Cohort Study

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Comparison of indocyanine green angiography vs intraoperative parathyroid hormone in early prediction of risk of post-thyroidectomy hypocalcemia: a prospective cohort study

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Introduction: Indocyanine green (ICG) angiography is the 'real-time intraoperative imaging' technique used to reduce the chances of hypoparathyroidism in post-thyroidectomy patients. In our study, the authors predicted the risk of early post-thyroidectomy hypocalcemia by intraoperative evaluation of parathyroid gland perfusion by ICG angiography.

Materials and methods: In patients who underwent total thyroidectomy, ICG angiography was done using the SPY PHI imaging system (Stryker). Post-thyroid specimen removal, scoring of parathyroids was done in spy contrast mode. All 4 or <4 visualized parathyroids were scored for vascularity with the highest score of 8. Serum ionized calcium was done 6 h postsurgery and on the morning and evening of postoperative days 1 and 2. Calcium supplements were given to only those who developed clinical or severe biochemical hypocalcemia.

Results: Out of 60, postoperative hypocalcemia was noted in 41 patients. Total ICG score ≤ 5 was seen in 34 patients, out of which 28 developed postoperative hypocalcemia showing PPV 82.3% and diagnostic accuracy of 68.3% while iPTH (4.28 pmol/l) showed PPV 76.7 and diagnostic accuracy 70 %. In eight patients, none of the glands was scored as 2 (White) and all these patients developed hypocalcemia requiring calcium infusion.

Conclusion: The absence of visualization of at least 1 well-perfused (score 2) gland on ICG angiography is highly predictive of hypocalcemia and the majority of patients with total ICG score ≤ 5 developed hypocalcemia in the immediate postoperative period. ICG is a good predictor of the absence of hypoparathyroidism after thyroidectomy and is comparable to iPTH in the prediction of post-thyroidectomy hypocalcemia.

Keywords: hypocalcemia, ICG (Indocyanine green angiography), ioPTH (intraoperative parathyroid hormone), post-thyroidectomy hypoparathyroidism

Introduction

The parathyroid glands play a significant role in maintaining good balance between serum calcium and phosphorus, but they are vulnerable to injury during surgical operations due to their small volume and variable location. Knowing the anatomical position and vascular supply of parathyroid glands is essential to avoid hypoparathyroidism post-thyroid surgery[1,2].

Temporary hypoparathyroidism with resulting hypocalcemia is the most common complication after total thyroidectomy (TT) and occurs in up to 30% patients who undergo total thyroidectomy[3,4]. Its incidence depends on the technical difficulty of the procedure and expertise of surgeon. Permanent hypocalcemia (hypocalcemia for more than 6 months after thyroidectomy) is reported in 1–10% of patients[5,6]. Reducing the rate of hypoparathyroidism is essential for improving quality of life, as postoperative hypocalcemia can result in prolonged hospitalization and multiple hospital visits, neuromuscular symptoms, need for life-long calcium and vitamin D supplementation, and long-term complications such as cerebral, vascular, ocular, and renal damage[7–11].

Angiography with indocyanine green (ICG) can be used as a technique to help identify the vascular blood supply of the PGs at risk for damage during thyroid gland dissection and to aid in the prediction of the functionality of the identified PGs. Accurate prediction of post-thyroidectomy hypocalcemia might lead to modification of surgical strategies. However, there is a need for reliable tools that can accurately predict whether a patient will develop hypocalcemia[5,12,13]. The current techniques for

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evaluating parathyroid function are based on calcium[14,15] and PTH[6,16–20] measurements at various time points during or after thyroidectomy. Unlike ICG-angiography, which has immediate results, calcium and PTH level measurements usually cannot guide intraoperative decision-making as their results require a long time to develop.

ICG is an inert, water-soluble, nonradioactive, and nontoxic contrast agent that has been used to enhance fluorescence imaging. It enables real-time assessment and direct imaging of tissue perfusion and vascularization. ICG is a 775-dalton-sized molecule with maximum absorption spectrum of 805 nm and with re-emission at 835 nm when excited by a light/laser at a wavelength in the near-infrared (NIR) spectrum.[21,22]. It is completely fixed to plasmatic proteins once in the bloodstream and circulates only in the intravascular compartment. Its half-life is 3–5 min and elimination occurs within 15–20 min by the liver. ICG is mixed with sterile water and injected intravenously. The injection can be repeated until maximum toxic dose of 5 mg/kg/day is reached. Reactions to the molecule are rare and fatal allergies have been reported in 1/333 000 cases. The catheter is purged after each injection for rapid image gain. After iv injection, ICG is distributed through the intravascular space and rapidly becomes bound to plasma proteins[23,24] (Fig. 1). After 1–2 min approximately, images are acquired using a SPY PHI camera (Stryker) (Figs. 2, 3).

