Prospective Study Evaluating Intraoperative and Postoperative Parathyroid Hormone Assay versus Serum Calcium Monitoring to Predict Hypocalcemia after Total Thyroidectomy

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ABSTRACT

Introduction: *the standard surgical procedure for the management of benign or malignant nodular thyroid disease now is total thyroidectomy. Hypocalcemia is the most frequent complication after total thyroidectomy. Measuring parathyroid hormone (PTH) is more frequently utilized now to predict those patients at risk of developing post-thyroidectomy hypocalcemia.* ***Aim:*** *to determine if PTH levels can predict hypocalcemia early to safely shorten hospital stay and to compare best timing for measuring PTH either intraoperative or 4 hours postoperatively.* ***Methods:*** *A prospective study in which fifty patients who underwent total or completion thyroidectomy were divided according to the occurrence of hypocalcemia into 2 groups, Group A with no hypocalcemia and Group B with hypocalcemia. Adjusted serum calcium was measured preoperatively and at 4, 24 and 48 h postoperatively while PTH was measured preoperatively, intraoperatively at time of skin closure and 4 hours postoperatively.* ***Results:*** *no significant difference in the preoperative and intraoperative data except for higher incidence of toxic goiter and thyroiditis in group B, also higher operative time. Statistically significant decline of both serum Ca and PTH in the postoperative data results. No statistically significant difference in measuring PTH intraoperatively or at 4h post thyroidectomy.* ***Conclusion:*** *PTH is useful, accurate and rapid predictor of post thyroidectomy hypocalcemia and can be measured up to 10 minutes after thyroid dissection and so can predict patients who can be safely discharged on the same day after operation.*

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Key Words: *Prospective Study, Parathyroid Hormone, Hypocalcemia, Thyroidectomy*

INTRODUCTION

Postoperative hypoparathyroidism, due to inadvertent devascularization or removal of parathyroid glands, leading to hypocalcemia is one of the most frequent morbidities following total thyroidectomy, with incidence ranging between 3 and up to 50 % in some literatures. Most cases of iatrogenic hypoparathyroidism are transient (defined as <6 months), but rates of permanent hypoparathyroidism have been reported to be as high as 14% [(1,2)].

Calcium (Ca) metabolism is a key element to maintain cellular homeostasis. Hypocalcemia can generate confusion, nausea, vomiting, tingling in the extremities and peri-orally, convulsions or cardiac arrhythmias. In addition, because potentially life-threatening hypocalcemia may not develop until 24–48h after surgery, hypoparathyroidism is a major reason for delayed hospital discharge and preventing surgeons from performing ambulatory thyroid surgery. Potential advantages related to early discharge include cost savings, improved patient comfort and convenience, and lower exposure to nosocomial pathogens [(3,4,5)].

Various approaches to facilitate timely hospital discharge without compromising patient safety to manage postoperative hypoparathyroidism/ hypocalcemia, had been described, namely, serial calcium monitoring, routine Ca supplementation, and parathyroid hormone (PTH)-directed supplementation [(6)].

Serial Ca monitoring is adopted by many surgeons due to wide availability of Ca testing but involves patients staying for at least 1–2 nights in hospital until either normal level of serum

calcium is established and/or a consistent level or upward trend is observed [6,7].

Because of its relatively short half-life, changes in PTH precede changes in calcium by hours. While the intraoperative PTH assay is widely adopted in parathyroid surgery, different reports exist regarding the sensitivity and specificity of PTH to accurately predict hypocalcemia after thyroidectomy [8,9].

There is no agreement about the best time to obtain PTH levels for accurately predicting the risk for clinically significant hypocalcemia. It is also unclear whether to use the absolute value of PTH or the percentage change from preoperative to intraoperative/ postoperative levels as a better predictor for postoperative hypocalcemia [10].

Aim of the study:

The aim of our study is to determine if single intra-operative PTH assay (at the time of skin closure) can accurately detect postoperative hypocalcemia in comparison to postoperative PTH assay and Ca monitoring.

