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ORIGINAL ARTICLE

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Efficacy of indocyanine green fluorescence in predicting parathyroid vascularization during thyroid surgery

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Abstract

Background: We examined the value of indocyanine green (ICG) fluorescence angiography in predicting parathyroid vascularization following thyroid and central compartment surgeries.

Methods: Data were prospectively collected on adult patients undergoing thyroid and/or central compartment surgeries. Outcomes were compared in surgeries performed with and without ICG use. ICG scoring was used to quantify the vascularity of parathyroid glands.

Results: One hundred eleven patients were included; 43 (38.7%) patients underwent ICG injections. There was no significant difference in mean parathyroid hormone (PTH) changes at the end of surgery (29.24 vs 23.48 pg/mL, $P = .38$), symptomatic hypocalcemia (7.9% vs 3.9%, $P = .37$), or length of stay (1.095 ± 0.22 vs 0.912 ± 0.07 days, $P = .51$) between surgeries performed with and without ICG. The average vascularization score among individuals undergoing ICG angiography was 2.89 out of a maximum of 8 points.

Conclusion: Low-flow ICG patterns are not associated with postoperative PTH changes or transient hypocalcemia and may lead to unnecessary parathyroid autotransplantation.

KEYWORDS
angiography, autotransplantation, ICG, parathyroid, thyroid

1 | INTRODUCTION

Iatrogenic injury to the parathyroid glands remains a common unintended outcome following thyroid surgery. Although the reported frequency varies, transient hypoparathyroidism after thyroid surgery is reported in up to 49% of cases.[1-4] Permanent postoperative hypoparathyroidism has been reported to an upper limit of 16.7%[1,5] in all thyroid surgeries. Both transient and permanent hypocalcemia can clinically present with Chvostek's and Trousseau's signs, muscle spasms, and paresthesia. Severe neurological manifestations can follow if this calcium ion imbalance is not adequately treated. Compared to patients without permanent hypoparathyroidism, there is a 2-fold increased risk of death in those with permanent hypoparathyroidism after total thyroidectomy.[6]

Although there are several etiological causes of hypoparathyroidism after thyroid surgery, iatrogenic devascularization of the parathyroid glands is a main cause. General consensus suggests that only half of one normal parathyroid gland can yield adequate parathyroid hormone. Parathyroid autotransplantation

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has been performed as a means to prevent postoperative hypocalcemia, yet this procedure remains controversial.[7]

In order to prevent unnecessary parathyroid gland autotransplantation and predict postoperative hypocalcemia, several intraoperative procedural techniques have been pursued. The use of intraoperative indocyanine green (ICG) fluorescence in thyroid surgery as a mechanism for determination for parathyroid autotransplantation is a novel idea with limited data regarding efficacy to date. Although several studies have used accumulated vascularization data, one study reported the rate of parathyroid gland autotransplantation based on ICG angiography is approximately 17%.[8]

Despite preliminary studies highlighting the benefits of ICG fluorescence angiography, there lacks a substantial body of evidence to justify its routine use in thyroid surgery. The aim of this study is to determine if low ICG angiography patterns, that is, potential parathyroid ischemia, correlates with a decrease in intraoperative parathyroid hormone (PTH) and/or postoperative hypocalcemia.

2 | PATIENTS AND METHODS

Experimental protocols and research methods were approved by the Tulane Institutional Review Board committee. Data were analyzed retrospectively from prospectively collected data on patients who underwent surgery at Tulane University Medical Center between January 2015 and December 2017. A total of 111 medical charts from patients who underwent thyroid surgery (total thyroidectomy, or concomitant central compartment neck dissection) were reviewed. ICG angiography was performed perioperatively in 43 cases to visualize vascularization of the parathyroid glands. Intraoperative changes in serum PTH levels were measured, whereas blood loss, length of stay, vocal cord injury, and clinical manifestations of hypocalcemia were also collected to assess postoperative outcomes. ICG vascularization scores, per parathyroid gland, were reported using a previously established methodology[7]: 0 (no vascularization), 1 (moderate vascularization), 2 (excellent vascularization). Forty-three ICG cases were compared to 68 conventional cases. Parathyroid surgeries or thyroid surgeries with concomitant parathyroidectomy were excluded.