In the present study, we aim to compare the prediction of risk of early post-thyroidectomy hypocalcemia by intraoperative PTH measurement and by evaluation of PGs perfusion by ICG angiography using a SPY PHI imaging system, which is even more relevant in iodine deficient population of north and central India where goiter is more prevalent and the thyroid gland is more vascularized increasing the chances of post-thyroidectomy hypocalcemia.

Aims and objective

1. To compare ICG angiography with intraoperative PTH measurement in early prediction of risk of developing postoperative hypocalcemia in patients undergoing thyroidectomy.
2. To study the correlation between parathyroid vascularization (intraoperative fluorescence) and postoperative glandular function (serum calcium and parathormone levels).

HIGHLIGHTS

- Prediction of risk of early post-thyroidectomy hypocalcemia.
- Comparison of indocyanine green (ICG) and intraoperative PTH measurement.
- Total ICG score ≤ 5 was seen in 34 patients, out of which 28 developed postoperative hypocalcemia showing PPV 82.3% and diagnostic accuracy of 68.3% while iPTH (4.28 pmol/l)showed PPV 76.7 and diagnostic accuracy 70%.
- In eight patients, none of the glands was scored as 2 (White) and all these patients developed hypocalcemia requiring calcium infusion.
- The absence of visualization of at least 1 well-perfused (score 2) gland on ICG angiography is highly predictive of hypocalcemia and the majority of patients with total ICG score ≤ 5 developed hypocalcemia in the immediate postoperative period.
- ICG is a good predictor of the absence of hypoparathyroidism after thyroidectomy and is comparable to iPTH in the prediction of post-thyroidectomy hypocalcemia.

Methodology

Study design

Prospective cohort study.

Sample size

Sample size was estimated using the software 'Power Analysis and sample size version-16 (PASS-16)'. Finally, 60 patients were included in the study; recruited till desired sample size reached.

Figure 1. Indocyanine green dye.

Figure 2. SPY PHI Camera.

Study type

Interventional

Single group patients undergoing TT with intraoperative infusion of intravenous indocyanine green. A prospective unicentric (tertiary level research center) and open clinical trial in which the fluorescence intensity of the parathyroid glands after indocyanine administration was measured and PTH was measured 20 min after surgery in all the patients and their diagnostic accuracy in prediction of early postoperative hypocalcemia was compared. Written consent taken. No incentives.

Intervention

Drug: indocyanine green

25 mg of lyophilized sterile powder ICG is mixed with 5 ml of sterile water for injection and shaken well for at least 3 min for the complete dissolution of the dye, resulting in a final concentration of 5 mg/ml and ICG dose 1.5–3.5 ml (0.3 mg/kg) of this solution is injected intravenously (Figs 4,5).

The injection can be repeated until a maximum toxic dose of 5 mg/kg/day is reached[25].

1. The reconstituents are withdrawn from the vial through the sterile syringe filter (0.2 microns) using a sterile syringe and 21 gage needle.
2. The purpose of using a sterile syringe filter is:
   a. To remove the undissolved dye in the solution due to inadequate dissolution, which cannot be observed visually since the dye is dark green in color.
   b. To avoid cross-contamination at the time of reconstitution.
3. Then syringe filter and the 21 gage needle is removed from the syringe and disposed of.
4. Fresh sterile 23 gage needle is attached to the syringe and ICG dye is injected into the patient via intravenous route.
5. Constituents are used within 10 h and stored at 2–35°C.

Parathyroid image captured in three different ICG modes of SPY PHI camera (Fig. 6)-

Spy overlay mode- ICG appears in green and non-ICG shows in normal image.

Spy contrast mode- ICG shows in White and non-ICG in black color.

Color segmentation mode- Higher ICG concentration shows in red color while lower ICG concentration shows in blue.

Scoring was done in spy contrast mode

The degree of ICG fluorescence on parathyroids was classified as:

0-black (nonvascularized);

1-gray/heterogeneous (partially vascularized);

2-white (well-vascularized).

Serum iPTH levels were measured 20 min after total thyroidectomy. Serum ionized calcium was done 6 h postsurgery and on the morning and evening of postoperative days 1 and 2.

