Intraoperative Mapping Angiograms of the Parathyroid Glands Using Indocyanine Green During Thyroid Surgery: Results of the Fluogreen Study

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Intraoperative mapping angiograms of the parathyroid glands using indocyanine green during thyroid surgery: results of the Fluogreen Study

Short title: Intraoperative mapping angiograms of parathyroid vessels

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Informed consent was obtained from all individual participants included in the study.
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Abstract

Background: During thyroid surgery, preservation of parathyroid glands (PG) feeding vessels is often impossible visually. The Fluogreen study aimed at assessing the feasibility of indocyanine green (ICG)-based intraoperative mapping angiograms of PG (iMAP).
Study design: Prospective study enrolling all patients undergoing thyroid lobectomy or total thyroidectomy at Hôpital Européen de Marseille between September and December 2018. After exploring the thyroid lobe by autofluorescence to locate PGs, a first ICG solution was injected intravenously to locate PG feeding vessels and guide dissection. A second ICG solution was injected at the end of lobectomy to assess the perfusion of PGs. Primary outcome was the quality of the angiogram, scaled iMAP 0 (not informative), iMAP 1 (general vascular pattern visible but no clear pedicle inflowing in the PG) or iMAP 2 (clear pedicle inflowing in the PG). Secondary outcome was the score of PG perfusion at the end of surgery, scaled from ICG 0 (no perfusion) to ICG 2 (intense uptake).
Results: 47 adult patients were analyzed, including 34 total thyroidectomies and 13 lobectomies. ICG angiography assessed 76 PGs and was scored iMAP 2 in 24 PGs (31.6%), iMAP 1 in 46 PGs (60.5%) and iMAP 0 in 6 PGs (7.9%). At the end of dissection, the ICG perfusion score was significantly better for PGs with informative angiography (iMAP 1 or 2), than for PGs with uninformative angiography (iMAP 0) or PGs not evaluated by vascular angiography ($p<0.05$).
Conclusion: iMAP is feasible and may help preserve post-operative PG perfusion. Its generalizability and impact on post-operative hypocalcemia warrants further evaluation.

Keywords: Thyroidectomy; Indocyanine green; Fluorescence; Parathyroid; Angiography.

Introduction

Identification and preservation of parathyroid glands (PGs) and their vascular pedicles during thyroid surgery are crucial. Indeed, PG damage, removal or devascularization can lead to postoperative hypocalcemia, which is a frequent (30-40% of patients), unpredictable and serious complication (1). Recently, real-time intraoperative imaging techniques using fluorescence showed they could help surgeons by enhancing the visual assessment of PGs (2-4). Indeed, intraoperative identification of PGs by autofluorescence, which uses the natural propensity of PGs to emit spontaneous fluorescent signal, can help to improve PG identification and preservation (5-7). More, intraoperative PG angiography using indocyanine green (ICG) has been used to assess PG perfusion at the end of thyroid resection and predict the absence of hypocalcemia after thyroidectomy. However, preserving PG feeding vessels during thyroidectomy is often impossible to certify visually, and existing intraoperative fluorescence imaging available techniques do not aim to visualize PG pedicles. Indeed, although the use of autofluorescence imaging has been shown to improve postoperative hypocalcemia rates in several studies, including a multicenter randomized trial, other authors found that the use of autofluorescence alone was not sufficient to improve patient outcomes, and pointed out the need for intraoperative visualization of parathyroid vascularization.

Consequently, a real-time ICG-based intraoperative mapping angiograms of PG (iMAP), performed immediately after PG autofluorescence identification, could be of interest to guide the surgical dissection.

The current study thus aimed at assessing the feasibility of real-time iMAP, to visualize PG feeding vessels during thyroid surgery and its capacity to improve PG residual perfusion at the end of surgery.

Methods

Study design and setting

We conducted a prospective non-comparative study, in Hôpital Européen de Marseille, France. Between September and December 2018, all consecutive patients planned to undergo unilateral thyroid lobectomy or total thyroidectomy were enrolled after written informed consent (see Figure 1, Flow Chart). Patients with preoperative parathyroid disorders were excluded from the study. Ethical approval was obtained from the regional ethical committee, Comité de Protection des Personnes Sud Est IV.

