



Prediction of hypocalcemia after total thyroidectomy using indocyanine green angiography of parathyroid glands: A simple quantitative scoring system

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ABSTRACT

Background: Hypocalcemia is one of the most common complications after total thyroidectomy. Recently, indocyanine green (ICG) angiography of the parathyroid glands (PGs) has been suggested as a reliable tool for predicting postoperative hypocalcemia. The aim of our study was to evaluate the performance of a simple quantitative score based on ICG angiography of the PGs (4-ICG score) for predicting postoperative hypocalcemia.

Methods: Thirty nine consecutive patients who underwent total thyroidectomy for multinodular goiter were included. For each patient, the 4-ICG score was calculated, adding the individual viability value of the four PGs. Discrimination and correlation analyses were performed.

Results: In 32/39 patients, the four PGs were identified. Patients with postoperative hypocalcemia (n = 6, 19%) had a lower 4-ICG score (2.5 [1.8–3.3] vs. 4.0 [3.0–6.0]; p = 0.003). The 4-ICG score showed good discrimination in terms of predicting postoperative hypocalcemia (AUC = 0.875 (0.710–0.965); p = 0.001) and a good correlation with postoperative parathyroid function.

Conclusions: The 4-ICG score predicts postoperative hypocalcemia and correlates well with postoperative parathyroid function in patients undergoing total thyroidectomy for multinodular goiter.

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Introduction

Hypocalcemia is one of the most common complications after total thyroidectomy. It has been reported in up to 30% of patients,¹ and in many cases is mild and manifests with symptoms including peripheral paresthesia, muscle cramps and anxiety. However, the condition is sometimes severe and can lead to acute life-threatening conditions such as tetany, confusion, seizures, arrhythmias and heart failure.² In addition, although most cases are

transient and self-limiting, they can become permanent in up to 10% of patients,^{3,4} which results in a need for lifelong calcium and vitamin D supplementation, repeated clinic visits and an increased risk of long-term complications.

In recent decades, several predictors of postoperative hypocalcemia have been proposed.³ Among these, parathyroid hormone (PTH) levels, measured at different time points during or after thyroidectomy, have been suggested as the most accurate predictor of postoperative hypocalcemia.^{5,6} However, reported studies have shown contradictory results.^{7,8} Moreover, PTH levels reflect overall parathyroid function and cannot be used to evaluate the viability of an individual parathyroid gland (PG). Therefore, reliable tools that both evaluate PGs viability to guide intraoperative decision-making and early prediction of postoperative hypocalcemia are highly desirable.

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Indocyanine green (ICG) is a water-soluble fluorescent dye that can be detected using dedicated specialised cameras.⁹ When administered intravenously, it enables intraoperative real-time assessment of tissue and organs blood supply. ICG-enhanced fluorescence imaging has been used for several years with many applications in different surgical procedures, enhancing procedural efficiency.¹⁰ In last years, ICG angiography has renewed interest in thyroid and parathyroid surgery. Recent studies have suggested that the evaluation of PGs viability using ICG angiography may be useful for predicting postoperative parathyroid function and hypocalcemia.^{11,12} However, these studies did not include all PGs for the postoperative parathyroid function evaluation. Given that postoperative calcium level depends on circulating PTH levels, and these could be attributed directly to the residual PGs functionality, we hypothesise that the ability to predict postoperative hypocalcemia can be improved considering the viability status of all PGs. For this application, we propose a simple quantitative scoring system based on ICG angiography findings in all PGs. In this study we evaluated the performance of this score for predicting postoperative hypocalcemia in patients undergoing total thyroidectomy for multinodular goiter. Moreover, we also evaluated the relationship between this score and the postoperative parathyroid function.

Methods

Study population

The present study complied with the Declaration of Helsinki and was approved by the local ethics committee. Written informed consent was obtained from all patients prior to inclusion. From September 2016 to November 2016 we prospectively include consecutive patients who underwent total thyroidectomy for multinodular goiter in two tertiary hospital. Patients with allergy or intolerance to ICG or iodine dyes; severe renal or hepatic impairment; concurrent parathyroid disease; previous thyroid or parathyroid surgery or who had previously received an ablative dose of iodine 131 were excluded. Demographic data, body mass index, thyroid size and localisation in preoperative imaging test and preoperative laboratory results were collected in detail.

