectomy, nodal dissection, and malignancy [9]. Monitoring for hypocalcemia varies depending on institutional practice and surgeon preference. Carr et al. in 2014 [10] showed that a 4-h postoperative parathyroid hormone (PTH) level predicted hypocalcemia and the need for calcium supplementation after total thyroidectomy in adult patients. The purpose of our study is to determine if the 4-h postoperative PTH level can predict hypocalcemia in children. We hypothesize that it can be used to determine which pediatric patients undergoing total thyroidectomy need to be monitored more closely for hypocalcemia and who can be sent home safely without calcium supplementation.

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1. Methods

This is a single-institution, retrospective review of all patients from our Multispecialty Pediatric Endocrine Surgery (MPES) clinic who had a total thyroidectomy or completion thyroidectomy with or without lymph node dissection from November 2010 through July 2018. Any patient more than the age of 18 was excluded from the study. The study was approved by the Institutional Review Board.

All of the thyroid resections during this time period were performed by a single pediatric surgeon. At the time of surgery, recurrent laryngeal nerve monitoring was used in all patients who underwent thyroid operations. Central or lateral node dissections were performed based on preoperative FNA diagnosis of papillary or medullary thyroid carcinoma and nodal metastases. Any devascularized parathyroid glands were reimplanted in the sternocleidomastoid muscle.

Prior to September 2014, all patients who underwent a total thyroidectomy had ionized calcium levels monitored the evening of the surgery or the following day. If the levels were less than 1.12 mmol/L, the lower limit of normal in our laboratory, we continued to check ionized calcium levels every six hours until it normalized. All patients were monitored for clinical symptoms of hypocalcemia while hospitalized. Regardless of calcium levels, every patient who underwent total thyroidectomy or completion thyroidectomy received supplementation with calcium carbonate 1250 mg tablets three times per day for the first two weeks, followed by a weaning schedule of 1250 mg twice day for the next week, and 1250 mg daily for the next week, at which time they were seen in clinic with a calcium level. Intravenous calcium supplementation was dependent on severity of clinical symptoms. Patients who had hypocalcemia and clinical symptoms of perioral or peripheral numbness or tingling also received calcitriol.

After Carr et al. showed that a 4-h postoperative parathyroid hormone (PTH) level predicted hypocalcemia in October 2014 [10], we changed our practice and began to draw 4-h postoperative PTH levels in all our pediatric total or completion thyroidectomies to monitor for hypocalcemia. Each patient also had a total calcium level obtained at the same time point. Per protocol, only patients who had low PTH levels (<10 pg/dl) were supplemented with calcium carbonate as described above. During the transition period to the new protocol, some patients were discharged home on oral calcium supplementation despite a normal PTH level. This was discontinued promptly when recognized. No patients received calcium supplementation prior to the collection of the PTH level 4 h postoperatively.

Data collected included age, sex, diagnosis, surgery, nodal dissection, parathyroid reimplantation, pathology, PTH, and calcium levels. Primary outcomes were 4-h postoperative calcium and PTH levels, as well as need for calcium supplementation and presence of symptomatic hypocalcemia. The data were stored using Microsoft Excel and converted to STATA for analysis purposes. Sample characteristics are reported as number of observations and percentage for categorical variables, and median and range for continuous variables. PTH levels were dichotomized prior to data analysis as either above or below 10 pg/dl owing to issues with reporting of lower levels of PTH in a noncontinuous fashion. Total calcium levels were used as the reference standard for analysis of the accuracy of PTH levels to predict hypocalcemia. Patients were determined to have hypocalcemia if they had any serum calcium or ionized calcium below the laboratory defined normal range for these tests based on their age in the postoperative period. The presence or absence of hypocalcemia was compared by age using simple logistic regression analysis. Comparisons between sex, diagnosis, low postoperative PTH levels, presence of malignancy, and parathyroid reimplantation, as well as analysis of changes before and after implementation of the PTH monitoring protocol were assessed by Chi-squared or Fisher's exacts tests as appropriate. Presence or absence of a normal 4-h postoperative PTH level was compared against presence or absence of symptomatic hypocalcemia using Fisher's exact test. Simple logistic regression analysis was used to assess the association between 4-h postoperative PTH level and 4-h hypocalcemia and derive the area under the curve (AUC). All analyses were conducted in STATA v15.1, STATACorp, College Station, TX, with a p value less than 0.05 being considered significant.