Procedures

During total thyroidectomies, the first thyroid lobe was explored, after medialization, by autofluorescence, using a near infrared camera, the Fluobeam® 800 (Fluoptics, Grenoble, France), held at the distance of 15 cm from the surgical field. After the PGs were visually identified, the lobectomy was performed. After having medialized the second lobe and visually confirmed the presence of PGs using autofluorescence, a first injection of 0.1 mg/kg ICG solution (Infracyanine ®, Serb, Paris, France) diluted in a saline solution, was performed intravenously to assess the parathyroid vessel angiography of the same lobe. The sequence was recorded through the camera, and replayed in slow motion, if needed, before surgery was resumed. Finally, a second injection was performed at the end of the second lobectomy, in order to assess perfusion of all remaining PGs from the two lobes (the protocol is described in a video, see supplementary materials). In total thyroidectomies, in order to be able to identify PGs by autofluorescence, on both sides, and since autofluorescence is not visible after ICG injection, we limited the injection to one lobe per patient. In total thyroidectomies, the first lobe was thus operated on using autofluorescence alone, and iMAP was performed on the second lobe. In unilateral lobectomies, the sequence was the same as in the second lobe of total thyroidectomies autofluorescence exploration followed by ICG-based angiography, then ICG-based assessment of PG perfusion of the removed lobe. Therefore, all patients received one injection for the angiography and one injection at the end of surgery for the assessment of PG residual perfusion. All patients were operated on by the same surgeon (FB).

Primary outcome was the quality of information given by the iMAP, scaled as iMAP 2 (clearly shows the pedicle inflowing in the PG, Figure 1), iMAP 1 (informs about where to dissect safely, but does not precisely show the PG pedicle, Figure 2) and iMAP 0 (not informative, Figure 3). Secondary outcome was the score of parathyroid perfusion at the end of surgery, performed using the Geneva subjective scale intensity assessment: ICG 2 (intense dye-uptake, Figure 4A), ICG 1 (moderate dye-uptake, Figure 4B) and ICG 0 (no perfusion, Figure 4C). Other collected data included: age, sex, preoperative calcium level, preoperative parathormone (PTH) level; number of parathyroid assessed by iMAP, presumed origin of parathyroid vascularization; corrected calcium during hospitalization and parathormone level at post-operative day 1; occurrence of postoperative hypocalcemia ($\leq$6 months or >6 months); non-parathyroid complications; complications related to the use of the autofluorescence system and/or ICG injection.

Statistical analysis

Quantitative data were reported using mean (standard deviation, SD) and qualitative data were reported using frequency and percentages. Comparisons between groups were performed using Tukey style test accounting for multiple comparisons. Statistical computations were performed using SAS software (V9.4, SAS Institute Inc., Cary, NC), with result considered significant at a α-level <0.05.

Results

Study population

Overall, 50 patients were initially included, with a mean age at 51.6 (16.3) year, and a sex ratio at 0.19 (Table 1). Three patients were secondarily excluded from the analysis: in one patient, the injection could not be performed because the ICG was not available when needed; in one patient, the injection was performed but an error of dilution of the ICG made the image not interpretable; and in one patient, there was a disruption of the software due to a handling mistake. Therefore, a total of 47 patients were analyzed, including 34 total thyroidectomies and 13 lobectomies.

Primary outcome

The iMAP was performed in the right lobe in 40 and in the left lobe in 7 cases, respectively. Of the 162 potentially visible PGs (in 81 lobes), 43 were not seen at all (26%), including 18 PGs in lobes assessed by iMAP. At the end, 76 PGs were assessed by iMAP and 43 were not assessed by iMAP (see flow diagram, Figure 1). The mapping angiogram was scored iMAP 2 in 24 PGs (31.6%), iMAP1 in 46 PGs (60.5%) and iMAP 0 in six PGs (7.9%) (Table 2).