Surgical procedure and ICG angiography

All procedures were performed by experienced consultant's surgeons of the Endocrine Surgery Unit of both participant institutions. Total thyroidectomy was performed according to the standard technique with attention to avoid devascularisation of PGs or incidental parathyroidectomy. Systematic search for PGs during total thyroidectomy was done. Once the thyroid specimen had been removed, ICG angiography of the PGs identified was performed following a pre-specified protocol. Through a peripheral venous access, 3–6 ml of a dilution of 25 mg of ICG in 10 mL of sterile water was administered. Repeated doses were allowed until a maximum toxic dose of 5 mg/kg was reached. The venous catheter was purged after each ICG dilution injection for rapid imaging gain. After 1–2 min approximately, ICG-enhanced fluorescence imaging of each PG was acquired using laparoscopic PinPoint camera (Nodadaq, Ontario, Canada). Two modalities of imaging were obtained: a normal colourised with superposed green fluorescence near-infrared view and a black and white near-infrared view (Fig. 1). To blind the assessment of viability from the visual appearance of PGs, acquired black and white imaging were recorded to be analysed later.

After surgery, clinical management decisions about each patient were made by the liable surgical team. The standard protocol at

authors' institutions included determination of calcium at 24 h after surgery, a supplementation with calcium and vitamin D in case of calcium levels <8 mg/dl. In all patients, symptoms of hypocalcemia and need for calcium and/or vitamin D supplementation at discharge were recorded. Patients requiring calcium and vitamin D supplements were followed-up and had their calcium and PTH regularly checked until they could maintain normocalcemia without supplements or a diagnosis of permanent hypoparathyroidism was made.

PGs viability

Three independent observers (SGP, NMT and JMR), previously trained in the assessment of PGs viability by means ICG angiography, analysed the recorded black and white imaging. In these, the PGs appear on a black and white scale depending on the amount of ICG flowing through them, reflecting the degree of perfusion. Thus, the colour of the gland can vary from black (suggesting that it is not vascularised and likely non-viable) to the white (suggesting that it is well vascularised and viable). PGs viability was rated in accordance with the following grading score: 0 when the PG was black, 1 when the PG was grey and/or heterogeneous; and 2 when the PG was white (Fig. 1). Each observer rated all PGs in an individual session. The viability value assigned to each PG was the value repeated by at least two observers. Finally, for each patient, we calculated a score (4-ICG score) adding the individual viability value of the four PGs (range 0–8). For this reason, only patients in which the four PGs could be identified were considered when analysing the 4-ICG score performance.

Laboratory

Calcium levels were adjusted according to serum albumin [corrected serum calcium (mg/dl) = serum calcium (mg/dl) + 0.8 · (4 - serum albumin (g/dl))]. Hypocalcemia was defined as corrected serum calcium of <8 mg/dl. Serum PTH was determined preoperative (PTH₀) and at various postoperative times: immediately at the end of surgery (PTH_{0h}), at 4 h (PTH_{4h}), at 24 h (PTH_{24h}) and at 1 week (PTH_{1w}) after surgery. Relative PTH drop was calculated as the following formula: (PTH₀ - PTH_x/PTH₀) · 100 ("x" denotes the postoperative measurement time).

Statistical analysis

Continuous variables were tested for a normal distribution by the Kolmogorov-Smirnov test. Normally distributed data are presented as the mean ± standard deviation (SD) and non-normally distributed data as the median (interquartile range [IQR]). Categorical variables are expressed as absolute frequency (percentage). Differences in baseline characteristics and results of PGs viability assessment between patients with and without postoperative hypocalcemia were compared using the Student t-test or the Mann-Whitney U test for continuous variables and the chi-square test for categorical variables.