PATIENTS AND METHODS

This prospective study was designed and evaluated in Ain shams university hospitals of consecutive fifty patients undergoing total thyroidectomy between September 2015 and March 2017.

All male and female patients who underwent either a total or a completion total thyroidectomy for benign or malignant thyroid disease were included in our study.

Patients with associated parathyroid disease, renal failure, preoperative calcium supplement intake, vitamin D deficiency, or patients refused to participate in the protocol were excluded from our study.

PTH concentrations were measured in all patients preoperatively one day before the operation day (as a control). The second PTH level measurements were taken immediately at the time of skin closure (approximately 10 min after the thyroid gland was removed) (PTH has a plasma half-life of two to four minutes) while the patient was still anesthetized (as an intra-operative PTH assay). The third PTH assay was taken approximately 4 h after operation (as a postoperative PTH assay). The reference range for PTH was as follows: 10-65 pg/mL and that was considered normal range.

Serum albumin-adjusted Ca and phosphate levels were measured and the total serum calcium concentration was considered normal between 8.5 and 10.2 mg/dL. Serum Ca and phosphate levels were checked preoperatively then at 4, 24 and 48 h postoperatively.

Surgical technique:

Total thyroidectomy was performed in a standardized manner under general anesthesia. Traditionally, a collar incision is used, created in a curvilinear fashion within a skin crease approximately 2 finger-breadths above the sternal notch. Dissection is carried through the subcutaneous fat to the platysma which was incised. Using monopolar cautery, subplatysmal flaps are elevated superiorly and inferiorly. In the midline between the strap muscles, the cervical linea alba was identified and incised superiorly and inferiorly. The strap muscles were separated and retracted laterally but in cases of large goiter or neoplasm, the strap muscles were divided to aid exposure.

When the lateral border of the thyroid was reached, the middle thyroid vein was identified and divided. The superior pole vessels are dissected out and ligated as close as possible to the thyroid capsule to avoid injury to the external branch of the superior laryngeal nerve. The inferior vascular pedicle and all remaining blood vessels going to and from the thyroid were ligated, allowing the gland to be rolled up and onto the anterior aspect of the trachea. Both recurrent laryngeal nerves and parathyroid glands were routinely identified and preserved.

Then, the isthmus was separated from the anterior aspect of the trachea, and the pyramidal lobe was followed cephalad as far as possible and resected en bloc with the thyroid. Dissection was continued onto the contralateral lobe using gentle traction of the mobilized isthmus to help expose that lobe and the same steps were repeated till the whole thyroid gland was removed.

Hemostasis was reassured and a closed-suction drain was placed for preventing a serous fluid collection. The neck was then closed in a layered fashion with special attention to a meticulous skin closure. At the time of skin closure, the intraoperative PTH sample was taken.

Follow up:

The patient was advised to keep a head up position of about 30° to minimize venous congestion and swelling of the soft tissues around

the wound. The patient was observed for signs of Early complications including hemorrhage into the wound, hoarseness and temporary aphonia, vocal cord paralysis, and postoperative thyroid storm.

Biochemical (asymptomatic) (i.e.: serum Ca less than 8.0 mg/dL) evidence of hypocalcemia were treated with oral calcium supplementation while Clinically evident hypocalcemia (symptomatic) (perioral numbness, fingertip paresthesia, or positive Chvostek's or Trousseau's sign) evidence of hypocalcemia were treated with intravenous calcium gluconate and oral vitamin D supplementation in addition to oral calcium. Otherwise, no routine calcium supplementation was prescribed in our study.

On hospital discharge, patients were divided into 2 groups: Group A (normocalcemic patients) and Group B (hypocalcemic patients) and their intraoperative and postoperative PTH measurements were analyzed and compared.

The drain was removed safely if the drain output was serous and decreasing in volume (less than 50 mL).

All patients were followed up at 1 week, 1 month, 3 months and 6 months' intervals and were asked specifically about symptoms of hypocalcemia after hospital discharge. For patients who developed hypocalcemia, serum Ca and PTH were measured with each visit.