Patients were labeled as:

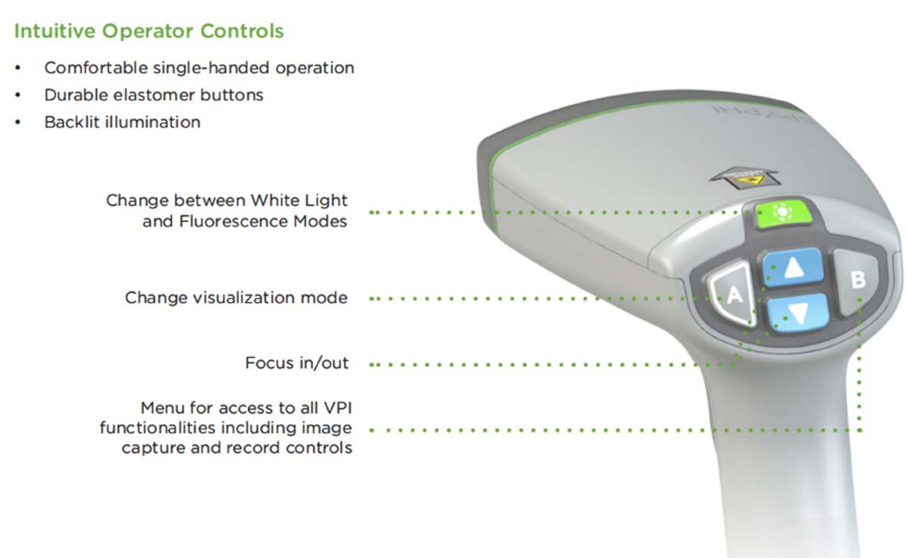

Figure 3. SPY PHI Camera - Controls.

Figure 4. Aurogreen (Indocyanine green).

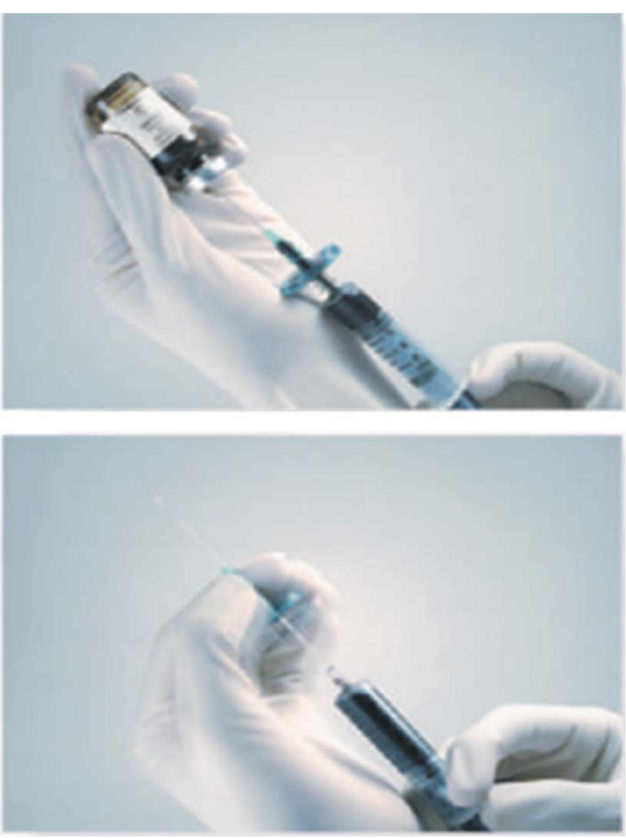

Figure 5. Technique for giving ICG injection.

1. Clinically hypocalcemic if they had symptomatic hypocalcemia (positive trousseau sign, muscle cramps, peri, oral, or acral paresthesias).
2. Biochemically hypocalcemic if serum ionized calcium levels <1 mmol on any blood draw (reference range 1.1–1.3 mmol). This threshold is selected because postoperative dilutional hypocalcemia is fairly common.

Prophylactic calcium supplements were not given in study subjects. Calcium supplements given to only those developing clinical or biochemical hypocalcemia[26].

Study arms

Biochemical

Measurement of PTH 20 min after surgery.

Experimental

ICG

Patients undergoing TT with visualization of the parathyroid glands under infrared light after intraoperative intravenous injection of ICG.

Intervention

Drug: ICG

Eligibility criteria

Inclusion criteria

1. Patients who underwent total thyroidectomy, with or without cervical lymph node dissection for both benign and malignant conditions.
2. Normal renal and hepatic functions.
3. Absence of history of hypersensitivity reactions to iodine or ICG.
4. Able to understand the nature and protocol of the study and its procedures.
5. Willingness to participate with signing of informed consent.

Exclusion criteria

1. Age <18 years.
2. Hepatic/renal insufficiency.
3. Hypersensitivity to iodine or ICG.
4. Pregnancy or lactation.
5. Inability to understand nature and procedures of study.
6. Previous thyroid and parathyroid surgery.
7. Patients with known preoperative hyperparathyroidism or any concomitant parathyroid disease.
8. Previous treatment with calcium.

Primary outcome measures

The primary endpoint was the need for calcium supplementation.

The degree of ICG fluorescence on parathyroids was classified as 0, 1, and 2 as described above.