To evaluate the predictive ability of the 4-ICG score for predicting postoperative hypocalcemia, we performed discrimination and calibration analyses. Receiver-operating characteristic (ROC) curve and area under the curve (AUC) were performed using binary logistic model. We calculated sensitivity, specificity, positive predictive value and negative predictive value, and the best cut-off point for this score was defined as the highest product of sensitivity and specificity. To evaluate the calibration of the 4-ICG score, we used the Hosmer-Lemeshow goodness-of-fit test.¹³ This test estimates a c-statistic based on the difference between the hypocalcemia event values observed and those predicted by the 4-ICG

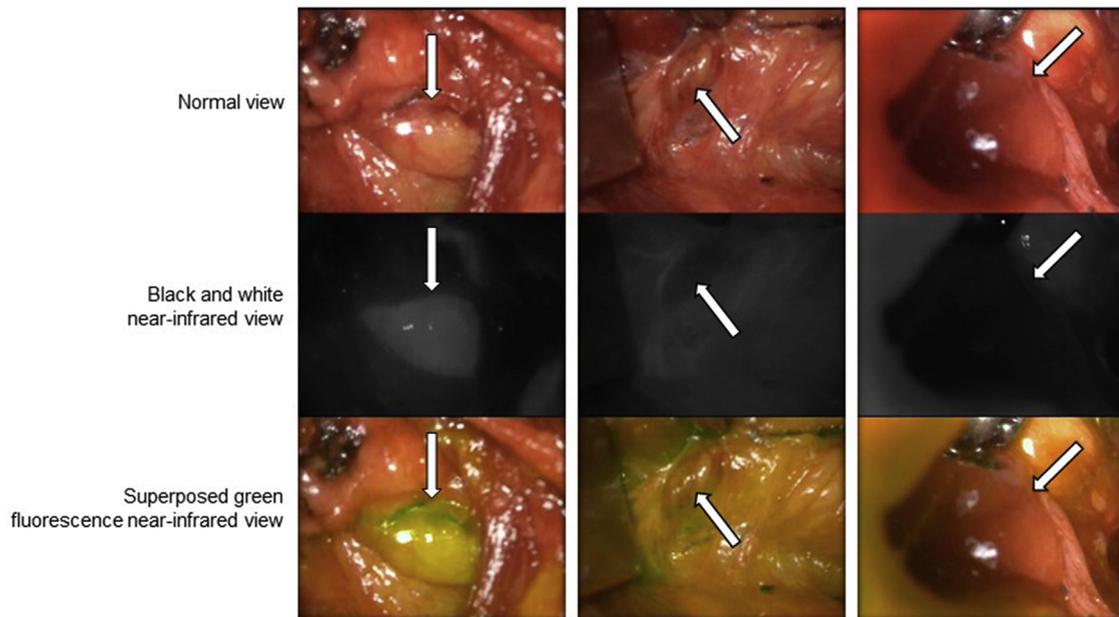


Fig. 1. Representative ICG angiography images. From left to right, a well vascularised PG (viability score = 2), a moderately well vascularised PG (viability score = 1) and a devascularised PG (viability score = 0). Arrows indicate the PGs.

score for different risk groups. The smaller the statistical value, the poorer calibrated the model. A p value > 0.05 indicates that the model is well adjusted to the data and therefore is a good predictor of patients' probability of events. We performed correlation tests to evaluate the association between the 4-ICG score and the postoperative parathyroid function (minimum post-surgical PTH levels and maximum relative PTH drop in the first 24 h). Moreover, we compared time course of the post-surgical parathyroid function parameters (PTH serum levels and relative PTH drop) based on the optimal cutoff value of the 4-ICG score to predict hypocalcemia. Two-sided $P < 0.05$ was accepted as statistically significant. All analysis was performed with SPSS version 22.0 (SPSS, Inc., Chicago, Illinois).

Results

Study population and PGs viability

A total of 39 patients underwent total thyroidectomy. In 32 (82%) patients the four PGs were identified (in 6 (15%) and in 1 (3%) only three and two PGs were identified, respectively). These 32 patients formed the study population. The [Table 1](#) shows the baseline characteristics of these patients. During surgical intervention 128 PGs were identified. ICG angiography was performed in all cases. There were 41 (32%) PGs with 2 points (well vascularised), 55 (43%) with 1 point and 32 (25%) with 0 point (non-vascularised). No ICG-related adverse reactions were observed.

Postoperative hypocalcemia

The incidence of postoperative hypocalcemia was 19% ($n = 6$). Baseline characteristics of study population in accordance with postoperative calcemic status are detailed in [Table 2](#). There were not differences between patients who developed hypocalcemia and those who did not. Patients with postoperative hypocalcemia had more non-vascularised PGs than those without hypocalcemia ([Table 3](#)).