2.1 | Surgical technique and ICG protocol

All thyroid surgeries were performed by the same surgeon with standardization of operative technique and general anesthesia. Intraoperative PTH monitoring was performed in all cases; PTH was measured both at the start and end of each operation. Blood supply to each parathyroid gland was preserved via extracapsular dissection. Each parathyroid gland was visually inspected for structural integrity.

ICG dye injection (5 mg) was performed intravenously at the end of the surgery. A near-infrared (NIR) camera attached to an Olympus scope was used to identify parathyroid gland uptake of ICG dye. Laparoscopic imaging was switched to NIR imaging on the camera. Using the NIR camera, fluorescent areas were identified as green, whereas nonfluorescent structures were displayed in black. ICG is a 775 Da molecule that has a maximum absorption and reemission spectrum of 805 and 835 nm, respectively. When injected, ICG binds to plasma proteins to circulate in the intravascular space. The molecule has a half-life between 3 and 5 minutes and is eliminated within 20 minutes via hepatic metabolism. A NIR camera attached to an Olympus scope was used to visualize anatomic structures containing this dye. The parathyroid glands appeared in shades of gray depending on the amount of ICG flowing through the parathyroid tissue, thereby reflecting the degree of vascular blood flow.[8] An imaging score for ICG was established: ICG 0, the parathyroid is black after the injection of ICG, indicating that the gland is not vascularized; ICG 2, the parathyroid is white, indicating the gland is well vascularized; or ICG 1, the parathyroid is gray or heterogenous, suggesting that the gland is partially vascularized.[8]

2.2 | Postoperative management

The vast majority of patients had same or next day discharge in both the conventional and ICG groups (97.1% vs 92.9%, $P = .31$). Patients were monitored for clinical signs of hypocalcemia and had systematic testing of serum calcium levels in the immediate postoperative time, postoperative day 1. All patients were prescribed Tums with or without symptoms of hypocalcemia and without collection of lab results. All patients had a postoperative visit 1 week after the procedure to undergo clinical assessment and to undergo biochemical lab testing.

2.3 | Statistical analysis

All statistical calculations were conducted using SPSSv20 (IBM Corp, Armonk, New York). Statistical analyses were performed with the Student t test and analysis of variance test where appropriate, with significance set at $P < .05$. The data distribution was assimilated to a normal distribution. Patient demographics and perioperative parameters were compared between the conventional surgery group and the group that had ICG technique during surgery. Statistical comparison of postoperative biochemical outcomes (PTH and calcium levels) focused on groups with high and low ICG uptake which was determined by the vascularization score detailed beforehand as well as graphical representation (Figures 1-3) of these variations.

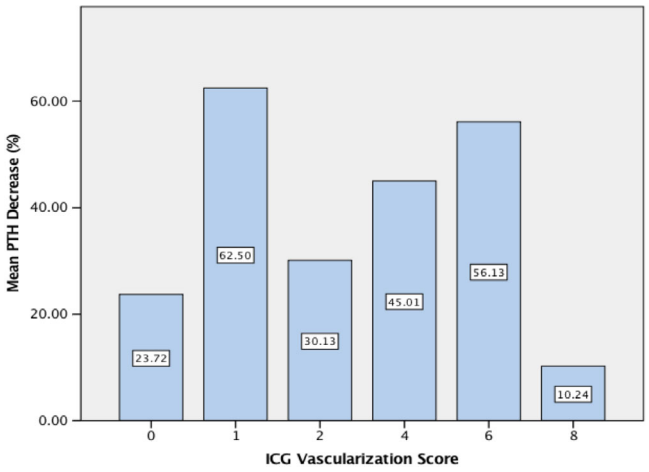

FIGURE 1 Mean postoperative parathyroid hormone (PTH) decrease based on the indocyanine green fluorescence (ICG) vascularization score [Color figure can be viewed at wileyonlinelibrary.com]