The iPTH levels were measured 20 min after completion of thyroid surgery using Serum iPTH assay done on plasma obtained from peripheral venepuncture. Architect Plus immunoassay analyzer (Abbott Diagnostics), which is a rapid assay

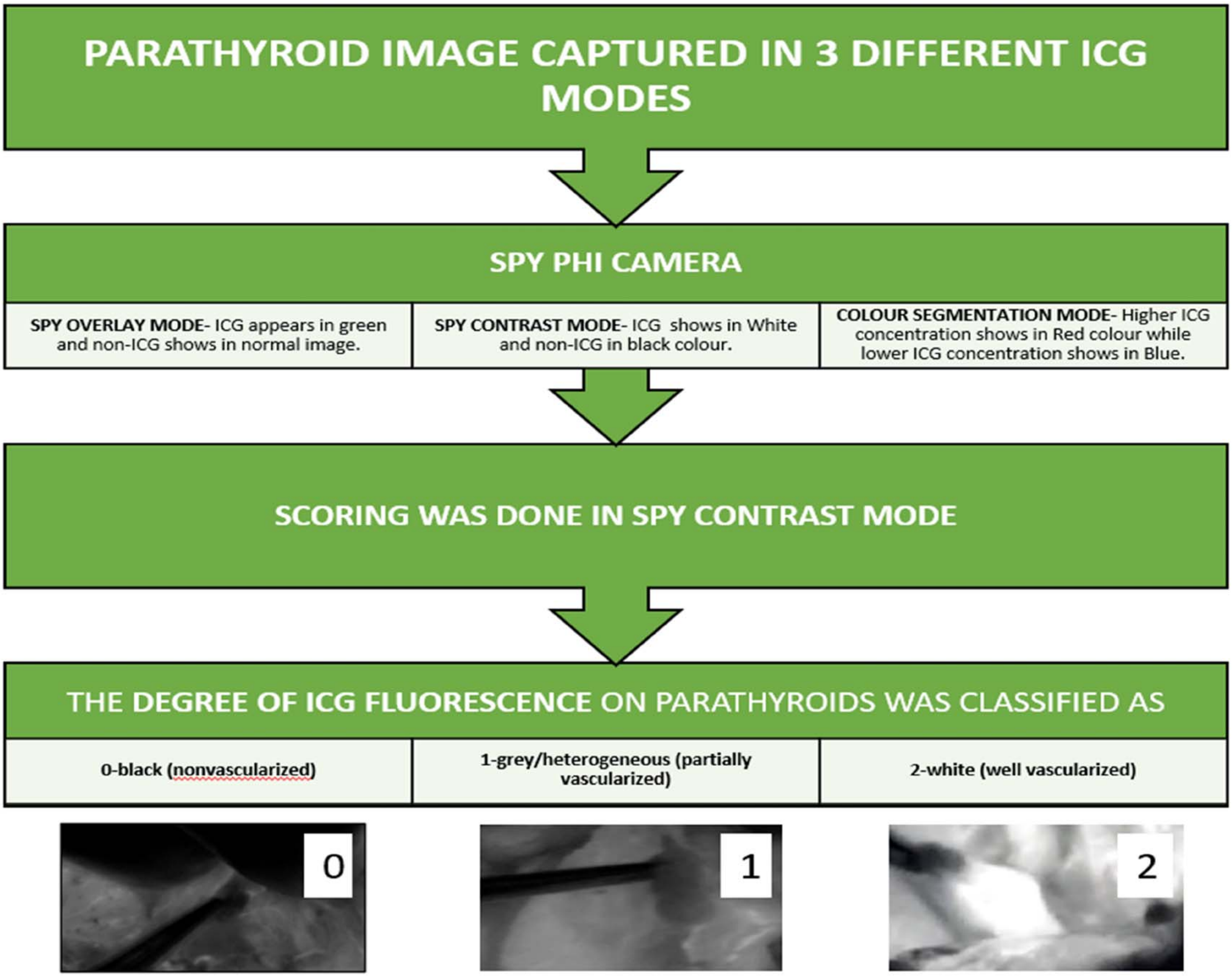

Figure 6. ICG Modes and scoring of parathyroid glands.

based on electrochemiluminescence will be utilized. The test has functional and analytical sensitivity of <0.5 pmol/l and <0.1 pmol/l, respectively.

Statistical analysis

The predictive ability of the 4-ICG sum score 5 for predicting hypocalcemia was evaluated using the receiver operating characteristics (ROC) curve. The statistical analysis was performed using SPSSv.23. Qualitative variables were compared with the χ^2test. Statistical significance was set at P-value <0.05. An inferential review was performed.

Table 1

Demographic profile.

