Indocyanine Green Angiography in Subtotal Parathyroidectomy: Technique for the Function of the Parathyroid Remnant

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The main indications for subtotal parathyroidectomy include hyperparathyroidism (HPT) of renal origin (patients with renal insufficiency and patients after renal transplantation) and primary HPT due to hyperplasia of all 4 glands. The major surgical steps consist of bilateral cervical exploration with identification and preservation of both recurrent laryngeal nerves, identification of the 4 parathyroid glands, and resection of 3½ parathyroid glands. The size of the parathyroid remnant varies according to primary disease and operative findings.[1,2]

The main complications of subtotal parathyroidectomy are recurrent laryngeal nerve palsy, persistent HPT, and definitive or transient hypoparathyroidism. Definitive hypoparathyroidism develops when all 4 parathyroid glands are removed or if the parathyroid remnant is not well perfused. Preserving a well-perfused parathyroid remnant prevents postoperative hypoparathyroidism, and selection of this remnant is currently based on subjective visual appreciation. To date, postoperative parathyroid hormone (PTH) or intraoperative PTH dosages are the only ways to assess the function of the parathyroid remnant.[3,4] However, PTH levels reflect a global parathyroid function (including orthotopic, ectopic, and supernumerary glands) and do not reflect the function of a single parathyroid gland. Moreover, the time needed to obtain reliable PTH dosage after parathyroidectomy does not allow intraoperative adjustment of the extent of surgical resection.[5]

Indocyanine green (ICG) angiography was initially used in detection of macular disease.[6] It has since been expanded to uses in oncologic surgery, such as to search for sentinel lymph nodes or vascular blood flow of intestinal anastomoses.[7,8] Intraoperative angiography using fluorescent ICG is a tool that can be used to assess and predict the function of the parathyroid glands after thyroid resection.[9-11] Some authors used ICG angiography essentially to help identify parathyroid glands during parathyroidectomy, but also suggested that ICG angiography could help avoid hypoparathyroidism in 6 patients undergoing subtotal parathyroidectomy.[12] The rationale to specifically study patients undergoing bilateral neck exploration with subtotal parathyroidectomy was to explore all parathyroid glands. In this situation, all glands other than the selected remnant are removed. Subsequently, the PTH secretion can be attributed to the visualized parathyroid remnant. This is not the case in focused parathyroidectomy or thyroidectomy, in which more than 1 parathyroid gland is left in place, so correlation between parathyroid perfusion, as visualized by peroperative angiography and postoperative PTH levels, is not guaranteed.

We present a series of 13 patients who underwent subtotal parathyroidectomy with ICG angiography. The aim was to evaluate the vascularization of the parathyroid remnant by intraoperative ICG angiography and determine whether it can predict postoperative remnant function.

METHODS

Between May 2014 and December 2015, 104 patients underwent parathyroidectomy. Of those, 16 patients underwent bilateral exploration with subtotal parathyroidectomy (independent of their pathology), and peroperative ICG angiography was performed in 13 patients (Fig. 1). The fluorescence imaging equipment was not available for 3 patients at the time of subtotal parathyroidectomy. The Ethics Review Board of the University Hospitals of Geneva approved the study.

Operations were performed by 3 experienced surgeons. Patients underwent subtotal parathyroidectomy with anterior cervicotomy, bilateral exploration and neuromonitoring of the recurrent nerve by intermittent

Drs Vidal Fortuny and Sadowski contributed equally to this work.

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Abbreviations and Acronyms

HPT = hyperparathyroidism
ICG = indocyanine green
MEN = multiple endocrine neoplasia
POD = postoperative day
PTH = parathyroid hormone

intraoperative neuromonitoring (or occasionally, continuous intraoperative neuromonitoring), and identification and morphologic evaluation of all parathyroid glands. A search for supernumerary glands was not performed when 4 parathyroid glands were visually identified. The search for ectopic glands was performed in and around the thymus if an inferior parathyroid gland was missing and a lateral-retro-esophageal search if a superior parathyroid gland was missing. Subtotal parathyroidectomy was performed by applying clips onto the parathyroid glands (Fig. 2).[10,13] Special attention was paid to avoiding application of clips onto the parathyroid hila where the vessels are located. Occasionally, a normal looking parathyroid gland was left in place entirely.