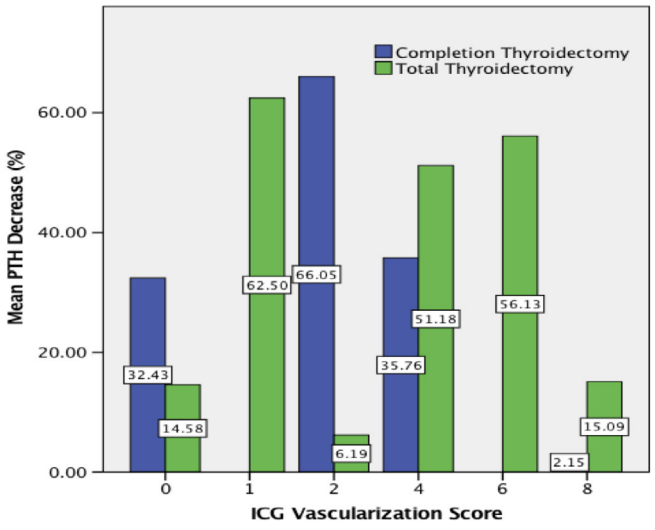

FIGURE 2 Mean postoperative parathyroid hormone (PTH) decrease based on indocyanine green fluorescence (ICG) vascularization score stratified by surgical procedure [Color figure can be viewed at wileyonlinelibrary.com]

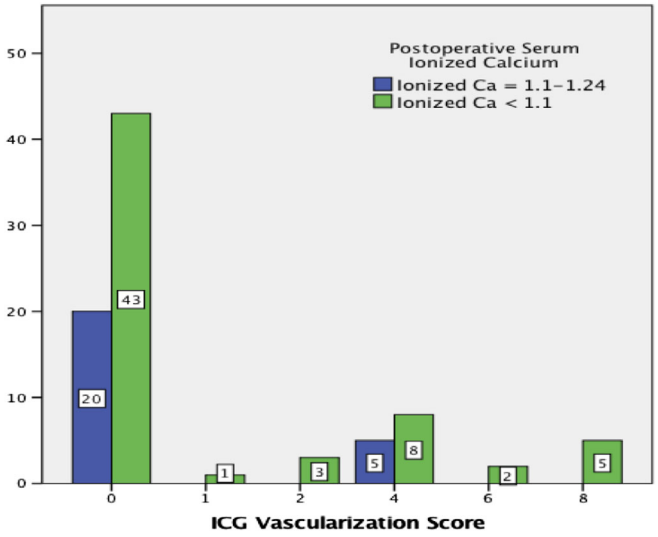

FIGURE 3 Clustered comparison of postoperative ionized serum calcium levels [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Demographic characteristics of patients undergoing thyroid surgery based on the intraoperative use of the ICG fluorescence technique for parathyroid gland visualization

		Conventional	ICG	*P* value
Age, y, mean, (SD)		51.56 (1.46)	50.51 (1.98)	.73
Sex	Female, %	83.80	90.70	.31
	Male, %	16.20	9.30	
Race	White, %	54.40	53.50	.88
	Black, %	38.20	41.90	
	Other, %	7.40	4.70	
BMI, kg/m^2, mean, (SD)		30.38	30.37	.99
Thyroid size, cm, (SD)		64.86	47.71	.40
Hashimoto disease, %		33.30	23.80	.21
Graves' disease, %		11.80	16.30	.50
Thyroid malignancy, %		36.80	34.90	.84

Abbreviations: BMI, body mass index; ICG, indocyanine green fluorescence.

3 | RESULTS

In total, 111 patients selected randomly were included in the study. Among these patients, 43 (37.9%) underwent ICG angiography during thyroid surgery. Demographic characteristics of all patients included in the analysis are shown in Table 1. There was no significant difference in average age, sex ($P = .31$), race ($P = .88$), body mass index ($P = .99$), thyroid size ($P = .40$), or thyroid disease including presence of Hashimoto thyroiditis ($P = .21$), Graves' disease ($P = .50$), or thyroid malignancy ($P = .74$).