Male	16 (26.67%)
Female	44 (73.33%)
Mean age	45.15 years
Maximum age	77 years
Minimum age	20 years

Results

Total no of patients - 60

Demographic profile (Table 1)

Out of a total of 60 patients recruited in the study, 44 were female while 16 were male with a mean age of 45.15 years.

Table 2

Etiology.

Benign	33
MNG	14
MNG + RSE	7
Toxic MNG	5
Graves	7
Malignant	27
PTC	21
FTC	4
MTC	2

FTC, follicular thyroid carcinoma; MNG, multinodular goiter; MTC, medullary thyroid carcinoma; PTC, papillary thyroid carcinoma; RSE, retrosternal extension.

Table 3

Surgeries.

		Benign				Malignant		
		MNG	MNG + RSE	Toxic MNG	Graves	PTC	FTC	MTC
TT	46	14	7	5	7	10	3	—
TT + CCLND	6	—	—	—	—	6	—	—
TT + CCLND + U/L SLND	5	—	—	—	—	4	1	—
TT + CCLND + B/L SLND	3	—	—	—	—	1	—	2

B/L, bilateral; CCLND, central compartment lymph node dissection; SLND, selective lymph node dissection; TT, total thyroidectomy.

Table 4

Hypocalcemia.

Present	41	68.33%
Biochemical	14	34.15%
Clinical	27	65.85%
Absent	19	31.67%

Table 5

Calcium supplementation.

Oral	19
1 Bolus + Oral	5
Infusion	17

ICG-Indocyanine green; iPTH-intra-operative parathyroid hormone.

Table 6

Characteristics of patients requiring infusion.

Mean Age	43.6 years (20–77 years)
M:F	3:14
ICG score	
≤ 5	15
> 5	2
iPTH	
< 4.28	16
> 4.28	1
Etiology	
Benign	**7**
Graves	1
MNG	1
Toxic MNG	1
MNG + RSE	4
Malignant	10
PTC	8
FTC	1
MTC	1
Surgery	
TT	11
TT + CCLND	2
TT + CCLND + SLND	4

Table 7

Total ICG score.

		Hypocalcemia	
Total ICG score	Total no of patients	Present	Absent
≤ 5	34 (56.7%)	28 (82.4%)	6 (17.6%)
> 5	26 (43.3%)	13 (50%)	13 (50%)
P-value = 0.007			

PPV, positive predictive value; NPV, negative predictive value.

Etiology (Table 2)

Thirty-three patients had benign etiology while 27 had malignant disease.

Surgeries (Table 3)

Forty-six patients underwent TT, six underwent total thyroidectomy with central compartment dissection (TT + CCLND), five underwent total thyroidectomy with central compartment dissection and unilateral selective neck dissection (TT + CCLND + U/L SLND) while three underwent total thyroidectomy with central compartment dissection and bilateral selective neck dissection (TT + CCLND + B/L SLND).

Hypocalcemia (Table 4)

Out of a total of 60, hypocalcemia was present in 41 patients, out of which 14 developed biochemical while 27 developed clinical hypocalcemia. Nineteen patients did not develop any hypocalcemia postoperatively.

Calcium supplementation (Table 5)

Out of 41 patients who developed hypocalcemia, 19 required oral supplementation, five required one bolus and oral supplementation and 17 patients required calcium infusion.

Characteristics of patients requiring Infusion (Table 6)

Out of two patients with ICG score > 5 requiring infusion, one underwent TT for toxic MNG while the other underwent TT + CCLND for PTC. iPTH was <4.28 in both of these patients.

One patient who had iPTH > 4.28, underwent TT + CCLND + Rt. SLND for PTC and had an ICG score of 5.

Total ICG score (Table 7)

Thirty-four patients had total ICG score ≤ 5 while 26 had score > 5. Hypocalcemia was present in 28 out of 34 patients with a score ≤ 5 and it was absent in 13 out of 26 patients with ascore > 5 (Table 8).

Total ICG score 5 was selected using a ROC curve (Fig. 7).

Table 8

ICG at score 5.

Specificity	68.42%
Sensitivity	68.29%
PPV	82.35%
NPV	50%
Diagnostic accuracy	68.33