The 4-ICG score and postoperative hypocalcemia

The median value of the 4-ICG score in the whole study population was 4.0 [3.0–6.0]. Patients with postoperative hypocalcemia had lower 4-ICG score than those without it (2.5 [1.8–3.3] points and 4.0 [3.0–6.0] points; $p = 0.003$).

To evaluate the discriminative performance of the 4-ICG score for predicting postoperative hypocalcemia, we constructed a ROC curve ([Fig. 2](#)). ROC curve analysis showed that the 4-ICG score had a good discrimination for predicting postoperative hypocalcemia (AUC = 0.875 (0.710–0.965); $p = 0.001$). The optimal 4-ICG score cut-off value was ≤ 3 . Using this cut-off value, the sensitivity, specificity, positive predictive value and negative predictive value for predicting postoperative hypocalcemia were 83% (36–100), 73% (52–88), 42% (15–72) and 95% (75–100); respectively. The calibration was also adequate (p value for Hosmer-Lemeshow test = 0.985).

Table 1
Baseline characteristics of study population.

	Study population n = 32
Age (years)	53 ± 16
Sex (women)	28 (88)
Body mass index (kg/m ²)	28 ± 4
Intrathoracic component	
No	27 (84)
Yes	5 (16)
Thyroid size	
Normal	10 (31)
Increased	22 (68)
Laboratory (preoperative)	
Creatinine (mg/dl)	0.7 ± 0.2
Calcium (mg/dL)	9.2 ± 0.3
Phosphorus (mg/dl)	3.2 ± 0.4
Magnesium (mg/dl)	2.0 [1.9–2.1]
PTH (pg/ml)	49.1 ± 21.3
Vitamin D (ng/ml)	20.0 [17.0–29.0]

Data are expressed as mean ± SD, median [IQR] or frequency (%). PTH denotes parathyroid hormone.

Table 2
Baseline characteristics of study population in accordance with postoperative calcemic status.

	Postoperative hypocalcemia n = 6	No postoperative hypocalcemia n = 26	P value
Age (years)	43 ± 18	55 ± 15	0.098
Sex (women)	6 (100)	22 (85)	0.566
Body mass index (kg/m ²)	26 ± 2	29 ± 5	0.216
Intrathoracic component			
No	4 (67)	23 (89)	0.228
Yes	2 (33)	3 (12)	
Thyroid size			
Normal	1 (17)	9 (35)	0.637
Increased	5 (83)	17 (65)	
Laboratory (preoperative)			
Creatinine (mg/dl)	0.6 ± 0.1	0.7 ± 0.2	0.403
Calcium (mg/dL)	9.1 ± 0.1	9.3 ± 0.3	0.160
Phosphorus (mg/dl)	3.3 ± 0.3	3.2 ± 0.5	0.744
Magnesium (mg/dl)	2.0 [1.9–2.1]	2.0 [2.0–2.1]	0.362
PTH (pg/ml)	58.4 ± 14.5	46.7 ± 21.9	0.227
Vitamin D (ng/ml)	21.5 [11.8–28.0]	20.0 [17.5–31.5]	0.582

Data are expressed as mean ± SD, median [IQR] or frequency (%). PTH denotes parathyroid hormone.

Table 3
PGs viability in patients with and without postoperative hypocalcemia.

	PGs in patients with hypocalcemia n = 24	PGs in patients without hypocalcemia n = 104	P value
PGs (viability score = 2)	2 (8)	39 (38)	
PGs (viability score = 1)	11 (46)	44 (42)	0.006
PGs (viability score = 0)	11 (46)	21 (20)	

Data are expressed as n (%). PGs denotes parathyroid glands.