Table 2 demonstrates the perioperative parameters and surgical approaches used for both the ICG and non-ICG cohorts. Central neck dissection accompanied specific total or completion thyroidectomy cases: 11.8% thyroidectomies in the conventional group vs 44.2% completion thyroidectomies in the ICG group ($P = .22$). There were no differences in estimated blood loss ($P = .92$), operative time ($P = .08$), length of stay ($P = .51$), perioperative complications ($P = .31$), mean PTH decreases ($P = .38$), or symptomatic hypocalcemia ($P = .37$) between the conventional and ICG groups.

A postoperative biochemical profile, including mean PTH changes, ionized calcium levels, and symptomatic

TABLE 2 Perioperative and postoperative characteristics based on ICG use during surgery

	Conventional	ICG	*P* value
Surgery, n	68	43	.10
Neck dissection, %	11.80	23.30	
Estimated blood loss, mL, (SD)	15.22 (0.92)	15.00 (1.40)	.92
Operative time, minutes, (SD)	128.13 (4.36)	147.93 (7.65)	.08
Length of stay, mean, (SD)	0.912 (0.07)	1.095 (0.22)	.51
Mean PTH decrease, pg/mL	23.48	29.24	.38
Perioperative complication, %	2.90	7.00	.31
Symptomatic hypocalcemia, %	3.90	7.90	.37
Completion thyroidectomy, %	48.50	32.60	.22
Total thyroidectomy, %	39.70	23.20	
Thyroidectomy + CLND, %	11.80	44.20	

Abbreviations: CLND, central lymph node dissection; ICG, indocyanine green fluorescence; PTH, parathyroid hormone.

TABLE 3 Postoperative biochemical profile based on ICG uptake

		ICG score <2	ICG score >2	*P* value
Mean PTH decrease, pg/mL		27.84	35.64	.43
Postoperative serum ionized calcium, %	Normal: 1.1-1.24 (mmol/L)	30.30	25.0	.65
	Hypocalcemia: <1.1 (mmol/L)	69.7	75.0	
Symptomatic hypocalcemia %		5.50	2.70	.30

Abbreviations: ICG, indocyanine green fluorescence; PTH, parathyroid hormone.

hypocalcemia, was measured at postoperative day 1 for all study subjects. No significant difference in PTH changes (27.84 vs 35.64, $P = .43$) or symptomatic postoperative hypocalcemia (5.5% vs 2.7%, $P = .30$) was found between those with an ICG vascularization score less than 2 compared to those with an ICG vascularization score greater than 2. This comparison is highlighted in Table 3. Furthermore, there was no significant difference between these specific two groups with respect to low ionized calcium levels, defined as ionized calcium levels lower than 1.1 mmol/L (69.7% vs 75.0%, $P = .65$).

The mean PTH changes varied according to ICG vascularization score, with no correlative pattern. Figure 1 illustrates the relationship between mean PTH percentage changes and the ICG vascularization score, whereas Figure 2 illustrates this relationship stratified by the specific operative procedure. The highest mean PTH percentage decrease (66.05%) was experienced among patients with an ICG vascularization score of 2 undergoing a completion thyroidectomy (Figure 2).

Transient postoperative hypocalcemia, as defined by ionized calcium less than 1.1 mmol/L or based on clinical symptoms, was experienced in each ICG vascularization score group. Transient postoperative hypocalcemia was the highest for patients with an ICG vascularization score of zero (43 individuals). Figure 3 highlights the relationship between transient postoperative hypocalcemia and ICG vascularization score. Twenty patients with a vascularization score of zero had normal postoperative ionized calcium levels (Figure 3). Five patients with a maximum ICG vascularization score experienced transient postoperative hypocalcemia (Figure 3).