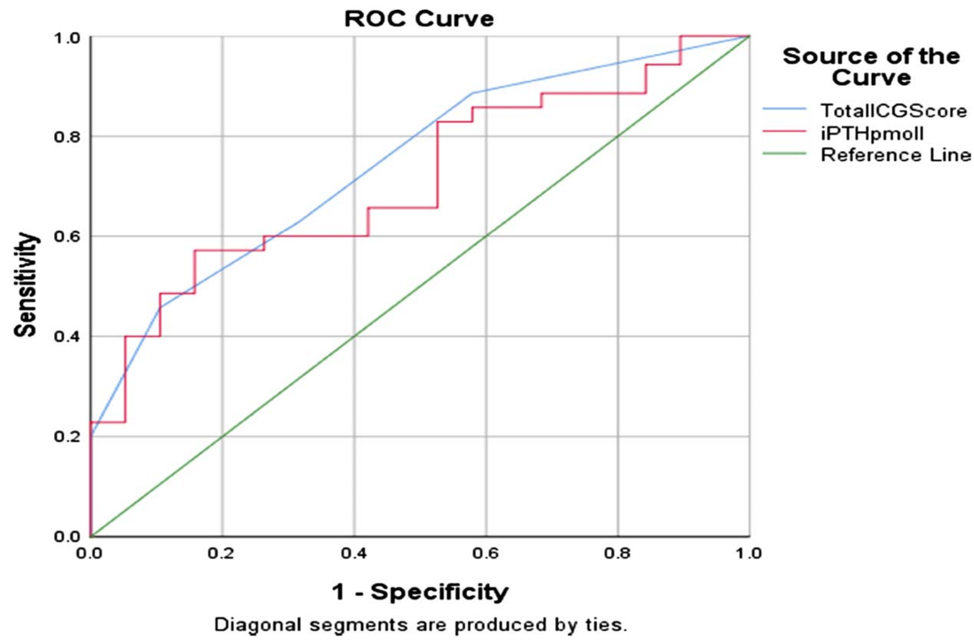

Figure 7. Total ICG score 5 was selected using a ROC curve.

Table 9

iPTH.

		Hypocalcemia	
iPTH (pmol/l)	Total no of patients	Present	Absent
< 4.28	43 (71.7%)	33 (76.7%)	10 (23.2%)
> 4.28	17 (28.3%)	8 (47.1%)	9 (52.9%)
P-value = 0.026			

Table 10

Prediction of hypocalcemia of iPTH at 4.28 pmol/l.

Specificity	47.36%
Sensitivity	80.5%
PPV	76.7%
NPV	52.9%
Diagnostic accuracy	70%

Table 11

No of patients having at least 1 white (score 2) parathyroid gland on ICG.

	Hypocalcemia	
No of patients with atleast 1 white gland (score 2) on ICG	Present	Absent
52 (Present) (86.7%)	33 (63.5%)	19 (36.5%)
8 (Absent) (13.3%)	8 (100%)	0 (0%)
P-value = 0.039		

iPTH (Table 9)

Thirty-three out of 43 patients with iPTH less than 4.28 pmol/l developed hypocalcemia, while 9 out of 17 patients with iPTH > 4.28 pmol/l showed that hypocalcemia was absent (Table 10).

No of patients having at least 1 white (score 2) parathyroid gland on ICG (Table 11)

Eight out of 60 patients had no white gland (score 2) on ICG and all of them developed hypocalcemia requiring calcium infusion postoperatively.

ICG vs iPTH in prediction of postoperative hypocalcemia (Table 12)

ICG score 5 was found to be significantly more specific in the prediction of postoperative hypocalcemia whereas the iPTH value of 4.28 pmol/l was found to be more sensitive in the prediction of early postoperative hypocalcemia but overall diagnostic accuracy of both ICG score 5 and iPTH value 4.28 was found to be almost similar in the prediction of postoperative hypocalcemia in post-TT patients.

Discussion

In endocrine surgery, temporary and definitive postoperative hypoparathyroidism are the most frequent complications of thyroidectomy and result from the disruption of the parathyroid vasculature or the inadvertent excision of the parathyroid glands. Because the parathyroid glands are difficult to accurately identify by the naked eye, and their tiny vessels are even more difficult to distinguish and preserve, these complications can occur in the hands of the most experienced surgeons[27].

The need for a reliable technique to identify parathyroid glands intraoperatively has driven associated research since the first

Table 12

ICG VS iPTH in prediction of postoperative hypocalcemia.

	ICG score 5	iPTH (4.28pmol/l)	*P*
Specificity	68.42%	47.36%	**0.002**
Sensitivity	68.29%	80.5%	**0.048**
PPV	82.35%	76.7%	0.323
NPV	50%	52.9%	0.682
Diagnostic accuracy	68.33%	70%	0.799

studies were conducted by Dudley[28] in 1971,who proposed methylene blue as an exogenous contrast agent. However, no consistent benefits were identified and because of the potential toxicity associated with the use of methylene blue, the literature has since discouraged the routine use of this contrast agent. While authors such as Van der Vorst *et al*. (2014) and Prosst *et al*. (2014) have explored new solutions to this issue, including, respectively, the use of near-infrared fluorescence imaging after the intravenous application of smaller doses of methylene blue and aminolevulinic acid as a contrast agent. These techniques did not gain popularity because of difficulties encountered during their application in intraoperative identification of parathyroid glands. In 2008, a poster presentation at the American Association of Endocrine Surgeons in Monterey, CA (USA) highlighted the preliminary results of a special optical characteristic of the parathyroid glands: autofluorescence. Parathyroid tissue exhibits a unique autofluorescence signature when excited at the NIR wavelength of 785 nm, re-emitting at a wavelength between 820 and 830 nm, with an intensity that is two to 11 times greater than that of the surrounding tissues, thereby allowing for the improved detection and the precise localization of the parathyroid glands[27].