Data were analyzed using Fisher's and chi-square test. All tests are considered significant if ($p \leq 0.05$).

RESULTS

Demographic data:

A total of fifty patients underwent total thyroidectomy of which forty-five patients (90 %) underwent a total thyroidectomy while five patients (10 %) had a completion total thyroidectomy. Those were combined with unilateral modified radical neck dissection in 3 (6%) patients with papillary thyroid carcinoma. The average age of our study patients was 47.5 years (range = 29–66 years) with the male to female ratio was 1:9. The surgical indication in 5 (10%) patients was thyroid cancer while of the remaining 45 patients, 43 (86%) had benign disease (simple and toxic multinodular goiter and thyroiditis) and 2 patients (4%) had incidental finding of thyroid cancer on histopathological examination.

Table 1: Comparison of patient baseline characteristics and surgical indication between both groups.

	Group A	**Group B**	**P value**
Number	42(84%)	8(16%)	
Age	49.5(33-66)	45(29-61)	0.122(NS)
Male: female	4:38	1:7	1.000(NS)
Indication:			
• Malignancy	6(14%)	1(12.5%)	0.434(NS)
• SMNG	32(76%)	4(50%)	0.065(NS)
• Toxic goiter	3(10%)	2(25%)	0.013(S)
• Thyroiditis	1(2%)	1(12.5%)	0.005(S)

SMNG: simple multinodular goiter. NS: non-significant. S: significant.

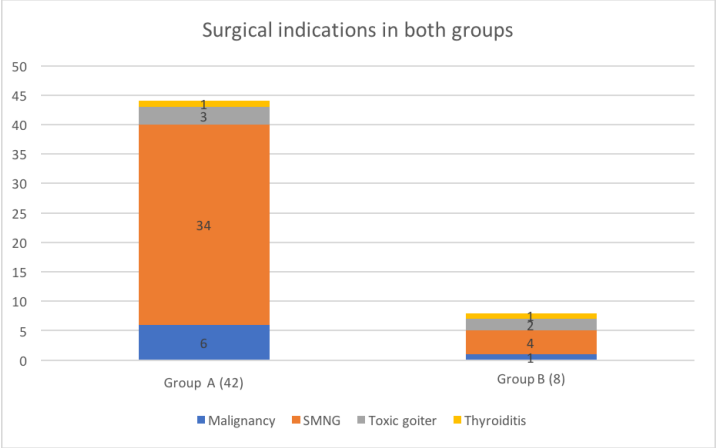

Fig. (1): Surgical indications in both groups

Postoperatively, 42 patients (84%) were normocalcemic (Group A) while in 8 cases (16%), postoperative hypocalcemia, clinically or biochemically, developed (Group B), requiring calcium and vitamin D supplementation. Table 1 shows comparison of patient baseline characteristics and surgical indication between both groups.

Intraoperative data:

Table 2: comparison of intraoperative data. NS: non-significant. S: significant.

	Group A	**Group B**	**P value**
Operative time (min.)	62-143(102.5)	100-180(140)	0.013(S)
Type of operation: • Total thyroidectomy • Completion thyroidectomy • With neck dissection	 38 4 2	 7 1 1	 0.328(NS) 0.076(NS) 0.004(S)
Blood Loss(mL)	10-50(30)	10-60(35)	0.659(NS)
Number of parathyroid glands identified	3.5	3.6	1.000(NS)