2. Results

Between November 2010 and July 2018 56 total or completion thyroidectomies were performed. After October 2014 when the 4-h postoperative PTH level monitoring protocol for hypocalcemia was implemented, there were a total of 37 total thyroidectomies. Demographics and pathology are listed in Table 1, and Fig. 1 demonstrates the flow of study participants.

Summaries of types of procedures performed can be found in Table 2. Overall, the most common indications for thyroidectomy were malignancy (35.7%) and Grave's Disease (26.8%), followed by goiter secondary to Hashimoto's thyroiditis (12.5%), MEN syndromes (8.9%), and follicular lesions on fine needle aspirate (FNA) (7.1%). There were no significant differences in age, gender or diagnosis between the groups defined as before and after implementation of the PTH monitoring protocol. Overall, in the preimplementation group 26.3% had hypocalcemia, vs 29.7% in the postimplementation group ($p = 0.226$). There were no associations between risk of hypocalcemia and age (logistic regression, $p = 0.148$) or gender (male 33.3% vs female 36.6%, $p = 1.00$) in our population.

In evaluating the cohort of patients operated on after the implementation of 4-h postoperative PTH monitoring protocol, eleven patients (29.7%) underwent thyroidectomies after having an FNA consistent with papillary carcinoma or medullary thyroid carcinoma. Ten of these patients (91%) underwent a central neck lymph node dissection, while one also required right modified lateral neck dissection. Two additional patients were found to have evidence of malignancy after a preoperative FNA which demonstrated only a concerning follicular lesion. The four-hour PTH level was considered to be low if it was less than 10 pg/dl, which is the lower end of the normal reference range at our institution. Four of eleven (36.4%) patients in the malignant group had low 4-h postoperative PTH levels, while there were seven of twenty-six (26.9%) in the benign group. All four of the patients with low PTH levels in the malignant group also had concurrent hypocalcemia, (Table 3) and all four patients had undergone nodal dissections. Six of seven (85.7%) patients with low PTH levels in the benign group had concurrent hypocalcemia. Notably, there was not enough statistical evidence to reject the null hypothesis of difference between rates of hypocalcemia or lower PTH measurements in patients undergoing thyroidectomy for malignant indications.

Table 1
Demographics.

Gender		
Male	15	26.8%
Female	41	73.2%
Age		
Median	14 yrs	
Range	9 mo–18 yrs	
Indications for Surgery		
Biopsy-proven cancer	20	35.7%
Grave's Disease	15	26.8%
Hashimoto's Thyroiditis	7	12.5%
MEN syndrome	5	8.9%
Follicular Lesion of Uncertain Significance	4	7.1%
Multinodular Goiter	3	5.4%
Bilateral nodules	2	3.6%
Pathology from FNA	**Malignancy**	**Benign Disease**
N (%)	18 (32.1%)	38 (67.9%)
Median age	14	13
Gender (M/F)	4/14	11/27

MEN = Multiple Endocrine Neoplasms.
FNA = Fine Needle Aspirate.