The 4-ICG score and postoperative PTH

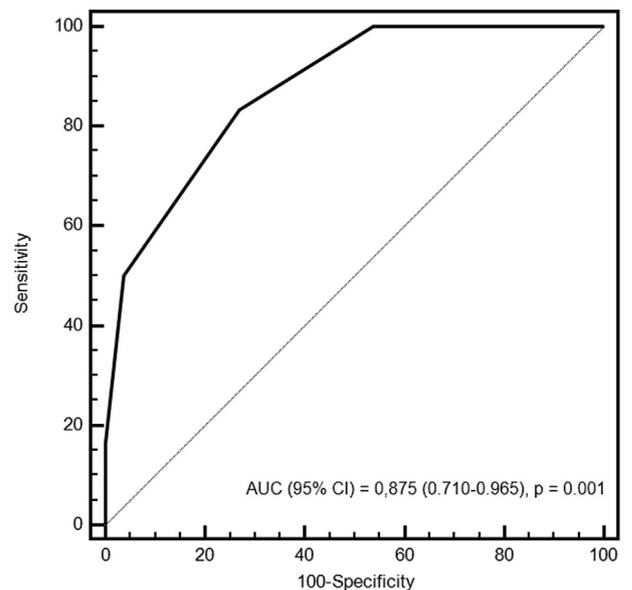
When analysing the correlation between the 4-ICG score and postoperative parameters, we found that the 4-ICG score showed a moderate positive correlation with the postoperative absolute PTH levels (Spearman's rho = 0.572; p = 0.001) and a strong negative correlation with the postoperative relative PTH drop (Spearman's rho = -0.701; p < 0.001). Finally, parathyroid function parameters (absolute PTH levels and relative PTH drop) at successive postoperative times based on the optimal cutoff value of the 4-ICG score are shown in Fig. 3. We found that differences between groups appeared since the first immediate postoperative determination and disappeared after one week, in both analysed parameters. However, it was at 4 h after thyroidectomy when differences between groups reached its maximum statistical significance.

Discussion

In the present study, we evaluated the feasibility of the 4-ICG score as a method to graduate the residual PGs viability and to predict postoperative hypocalcemia after total thyroidectomy. The proposed method is a simple quantitative score that can be easily calculated in the operating room and it based on the analysis of the ICG angiography of each PG. We found that the 4-ICG score properly predicts the development of hypocalcemia in the first postoperative day and correlates with the postoperative parathyroid function. The negative predictive value for postoperative hypocalcemia with a 4-ICG score >3 was 95% (75–100). The high accuracy of the 4-ICG score in predicting hypocalcemia is likely related to the better evaluation of the PG viability using ICG angiography instead visual assessment. Visual inspection of PG is subjective and has been demonstrated to be inaccurate to evaluate PG viability.¹⁴ In addition, the proposed score provides a global evaluation of all PGs. It has demonstrated that the number of PGs left in situ correlates to postoperative parathyroid function and rate of postoperative hypocalcemia,¹⁵ suggesting that reduction in functional parathyroid

parenchyma after thyroidectomy is a determining factor in PTH levels and calcium homeostasis.

The utility of ICG angiography in patients undergoing total thyroidectomy has been previously reported. Zaidi et al.¹¹ found that the mean PTH levels on the first postoperative day in patients with two or more under-perfused PGs using ICG angiography was statistically lower than those with one or no PGs demonstrating low ICG uptake. In this study, individual PGs viability were graded using a four degrees scale, different from the one used in our study,



Criterion	Se (95% CI)	Sp (95% CI)	PPV (95% CI)	NPV (95% CI)
≤3	83 (36-100)	73 (52-88)	42 (15-72)	95 (75-100)

Fig. 2. ROC curve of the 4-ICG score to predict postoperative hypocalcemia.