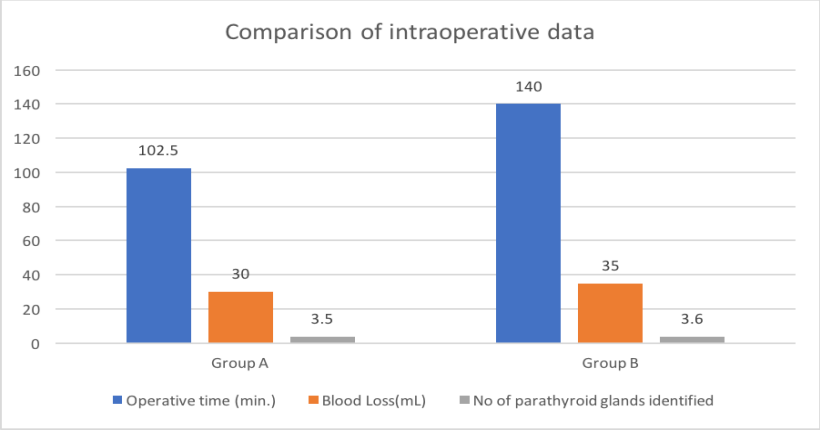

Fig. (2): Comparison of intraoperative data

Statistically significant differences were noted in the two groups in terms of operative time. In group A, the operative time was 62-143 minutes (average 102.5 minutes) while in group B it was 100-180 minutes (average 140 minutes) (P value 0.013), perhaps reflecting the difficulty of the procedure. There were no statistically significant differences noted as regard the operative blood loss (average 20 mL), also in the number of identified and preserved parathyroid glands (average 3.6 glands).

Postoperative data:

There was no mortality in both groups while the morbidity in the form of hypocalcemia (either clinically apparent and/or biochemically i.e. serum albumin-adjusted Ca less than 8 mg/dL) occurred in 8 patients i.e. Group B.

No statistical difference was found in preoperative values of the tests when the serum calcium and PTH assays were compared between normocalcemic and hypocalcemic groups. This is shown in table 3.

Table 3: Comparison between preoperative serum Ca and PTH in both groups. NS: non-significant.

	Group A	**Group B**	**P value**
Preoperative serum Ca (mg/dL)	8.7-10.5(9.6)	8.5-10.2(9.35)	0.954(NS)
Preoperative PTH (pg/mL)	11-66(38.5)	10.5-77(43.75)	0.490(NS)

In comparison to the preoperative values, adjusted serum Ca assay at 4h postoperatively was significantly lower in Group B than Group A with the average value in Group B 7.7mg/dL (range 6.9-9.5 mg/dL) while in Group A the average was 9.1 mg/dL (range 8.3-9.9 mg/dL). Serum calcium levels continued to decrease at 24h and 48 h after surgery in the hypocalcemic Group B, but not in the normocalcemic Group A.

As regard the intraoperative PTH, average serum PTH concentrations of the hypocalcemic Group A decreased significantly to 6.1 pg/mL (range 2.5-9.4 pg/mL) at the time of skin closure. Same results were obtained at 4 hours after surgery (average 6.3 pg/mL; range 2.3 to 9.8 pg/mL). As for Group A, intraoperative and postoperative PTH values remained above 10 pg/mL (average 10.2-55 pg/mL) which was lower than preoperative values but not statistically significant. Detailed data comparison is shown in table 4.

Table 4: Postoperative data results of serum Ca and PTH. S: significant.

	Group A	**Group B**	**P value**
Postoperative Serum Ca (mg/dL)			
• At 4h	9.1(8.3-9.9)	7.7(6.9-9.5)	0.018(S)
• At 24h	9.0(8.3-9.7)	7.1(6.0-8.4))	0.014(S)
• At 48h	9.2(8.4-9.6)	6.5(5.8-7.8)	0.023(S)
Intraoperative PTH (pg/mL)	33.5(10.2-62)	6.1(2.5-9.4)	0.0412(S)
Postoperative PTH (pg/mL)	33.3(10-55)	6.3(2.3-9.8)	0.009(S)