4 | DISCUSSION

To the best of our knowledge, this observational study is the largest series to date in North America to evaluate thyroid surgery outcomes in the setting of ICG angiography. Although ICG angiography has recently become a common tool to study parathyroid gland vascularization during thyroid surgeries, our study indicates that there is no association between ICG angiography and prediction of parathyroid integrity and transient postoperative hypocalcemia. Ionized calcium levels were drawn on postoperative day 1, and thus our results should be interpreted in the setting of transient postoperative hypocalcemia. Furthermore, our findings demonstrate that low ICG angiography patterns, in theory suggestive of poor parathyroid gland blood flow, do no not correlate with a

decrease in intraoperative PTH levels or subsequent transient hypocalcemia. Such findings, along with the fact that there is an absence of randomized controlled trials regarding this intraoperative practice, suggest that ICG angiography is not a perfect predictive tool of hypoparathyroidism and/or hypocalcemia. Endocrine surgeons must thus qualitatively and quantitatively interpret ICG data with caution, if using this technique to guide postoperative care for patients following thyroid surgery.

There has been a growing interest in the use of ICG angiography to predict parathyroid gland integrity during thyroid surgeries. Furthermore, few previous studies have suggested that ICG is a perfusion marker that can predict transient postoperative hypocalcemia.[7-9]

Although ICG angiography is an appealing novel real-time procedure, immediate parathyroid gland angiography following thyroid surgery may not correlate with long-term outcomes. Previous studies that been conducted on this topic have not followed patients past the immediate postoperative period,[8] therefore there is a lack of data regarding ICG angiography and development of permanent hypocalcemia or hypoparathyroidism. Due to this fact, we believe that surgical decision making based on ICG angiography data is contributing to potential unnecessary parathyroid autotransplantations. Previous research has demonstrated that the need for parathyroid autotransplantation after parathyroidectomies is very low (1%).[10]

None of our patients required parathyroid autotransplantation following thyroid surgery to avoid transient postoperative hypocalcemia, according to our optimal PTH test. For this reason, we chose against implementation of ICG angiography. Our optimal PTH test is intraoperative PTH monitoring combined with one postoperative PTH assessment immediately after surgery. In our protocol, all patients, with or without symptoms of hypocalcemia, are prescribed Tums. This postoperative protocol also does not rely on calcium lab results. Autotransplantation, if deemed necessary based on ICG findings, would have been performed on the same intraoperative day, right after thyroid gland excision.

The main challenge with ICG angiography is identifying parathyroid glands with accuracy and precision. Accurate visual interpretation of anatomical structures remains a difficulty for even the most experienced thyroid surgeons,[11] therefore using ICG technology to guide surgical decision making may lead to unnecessary parathyroid autotransplantation during thyroid surgery. For example, in one randomized clinical trial that used ICG to guide surgical management, 23 parathyroid glands were autotransplanted in 34 patients. Such high autotransplantation rates, in addition to a wide documented range of parathyroid autotransplantation successfulness, suggest that ICG angiography may not be the most optimal method to guide surgical decision making in thyroid and central compartment surgeries.

Our study does have limitations. Our research was retrospective in nature, which may have introduced selection or misclassification biases. However, the data were collected with the intention to examine the value of ICG utilization in thyroid surgery, reducing the potential for systematic error. Additionally, given our postoperative calcium supplementation protocol, it is possible that our patients have lower rates of transient postoperative hypocalcemia compared to other practices that do not routinely supplement with calcium, potentially decreasing our power to detect a significant association of ICG with transient hypocalcemia. However, our postoperative calcium supplementation protocol is performed in all patients, and therefore did not introduce differential bias into our results.

Our study demonstrates that the use of ICG angiography did not significantly improve thyroid surgery outcomes. In particular, poor vascular perfusion denoted by ICG angiography scores did not correlate with postoperative reductions in PTH level or transient hypocalcemia. We believe that intraoperative PTH monitoring in thyroid surgeries should remain as a more optimal method for predicting parathyroid gland vascularization compared to ICG angiography. Furthermore, ICG angiography is currently not a perfect predictive tool and endocrine surgeons must interpret results with caution when delivering postoperative care in the setting of thyroid surgeries.

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