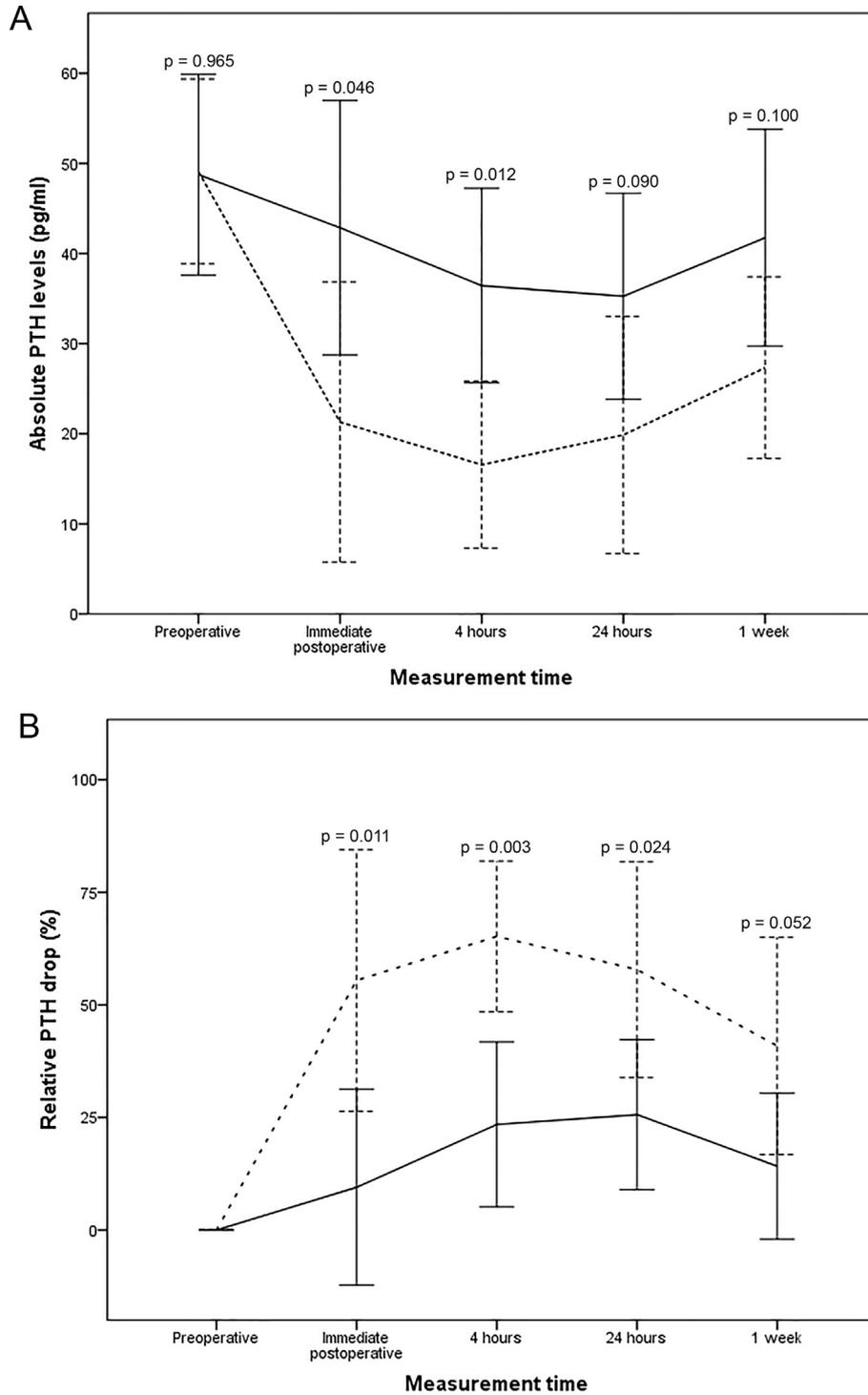


Fig. 3. Time course of the parathyroid function parameters (absolute PTH level (A) and relative PTH drop (B)) in patients with 4-ICG score ≤ 3 (dotted line) and > 3 (solid line). The median, 95% confidence interval (error bars) and the P-value from the comparison between groups in each measurement time are shown.

so attempts of direct comparisons with our results are useless. Vidal Fortuny et al.¹² also found a good correlation between PGs vascularisation evaluated with ICG angiography and postoperative PTH levels. They used the same grading scale that we used in our study. All patients with at least one well vascularised PG had normal postoperative PTH levels and only one developed asymptomatic postoperative hypocalcemia. At least one well vascularised PG would correspond a punctuation ≥ 2 of our proposed score.

However, in this study the viability of the rest of the PG (both identified or unidentified) are not considered. Given that it is expected that the rest of the PGs have some viability and functionality, it is very possible that many patients reached the cut-off value of > 3 , and therefore their findings are even closer to ours. Finally, Lang et al.¹⁶ conducted a very well-designed study in which the fluorescent intensity (FI) of each PG was objectively measured with a specialised equipment. They found that both greatest FI value and

the average FI value of the four PGs predicts postoperative hypocalcemia. Our findings are in accordance with these studies. However, we appreciate some advantages of our proposed score. First, it provided an overall evaluation of all PGs and is not limited to “white” or “black” PGs, since it also considers “grey” ones, that were the more common in our study. This increases its applicability of the score. Second, although this score has been evaluated in patients in which the all four PGs have been identified, it could be applicable in more patients, given that a punctuation of >3 could be reach with less than four PGs evaluated. Finally, it does not require specialised measurement systems and is very simple of calculate. This may mitigate to some extent the greater complexity of evaluating PGs using ICG angiography, as well as the increased duration of surgery.