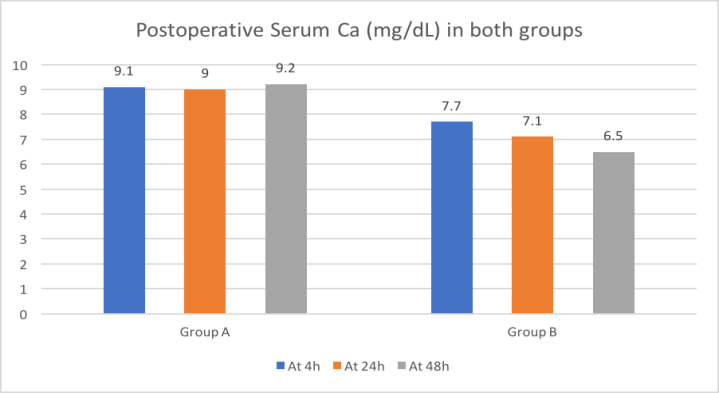

Fig. (3): Postoperative serum Ca (mg/dL) in boh groups

When the intraoperative and postoperative PTH values were compared, there was no statistically significant difference. That is shown in table 5.

Table 5: Comparing intra- and post-operative PTH. NS: Non-significant.

	Intraoperative PTH (pg/mL)	**Postoperative PTH (pg/mL)**	**P value**
Group A	33.5(10.2-62)	33.3(10-55)	0.116(NS)
Group B	6.1(2.5-9.4)	6.3(2.3-9.8)	0.237(NS)

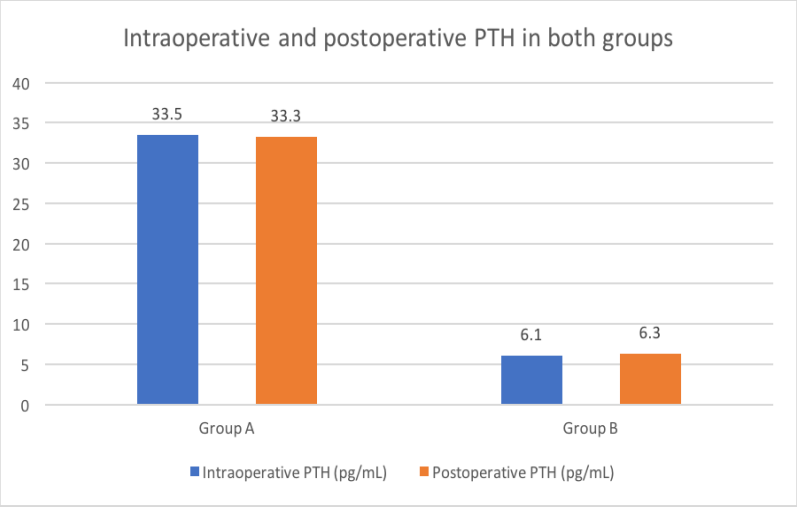

Fig. (4): Intraoperative and postoperative PTH in both groups

The important finding that we have noticed was all the eight patients in Group B had intra- and postoperative PTH values less than 10 pg/mL while at the same time frame only three patients had adjusted serum Ca lower than 8 mg/dL. Four more patients developed low serum Ca at 24 h postoperatively and one more patient at 48 h after the operation.

Follow up:

For Group A, average hospital stay was 2.5 days (2-3 days). No patients in this group had reported any symptoms of hypocalcemia in the follow up visits in our out-patient clinic.

While in Group B, average hospital stay was 6 days (5-7 days). This was the time required for control of patients' hypocalcemia. Patients were discharged on oral calcium supplementation and calcitriol (oral vitamin D). One patient had dose adjustment due to persistent symptoms. No need for hospital readmission was reported. The decreased calcium and PTH levels slowly increased from 7 days and recovered completely at approximately 3 months after surgery.

During follow-up, seven patients (87.5%) of the hypocalcemic Group B were successfully taken off supplements over an average duration of 2 months (range 1–3 months) while one patient (12.5%) continued to take calcium and calcitriol. Since this patient took supplements for more than 6 months, she was regarded as having permanent hypoparathyroidism. The overall incidence of permanent hypocalcemia in our study was 2%.