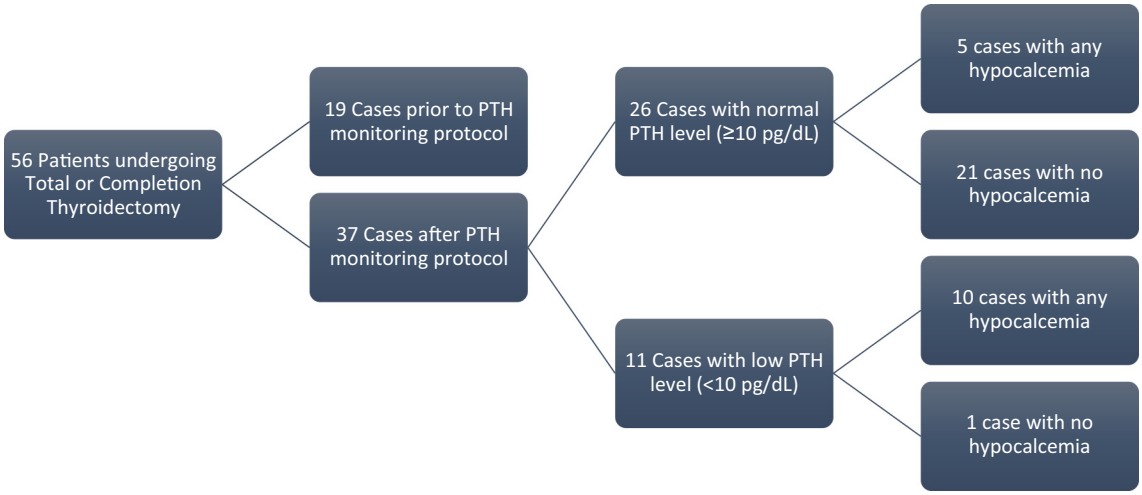

Fig. 1. Study participants.

We collected data regarding incidentally noted parathyroid glands that had been removed on the final pathology reports. Overall, approximately 18% noted incidentally found parathyroid glands on the final specimen, with no difference in the rates of this finding before and after implementation of the PTH monitoring protocol (Table 2). There was no statistically significant association in our sample between incidentally removed parathyroid glands and low postoperative PTH (20.0% low postoperative PTH with incidental parathyroid glands vs. 31.3% without, p = 0.528) or incidence of hypocalcemia (50.0% hypocalcemia with incidental parathyroid glands vs. 67.4% without, p = 0.246). Of note, of the 10 total parathyroids that were found incidentally on pathology, 7 of these were associated with the central lymph node dissection portion of the case.

Five patients required parathyroid reimplantation during their thyroidectomy. Of these, three (60%) had a low postoperative PTH level, and two (40%) had a normal postoperative PTH level. All of the patients with a parathyroid reimplantation and a low PTH level had hypocalcemia and required calcium supplementation, as did one of the two who had a normal PTH level postoperatively. Each patient had one parathyroid reimplanted into the sternocleidomastoid muscle. Two of these patients underwent reimplantation owing to intrathyroid location of a parathyroid gland, and one owing to devascularization of the parathyroid gland. While these values do not reach the level of statistical significance, they represent an important clinical decision point.

There was no difference between length of stay between the pre- and postimplementation groups, and there were no readmissions or emergency department visits for patients in either group. In the preimplementation group, all patients were discharged on oral calcium supplementation. After implementation of the PTH monitoring, this was reduced to 40.5%. A minority of patients required IV supplementation (5.3% in preimplementation group vs 13.5% in postimplementation group, p = 0.652).

A low 4-h postoperative PTH level had a specificity of 90.0% and sensitivity of 80.7% in detecting our pediatric patients with hypocalcemia after total thyroidectomy, with an area under the receiver operating characteristics curve of 0.835 (95% CI 0.705–0.965). (Fig. 2) Of the patients with a low PTH postoperatively, 72.7% had hypocalcemia the next day, and 25.5% were symptomatic at some point in their care. Of the patients with a normal PTH 4 h postoperatively (n = 26), only 5 (19%) had hypocalcemia. Two of these cases occurred early after the protocol was implemented, and therefore were discharged home on oral calcium supplementation, which was tapered over the next four weeks. Three patients had low calcium levels and received no calcium supplementation, per protocol. None of these patients developed symptomatic hypocalcemia, required long-term oral calcium supplementation, or required IV calcium supplementation, for a negative predictive value of 100%. Patients who experienced symptoms from hypocalcemia reported numbness or tingling. No patients suffered seizures, or required ICU admission for monitoring.