Secondary outcomes

There was a significant difference in ICG perfusion score at the end of surgery between PGs with informative angiogram (iMAP 1 or 2), PGs with uninformative angiogram (iMAP 0) and PGs not evaluated by iMAP ($p<0.05$): 72.9% of PGs scored iMAP 1 or 2 exhibited a good perfusion (ICG2) at the end of lobectomy, whereas only 16.7% of PGs with uninformative angiogram (iMAP 0) and only 25.6% of PGs not evaluated by iMAP exhibited a good perfusion at the end of surgery (Table 3). Conversely, only 1.4% of PGs with informative iMAP (iMAP 1 or 2) were not perfused (ICG0) at the end of lobectomy, while 27.9% of PGs not evaluated by iMAP remained unperfused (Table 3). The proportion parathyroids with an ICG1 score at the end of surgery was not significantly different between the three groups (Table 3). ICG perfusion at the end of surgery could not be assessed for 11 PGs: one PG with informative angiogram, three PGs with uninformative angiogram and seven PGs not evaluated by iMAP (Table 3). This was due in 8 cases to the fact that the PGs were autotransplanted at the end of surgery, in 2 cases because the recording failed and in one case because at the end of surgery, the PG, located in thyrothymic position, was difficult to find without extensive dissection. Parathyroids were autotransplanted because they were not possible to keep intact in 5 cases (3 in the central neck dissection in 2 patients, 2 because they were included in the thyroid lobe in the same patient, having a Graves disease) and because at the end of dissection, they remained disconnected from any vascular supply in 3 cases.

Other results of interest

Superior PGs were vascularized by a branch of inferior and superior thyroid artery in 97% and 3 % respectively, while all inferior PGs were vascularized by inferior thyroid artery. No patient had temporary or permanent hypoparathyroidism in this study. One patient had temporary laryngeal nerve palsy. Mean postoperative parathormone level at postoperative day 1 was 38.7 pg/ml (20.6). There was no complication related to the use of the autofluorescence system or the ICG injection.

Discussion

This prospective cohort is the first, to our knowledge, to show that intravenous ICG injection can be used to map parathyroid feeding vessels during surgery, and appears to be effective in preserving postoperative PG perfusion.

The results of this study are important because parathyroid vascular mapping is an appropriate complement to the identification of PGs by autofluorescence, which allows PGs to be identified at an early stage, when the eyes cannot yet distinguish them so clearly (5,7). It is then possible to best dissect these glands in order to try to identify their vascular pedicles that iMAP can then reveal. By coupling these two techniques with the evaluation of the perfusion of PGs by ICG at the end of dissection (8), we obtain a real-time multimodal imaging technique that can improve the identification of PGs, better see their vascular pedicles and control their good perfusion at the end of the operation. This represents a considerable change from the conventional technique, in which all these important steps are not feasible.

We observed that iMAP was instructive in a high number of cases (82%). This rate may eventually increase with experience. Indeed, as this study included the very first 50 patients to have been operated on using this technique, progressive adjustments were made during the learning curve. For example, the timing of the injection changed slightly as the experiment progressed: starting with an injection immediately after visualization of the parathyroids by autofluorescence, we gradually came to inject after having well dissected and exposed visually the parathyroids and their potential vessels, but before ligating any of them. We also progressively modified the way we held the thyroid to expose both parathyroid glands in the field, and we have moved from a static to a dynamic grip, mobilizing the thyroid and peri-thyroid tissues, in order to mentally reconstruct the vascularization in 3 dimensions. The way of wearing the camera also changed naturally, progressively focusing on the potential areas of interest, as we learned the main patterns of vascularization.

Another adjustment of the technique that we had to perform concerns the sequences of use of autofluorescence and ICG injection. Since ICG injection excludes the subsequent use of autofluorescence, we deliberately chose to perform the injection to only one lobe per patient. Another option would have consisted in identifying the four glands by autofluorescence, before mapping each side. However, such an option implied an extensive bilateral dissection at the beginning of the operation, and a riskier re-intervention if the operation had to be stopped, in case of a loss of neuromonitoring signal of the recurrent nerve, at the end of the first lobectomy.

It is interesting to note that, consistent with what we know about the distribution of parathyroid vascularization (9), 97% of the upper parathyroid was vascularized by the lower thyroid artery, often by a branch along the posteromedial border of the thyroid, which must be preserved. However, this study did not intend to describe anatomically the vascular origin of the pedicles, and the injections were mostly performed on the right side, due to the surgeon's habit of starting total thyroidectomies from the left. The distribution of parathyroid arterial blood support on the left side may be different from the one on the right side (9).