Understanding the pathophysiology and identify predictors and strategies to preserve parathyroid gland function are all important components of current best practice in thyroid surgery. Although not fully elucidated, the proposed underlying mechanism for hypocalcemia after total thyroidectomy is related to the development of hypoparathyroidism. It might result from intraoperative damage to the PGs due to mechanical or thermal trauma, devascularisation, venous obstruction or inadvertent removal. The most effective strategy to avoid this complication is adopting vascular preservation techniques.¹⁷ However, occasional inadvertent injury or excision of a PG is unavoidable. In this case, PG autotransplantation can be performed.¹⁸ Nevertheless, the results of this technique has been inconsistent and a controversy exists about its utility.^{19,20} This may due in some extent because decisions regarding autotransplantation has been based on PG viability evaluated intraoperatively by visual inspection, that has been found to have low accuracy for this application.^{14,21} Therefore, the clinical utility of the ICG angiography in the thyroid surgery encompasses two issues. On the one hand, it allows accurate and real-time assessment of the viability of each PG separately and does not limit the evaluation to the overall parathyroid gland function. This could help in making decisions regarding autotransplantation and improve the results of this technique. On the other hand, it allows accurate prediction of hypocalcemia immediately after thyroid resection, as demonstrated in current and previous studies. Accurate prediction of hypocalcemia would allow risk-based management of patient (e.g. prophylactic treatment of hypocalcemia in high-risk patients or safety early discharge in low-risk patients). None of the currently used methods (even the intraoperative PTH measurements) fulfil this application. In our study, we found that the higher difference in postoperative parathyroid function (PTH levels and relative PTH drop) between patients with a 4-ICG score ≤ 3 and > 3 was at 4 h. These findings support the lower utility of early measurements of PTH to predict postoperative hypocalcemia and are in accordance with the reported role of the 4-h postoperative PTH level as an accurate predictor for the development of hypocalcemia.²² In this way, a recent randomised clinical trial has demonstrated the utility of the ICG angiography in this context. Vidal Fortuny et al.²³ demonstrated the safety of the postoperative management of patient based on ICG angiography results and suggest that calcium and/or PTH measurement could be obviated in patients with at least one well perfused PG on ICG angiography.

ICG angiography is a safe technique. Adverse reactions in patients who receive ICG injections are rare. Mild reactions include nausea, vomiting, and extravasation of dye, while fatal allergic reactions occurring in 1/333,000 of cases.²⁴ In our study there were no ICG-related adverse reactions. Regarding costs, the current price of a vial of 25 mg of ICG is around 70\$, while that of the laparoscopic imaging camera system amount to about 47,000\$. However, it produces high-quality images and can also be used in other surgical procedures, making the equipment more cost-effective.

Our study has several limitations. The main limitation is the small sample size. Larger studies confirming our finding and the suggested cut-off value should be conducted. In this study, only patients with multinodular goiter were included, and therefore the results may not be valid for patients undergoing total thyroidectomy for other reasons. PGs were identified visually and no systematic biopsy were performed. However, it has been demonstrated that in experienced hands, the rate of correct identification of a structure as a parathyroid gland should exceed 95%.¹⁶ Moreover, there is a possibility of compromising the function of the biopsied PG. Another limitation is the subjective nature of visual assessment of ICG angiography. The equipment necessary to quantify the intensity of fluorescence was not available in the participant institutions at the time when the study was conducted.

In conclusion, we have demonstrated that the 4-ICG score predicts postoperative hypocalcemia and correlates with postoperative parathyroid function in patients undergoing total thyroidectomy for multinodular goiter. We suggest that the 4-ICG score could be a reliable tool for assessing intraoperative PGs and a 4-ICG score >3 could allow early discharge of patients given its high negative predictive value for postoperative hypocalcemia. However, our findings should be interpreted with caution and considered as hypothesis-generating. Larger studies are necessary to confirm our results.

Conflicts of interest

None.

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