All patients had their calcium levels repeated in clinic at follow up approximately one month after discharge. None of the patients with normal PTH levels 4 h after surgery developed hypocalcemia at that time. Some patients had PTH levels repeated at their postoperative

Table 2
Operative details, pathology, and outcomes.

	Pre-PTH Protocol	Post-PTH Protocol	p-values
Type of Operation	Total = 19	Total = 37	
Total Thyroidectomy alone	11 (57.9%)	25 (67.6%)	
Completion thyroidectomy alone	0 (0%)	1 (2.7%)	0.464
Total Thyroidectomy + LND	7 (36.8%)	11 (29.7%)	
Completion Thyroidectomy + LND	1 (5.3%)	0 (0%)	
Parathyroid Reimplantation	1 (5.3%)	5 (13.5%)	0.327
Incidental Parathyroid on Pathology	5 (26.3%)	5 (13.5%)	0.205
Symptomatic Hypocalcemia	4 (21.1%)	5 (13.5%)	0.470
Length of stay (days; median, IQR)	1 (1–2)	1 (1–2)	0.728
Readmissions	0 (0%)	0 (0%)	1.00
Required calcium supplementation	19 (100%)	15 (40.5%)	0.000
Oral supplementation	19 (100%)	15 (40.5%)	0.000
IV supplementation	1 (5.3%)	5 (13.5%)	0.652
Required calcitriol supplementation	3 (15.8%)	10 (27.0%)	0.507

LND = Lymph Node Dissection; IQR = Interquartile range.

Table 3
Total thyroidectomies after implementation of PTH monitoring.

	Malignancy N = 11	Benign N = 26	p-value
Low postop PTH	4 (36.4%)	7 (26.9%)	0.420
Low PTH + Hypocalcemia	4	6	0.636
Low PTH + Normal Calcium	0	1	
Normal postop PTH	7 (63.6%)	19 (73.1%)	0.420
Normal PTH + Hypocalcemia	3	2	0.101
Normal PTH + Normocalcemia	4	17	

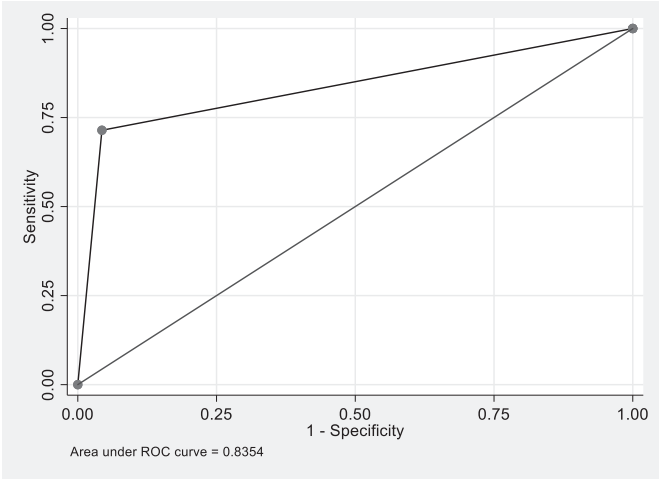

Fig. 2. Receiver operating characteristics curve of PTH level for hypocalcemia.

visit, and of the patients with a low postoperative PTH level, eight of the nine (88.8%) had normal PTH levels when repeated in clinic.