Despite the benefits, autofluorescence is neither able to analyze the perfusion status of the parathyroid tissues nor the vitality of parathyroid glands. The properties of autofluorescence are also preserved after gland resection, with the fluorophore known to be resistant to heat, freezing, and formalin fixation[29,30]. As previously mentioned, the vitality of the parathyroid gland is of paramount importance in thyroid surgery when aiming to reduce postoperative hypoparathyroidism, which remains the most

Table 13

Review of literature.

Year	Study	Conclusion
2014	Suh *et al.*[33]	PG visualization using ICG NIR in dogs
2015	Hyun H *et al.*[34]	Differential visualization of the thyroid and PGs using NIR imaging in pigs
2016	Zaidi *et al.*[35]	ICG uptake correlated with post-op PTH levels. ICG is an adjunct to identifying pts. at risk for Post-thyroidectomy hypoparathyroidism
2016	Fortuny *et al.*[36]	iPTH levels on POD 1 were normal in all patients who had at least one well-vascularized parathyroid gland demonstrated by ICG angiography, and none required treatment for hypoparathyroidism
2017	Yu *et al.*[37]	The ICG group had a significantly lower rate of incidental parathyroidectomy than the control group. BABA robotic thyroidectomy combined with Firefly improved the PG identification
2017	Lang *et al.*[38]	The greatest ICG correlated with postoperative normal PTH. It is a promising operative adjunct in determining residual parathyroid glands function and predicting postoperative hypocalcemia risk after total thyroidectomy
2018	Alesina *et al.*[39]	The superiority of combined AF/ICG vs. simple visualization to reduce the rate of postoperative hypoparathyroidism has not been demonstrated
2019	Rudin *et al.*[40]	At least two vascularized glands on ICGA may predict postoperative parathyroid gland function
2019	Fortuny *et al.*[41]	None of the patients with at least one well-perfused gland on the ICG angiography (score 2) presented with hypoparathyroidism. However,22% of the 50 excluded patients, in whom no well-perfused parathyroid gland could be identified by angiography, presented with hypoparathyroidism, which was significantly different from the findings in randomized patients ($P=0.007$)
2019	Jin *et al.*[42]	22 patients who had at least one PG with ICG score > 2 had normal PTH levels postoperatively. In contrast, of four patients with PG ICG score < 2, two of them developed transient hypoparathyroidism
2019	Razavi *et al.*[43]	Low-flow ICG patterns are not associated with postoperative PTH changes or transient hypocalcemia and may lead to unnecessary parathyroid auto-transplantation
2019	Pastor *et al.*[44]	The 4-ICG score had good discrimination in predicting postoperative hypocalcemia. A 4-ICG score > 3 had a high negative predictive value for postoperative hypocalcemia, which may be useful in identifying patients eligible for early discharge
2020	Demarchi *et al.*[27]	Concluded that NIRAF imaging is a new and valuable intra-operative tool for identifying both healthy and diseased parathyroid glands, which ensures better patient outcomes for thyroid surgery
2021	Priyanka *et al.*[45]	In this study, there was no additional benefit of ICG and NIRF cameras in the identification of parathyroid glands. However, ICG angiogram seems to be a good adjunct for the intraoperative assessment of the viability of the parathyroid glands and accurately predicts the development of postoperative hypoparathyroidism
2021	Llorente *et al.*[46]	The diagnostic accuracy of ICG angiography and ioPTH was similar. The presence of one well-perfused parathyroid gland (ICG score 2) using ICG angiography or ioPTH decline, measured before and after completion of thyroid surgery, is both reliable method in prediction of early post-thyroidectomy hypocalcemia independently of the number of glands identified intraoperatively
2021	Liang *et al.*[47]	Patients who retained at least one well-perfused parathyroid gland (ICG 2 ≥ 1) had significantly higher PTH levels and were less likely to develop hypoparathyroidism on postoperative day one than those without any well-ICG-enhanced parathyroid gland (ICG 2 = 0) ($P=0.038$). This study concluded that ICG angiography could be a helpful adjunct procedure for parathyroid gland identification and functional outcome prediction during transoral endoscopic thyroidectomy
2022	Abdelrahim *et al.*[48]	The diagnostic accuracy of ICG angiography and ioPTH level assay was high and almost similar (82.22 versus 87.78%). Both were higher than surgeons' diagnostic accuracy of visual inspection (62.22%)
2022	Quere *et al.*[49]	ICG angiography used in thyroid surgery could assist the surgeon in the identification of parathyroid glands, sparing them in one-third of cases
2023	Our study	ICG angiography is a good predictor of the absence of hypoparathyroidism after thyroidectomy, in contrast to the visual evaluation of the parathyroid glands alone and is comparable to iPTH in the prediction of post-thyroidectomy hypocalcemia

common complication of thyroidectomy, occurring in as many as 30% of patients[31,32].