This study also suggests that iMAP can help preserve parathyroid vascularity during surgery. Indeed, only 1.4% of PGs that had been evaluated by iMAP were devascularized at the end of surgery (ICG score at 0), compared to 27.9% of PGs evaluated by autofluorescence alone. This may suggest that real-time iMAP allows better guidance of surgical dissection and preserves better parathyroid vascularization at the end of surgery. However, ICG perfusion at the end of the procedure could not be evaluated for 11 PGs due to technical problems, and furthermore, the sides dissected without the angiograms were mostly the left sides and those dissected with the angiograms were mostly the right sides, which introduces a bias of interpretation. It is therefore difficult to draw definitive conclusions on the ability of angiography to improve vascular preservation, and this will have to be specifically studied.

The main limitations of the study are related to its monocentric nature and to the fact that it uses subjective scales to evaluate the mapping, which any image interpretation implies, however. Finally, the generalization of indocyanine green injection must take into account the very low (<1/10,000 patients) but real allergic risk (10). However, it has been shown that permanent hypoparathyroidism is responsible for an increase in overall mortality and cardiovascular and renal morbidity (11,12). If the technique described here shows in the future that it can improve parathyroid dissection and decrease parathyroid-related morbidity after thyroid surgery, then the benefit/risk ratio may remain largely favorable.

It is likely that further technical improvements will have a positive impact on image quality and ease of use of the technique. Further progress in near infrared imaging systems is still to be made, which could, for instance, increase the contrast between tissue and vessel enhancement, increase image fluidity by increasing the number of images/second, increase image resolution and improve the visualization of small vessels. Next generation systems could integrate artificial intelligence to more precisely identify the origin of the pedicles specific to the parathyroid, or to differentiate arterial and venous vascularization, which remains difficult today.

Conclusion

The prospective Fluogreen study shows that real-time indocyanine green-based intraoperative mapping angiograms of parathyroid gland (iMAP) is feasible and may have a positive effect on the preservation of parathyroid gland perfusion. This and the capacity of iMAP to help prevent post-operative hypocalcemia however warrant further evaluation.

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Tables and Figures

Table 1 – Patient characteristics

Age – mean (SD)	51.6 (16.3)
Sex ratio (M/F)	0.19
Diagnosis – N (%)	
Graves	11 (23%)
Multinodular goiter	17 (36%)
Redo multinodular	1 (2%)
Nodules	12 (25%)
Cancer	6 (13%)
Extent of thyroid resection	13 lobectomies 34 total thyroidectomies (= 81 lobes operated on)
Number of lobes evaluated by iMAP	47 (40 right lobes and 7 left lobes)
Preoperative calcium level in mmol/l – mean (SD, range)	2.38 (0.6, 2.2-2.52)
Preoperative parathormone (PTH) level in pg/ml– mean (SD, range)	58.8 (33.5, 27-129)
Postoperative calcium level in mmol/l – mean (SD, range)	2.25 (0.08, 2.05-2.33)
Postoperative parathormone (PTH) level in pg/ml – mean (SD, range)	38.7 (20.6, 7-90)
Complications	
Transient or Permanent hypocalcemia	0
Transient laryngeal nerve palsy	1

SR, standard deviation

Table 2 - Primary outcome: Quality of the intraoperative mapping angiograms of the parathyroid glands (iMAP)

Information provided by the iMAP	N (%)
- Direct information (iMAP 2)	24/76 (31.6%)
- Indirect information (iMAP 1)	46/76 (60.5%)
- No information (iMAP 0)	6/76 (7.9%)

iMAP: intraoperative mapping angiogram of the parathyroid glands

Table 3 - Secondary outcomes: Parathyroid perfusion at the end of surgery

	Parathyroids assessed by iMAP (n=76)			D- Parathyroids not assessed by iMAP (n=43)	p
	A- iMAP 2 (n=24)	B- iMAP 1 (n=46)	C-iMAP 0 (n=6)		
ICG 2 (n, %)	17	34	1 (16.7%)	11 (25.6%)	(A vs. B): NS* (A vs. C): <.05* (B vs. C): NS*
ICG 1 (n, %)	6	11	2 (33.3%)	13 (30.2%)	
ICG 0 (n, %)	1	1	3 (50%)	19 (27.9%)	

*Tukey style test for multiple comparisons of proportions

iMAP: intraoperative mapping angiogram of the parathyroid glands

ICG 0: no perfusion; ICG 1: moderate dye-uptake; ICG 2: intense dye-uptake after the second injection

Not assessed: number of PG that could not be assessed for perfusion quality, after the second injection

Figure 1 – Flow diagram