3. Discussion

Since hypocalcemia is the most common complication after thyroidectomy in the pediatric patient, it is important to have an algorithm that can identify and treat these patients early [11]. Carr et al. showed that a 4 h PTH level after surgery was equivalent to a 24-h level in predicting adult patients who would not need calcium supplementation [10]. Our study showed that a low 4 h PTH level (<10 pg/dl) after total thyroidectomy in children was predictive of hypocalcemia, with a sensitivity of 80.7% and specificity of 90%. Early identification of hypocalcemia allows for earlier treatment, minimizing the sequelae of hypocalcemia, leading to a decreased requirement for blood draws, and avoiding calcium supplementation in those who do not require it. These factors are more important in children, given that some of our young patients may not be able to verbally express symptoms of hypocalcemia or may have difficulty with medication compliance. Though same-day discharge has been cited as a benefit of early identification of hypocalcemia after total thyroidectomy [11,12], our patients come from a wide catchment area, and we prefer to monitor our patients overnight at a minimum.

In the Carr et al. study, only two patients with PTH > 10 pg/dl were supplemented. Only one developed symptomatic hypocalcemia and was supplemented with calcium and calcitriol, while the other had asymptomatic hypocalcemia that was treated with calcium alone [10]. During implementation of the new monitoring protocol, four of our patients with normal 4 h PTH levels received calcium supplementation upon discharge based on pediatric endocrinology recommendations. We did not routinely check postoperative day one calcium levels in our patients with normal 4 h PTH levels. No patients with normal 4-h PTH called in with complaints of hypocalcemia or had to be started on calcium or calcitriol supplementation prior to their one-month follow-up visit. At the follow-up visit, none of these patients had clinical evidence of hypocalcemia.

As a result of our data, we do not recommend routine calcium supplementation of our pediatric total thyroidectomy patients with normal 4-h PTH >10 pg/dl, as none of these patients required supplementation for symptomatic hypocalcemia, with the exception of patients who require parathyroid reimplantation. We routinely supplemented our patients with low 4 h PTH levels <10 pg/dl with oral calcium. Patients who reported symptoms or had persistent hypocalcemia despite