DISCUSSION

Transient hypoparathyroidism is one of the most frequent morbidities following total or completion thyroidectomy and is a major reason for delayed hospital discharges beyond the 24-hour point because potentially life-threatening hypocalcemic symptoms may not occur until 24–48 h after surgery [1,11]. various approaches have been adopted to safely manage postoperative hypocalcemia including serial calcium monitoring wherein calcium levels are typically drawn until a

normocalcemic plateau or a stable upward trend is demonstrated. Others has proposed routine calcium supplementations for all postoperative patients. Given that neither routine postoperative calcium supplementation to all patients nor prolonged hospitalization for serial serum calcium determinations are cost-effective policies, reliable markers for early diagnosis of hypocalcemia have been thoroughly sought [2,12,13].

Also, since most patients do not develop hypocalcemia severe enough to require hospitalization after thyroidectomy, measurement of PTH levels and classifying patients according to relative risk for hypocalcemia can enhance decision making thus reducing unnecessary inpatient admissions [3].

In our study, we found no relationship between patient characteristics or preoperative laboratory data results and development of hypocalcemia. Otherwise, like other investigators (as Puzziello et al, Pardo et al and Roh et al), we found that toxic goiter, thyroiditis, duration of the operation and neck dissection were factors associated with statistically more hypocalcemia [4,5,6]. This may be explained by the increased risk of parathyroid gland injury or devascularization.

The primary aim of our study was to asses if PTH assay can identify patients at risk of clinically significant hypocalcemia earlier than serum calcium monitoring after thyroidectomy. Our study had revealed that the PTH assay can lead to earlier prediction of hypocalcemia after thyroidectomy with a higher sensitivity and specificity up to 100%. This was similar to AlQahtani et al who found that PTH levels at 1 h postoperatively accurately predicted hypocalcemia with a 100 % specificity [7]. While others like Roh et al had reported sensitivity and specificity of 85% and 84%. This practice should potentially shorten hospitalization of post thyroidectomy patients [8,9].

Two main approaches for PTH assay was described, the percentage drop in PTH level from the preoperative to the postoperative period or a single postoperative PTH level sometime after surgery with a cutoff value. We chose the latter approach because to decrease the need for drawing multiple blood samples, reduce the clinical workload and the overall cost.

There is no consensus in the literature regarding the best time to obtain the PTH value. In our study, we did not identify any statistically significant disadvantage for measuring PTH intraoperatively at the time of skin closure (approximately 10 min after the thyroid gland was removed) versus early postoperatively (4h after thyroidectomy) for predicting hypocalcemia with p value of 0.237.

Lombardi et al [9] suggested that measuring serum PTH earlier than 1 hour postoperatively were less accurate in predicting hypocalcemia and therefore PTH levels were measured at 1 hour or later postoperatively for more confident prediction of postoperative hypocalcemia in several studies like Lam et al and Payne et al [10,11]. But like our study, others like Islam et al, Lang et al and Chindavijak et al, have advocated that intraoperative PTH levels obtained immediately after thyroid removal could be used reliably to predict postoperative hypocalcemia [12,13,14]. Also, the intraoperative PTH has the advantage of no pain to the patient as the patient is still anaesthetized and the results comes more rapid thus more shortening of the hospital stay.

Based on our study, patients can be separated into two groups with respect to risk for hypocalcemia; those at risk (PTH <10 pg/mL) (Group B) and those at no risk (PTH ≥10 pg/mL) (Group A). For the at-risk patients, earlier calcium and vitamin D supplementation were given to prevent symptomatic hypocalcemia while in whom PTH levels more than 10 pg/mL who report no symptoms of hypocalcemia could be safely discharged the same day of the surgery (i.e. an early discharge (<24 h) would be possible in almost 84 % of patients after total thyroidectomy) without calcium supplementation and do not have laboratory tests checked at their postoperative visit. Other colleagues who agree with our recommendation include Lang et al, Azadeh et al, Noordzij et al and reddy et al [13,15,16,17].

Conclusion:

The PTH assay can be used to improve decision making regarding immediate postoperative management and discharge planning for patients undergoing total thyroidectomy. Based on our study, there appears to be no disadvantage to using intraoperative PTH measurement as early as 10 minutes after thyroid excision versus that obtained 4 hours postoperatively to guide initial clinical management of serum calcium.

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