The use of ICG to enhance fluorescence imaging enables the real-time assessment and direct imaging of tissue perfusion and vascularization. ICG is the only clinically approved NIR fluorescent dye, with approval first received for clinical use in 1956. Its earliest applications, dating to the 1970s, were in ophthalmology. In the last few years, this technique has demonstrated its utility in the real-time assessment of intestinal microvascularization when evaluating intestinal anastomoses during colorectal surgery or various other procedures including intraoperative angiography in reconstructive surgery, cholangiography, and lymph node mapping and dissection.

ICG has most recently emerged as a technique for assessing the vascularization of the parathyroid glands, which seems to be closely correlated with parathyroid function, after thyroid resection[27]. The results of the studies as described in Table 13 are consistent with regard to the concept that patients with at least one well-vascularized parathyroid gland post-thyroidectomy, as demonstrated by ICG angiography, also exhibited normal PTH levels during the first postoperative day, thereby excluding postoperative hypoparathyroidism with a 100% positive predictive value.

In contrast, some studies report fewer positive results. This could be related to the subjective visual interpretation of gray scale imaging during angiography in the absence of a standardized normal criterion and variable baseline calcium and vitamin D levels in different populations.

The results of our study are in concordance with the above studies with almost comparable efficacy of both ICG and iPTH. The absence of even 1 fully vascularized gland (white) is highly suggestive of the patient developing hypocalcemia and requiring calcium supplementation. This observation can also be extrapolated in the prevention of hypocalcemia by considering the option of parathyroid auto-transplantation at the time of surgery. Thus, ICG angiography is a promising technique that can help identify healthy and diseased parathyroid glands on the basis of vascularity, thus predicting the development of hypocalcemia post-thyroidectomy. A high number of patients developing hypocalcemia seen in our study could be attributed to inherent hypocalcaemia and vitamin D deficiency in the north and central Indian population due to the low calcium and vitamin D diet taken.

Nonvisualization of all parathyroid glands in some cases, the subjective nature of scoring and the learning curve in scoring of parathyroid glands are the main limitations of our study. Another limitation of our study is that the number of patients is not very high, which is due to limited time frame and availability of SPY PHI equipment. Another caveat is inherent calcium and vitamin D deficiency seen in the north and central Indian population, which should be either corrected or at least identified prior to surgery. As ICG angiography is nonselective, the fluorescence of a thyroid nodule, fat, or lymph node would sometimes be misidentified as a parathyroid gland emission thus leading to the preservation of these tissues and removal of the actual parathyroid gland[50].

In conclusion, ICG angiography is a good predictor of the absence of hypoparathyroidism after thyroidectomy, in contrast to the visual evaluation of the parathyroid glands alone and is comparable to iPTH in the prediction of post-thyroidectomy hypocalcemia. Authors suggest that a combination of autofluorescence to locate parathyroid glands followed by an ICG perfusion study to assess gland vascularity will be more effective in the prediction of postoperative hypocalcemia. Pixel/color analyzing computer programs could be used in the future to score the angiography results objectively.

Ethical approval

Ethical clearance obtained from SGPGI IEC (Institutional Ethics clearance) on 16-Jul -2021.
IEC code: 2021-137-MCh-120.

Consent

Written informed consent was obtained from the patient for the participation in this research study. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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None.

Author contribution

Y.D.: study design, data collection, data analysis, writing the paper; S.M.: study design, data interpretation, writing, and editing; A.M., G.C., G.A., and A.A.: data analysis and editing.

Conflicts of interest disclosure

The authors declare that they have no financial conflict of interest with regard to the content of this report.

Research registration unique identifying number (UIN)

1. Name of the registry: Clinical Trials Registry – India (ICMR-NIMS).
2. Unique identifying number or registration ID: CTRI/2022/04/042270.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://ctri.nic.in/Clinicaltrials/rmaindet.php?trialid=64331&EncHid=83348.2242&modid=1&compid=19.

Guarantor

Yuvraj Devgan and Prof. Sabaretnam Mayilvaganan.

Data availability statement

Available upon reasonable request.

Provenance and peer review

None.

Presentation

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