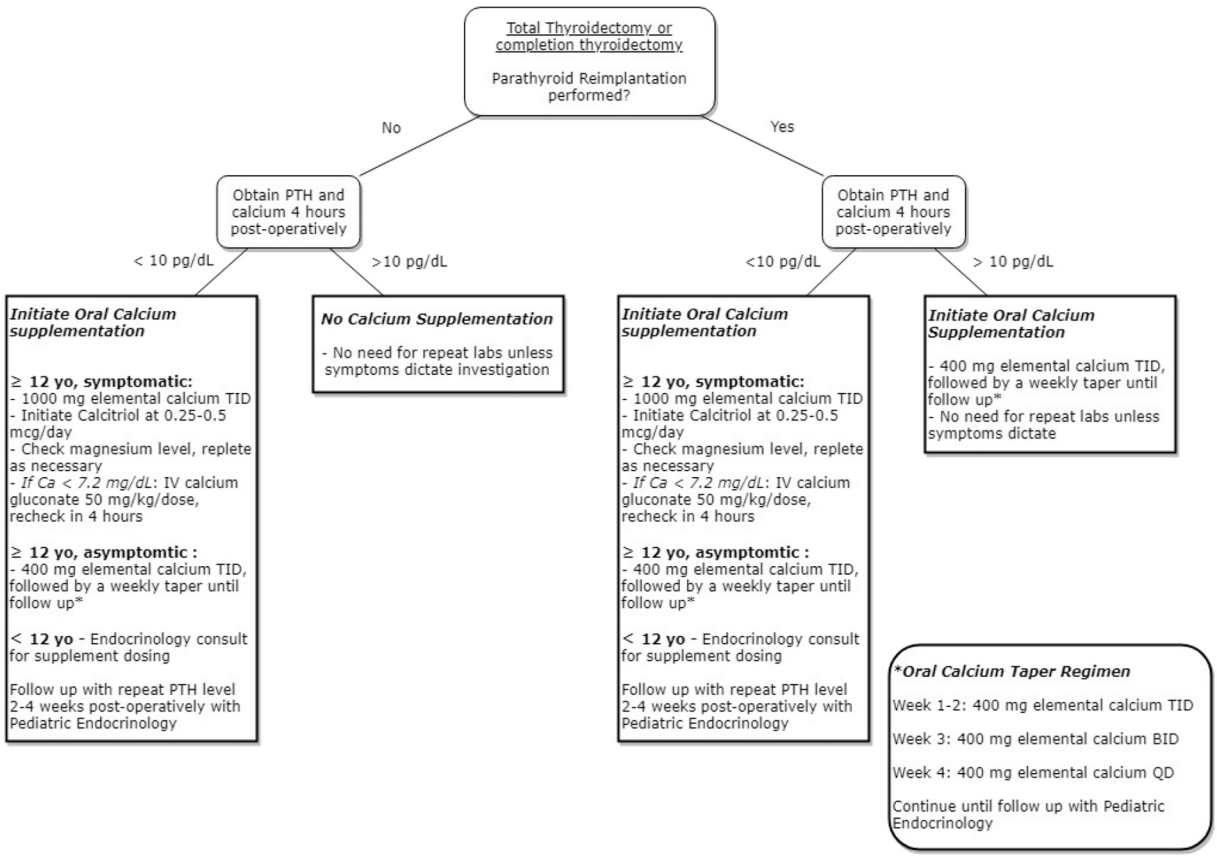

Fig. 3. Recommended management algorithm.

calcium supplementation received calcitriol as well. Additionally, while our group of patients with parathyroid reimplantation was too small to make any strong conclusions, we recommend the routine supplementation of patients who require parathyroid reimplantation, owing to the potential for transient hypoparathyroidism in the immediate postoperative period in these patients (Fig. 3).

All patients were evaluated by the same pediatric surgeon, who performed all the operations, and one of two pediatric endocrinologists prior to surgery at MPES clinic. The benefit of our MPES clinic is that patients can be completely evaluated in one visit. They have their labs drawn, undergo an ultrasound evaluation, which is interpreted immediately by a pediatric radiologist, see both the pediatric endocrinologist and surgeon, and then have an ultrasound-guided fine needle aspiration (FNA) with sedation if necessary. This allows close collaboration between several specialties and minimizes the time spent by the patient waiting for results and treatment.

This study has limitations. The retrospective nature of this study introduces inherent bias, most notably that we rely on completeness of documentation in some of our outcomes, specifically medication administration and reports of symptomatic hypocalcemia. Our population is quite heterogenous. While this is representative of a typical pediatric surgical practice, it may introduce some degree of bias in analysis of subgroups within our study. As with many single institution pediatric surgery case series, our numbers are small compared to adult studies, despite accumulating patients over an eight-year period. For the majority of patients, hypocalcemia was determined based on total calcium levels rather than ionized calcium levels, as this has been the traditional approach to monitoring. This is, however, subject to alterations in the setting of hypoalbuminemia, which was not routinely monitored in our patient population, and may introduce bias. Optimal monitoring of calcium levels and supplementation with calcium and calcitriol for our pediatric patients with low 4-h PTH cannot be determined from this study owing to the low numbers in this group. Additionally, with some of our patients too young to express hypocalcemia symptoms, there may be underreporting of symptoms in this group.

While other studies in pediatric patients have looked at predictive factors for hypocalcemia and other morbidities after total thyroidectomy [2,9,12,13], this is the first study to evaluate the role of the 4-h PTH in predicting hypocalcemia in pediatric total thyroidectomy patients. A large, multicenter, prospective controlled trial going forward is needed to further test the utility of the protocol we have proposed.

4. Conclusion

Predicting hypocalcemia after total thyroidectomy in the pediatric patient is possible with a 4-h PTH level after surgery, with a sensitivity of 80.7% and specificity of 90.0%. This allows us to start earlier treatment to potentially decrease severity and durations of symptoms in patients who are at risk for hypocalcemia, and allows for safe discharge of patients with normal levels without unnecessary medications. This is particularly important for our pediatric patients who are unable to verbally express symptoms of hypocalcemia.

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