Criteria such as anatomic localization, vascularization, and morphologic aspect of the glands were used to select the gland for subtotal resection (remnant). Ideally, an inferior or small gland, or a gland with no macroscopic nodule was selected. Before resection of the parathyroid glands, adequate perfusion of the selected remnant was controlled by injecting 3.5 mL of ICG solution. During subtotal parathyroidectomy, our aim is to keep a parathyroid gland/parathyroid remnant that corresponds to the size of 1 to 2 normal parathyroid glands. The final size of the remnant was calculated by estimating size in 3 dimensions and calculating its volume (height × length × width / 2).

The ICG powder (25mg, ICG Pulsion, Pulsion Medical Systems) was suspended in 10 mL of sterile water and was injected intravenously.[14] If needed, the injection was repeated to a maximum toxic dose of 5 mg/kg/day. Indocyanine green has a peak spectral absorption at about 805 nm and a peak of emission at 835 nm that can be specifically detected by fluorescence equipment. After IV injection, ICG remains in the intravascular compartment linked to plasma proteins; it has a half-life of 3.4 ± 0.7 minutes and is removed and degraded by the liver within 15 to 20 minutes. Adverse events are rare, but vasovagal reactions and allergies are reported in 1 in 333,000 cases.

After ICG injection, a laparoscopic system (Pinpoint Endoscopic Fluorescence Imaging System, NOVADAQ) was used to visualize gland perfusion. The gland is visualized in green or white, depending on the viewing mode. The more intense the color is, the better the vascularization. Selection of the remnant was based on a nonperfused to well-perfused scale of ICG fluorescence intensity. In our previous study on parathyroid gland angiography after thyroidectomy, a score was used in order to avoid early postoperative hypoparathyroidism (ICG 0, the parathyroid is black after the injection of ICG, indicating that the gland is not vascularized; ICG2, the parathyroid is white, indicating that the gland is well vascularized; and ICG1, the parathyroid is grey or heterogeneous, suggesting that the gland is partially vascularized).[9] In this study on subtotal parathyroidectomy, the aim was to avoid long-term hypoparathyroidism; however, to have low levels of PTH immediately after parathyroidectomy was not considered deleterious. Perfusion of the glands and the remnant was defined by a visual grey scale. Further, parathyroid gland blood supply was not manipulated during localization and imaging procedures in order to not disturb their perfusion (Fig. 3).

All patients were followed according to a standard postoperative protocol used at our center. Hospital stay was at least 24 hours, with regular calcium and PTH monitoring (at least once a day). Patients received systematic calcium supplementation with 1g of calcium and 800 IU of 25-OH-vitamin D twice a day until the postoperative clinic visit (postoperative day [POD] 10 to 15). Patients with HPT of renal origin systematically received 1.25-OH vitamin D supplementation (0.5 μg twice a day) starting 5 days before parathyroidectomy. Patients with primary HPT received 1.25-OH vitamin D supplementation when calcium levels dropped below 2.0 mmol/L. When calcium was < 2.0 mmol/L (8 mg/dL) and/or when hypocalcemic symptoms were present, a calcium perfusion was initiated. Values of PTH and calcium for each patient were collected preoperatively, at day 1, day 10, and at follow-up visit. Albumin level was always measured with the calcium level, and results are given as "corrected calcium level." Normal values for the assays at the author's institution are 2.20 to 2.52 mmol/L and 1.1 to 6.8 pmol/L for calcium and PTH levels, respectively. Hypocalcemia was defined as a corrected calcium value < 2.0 mmol/L.

Statistical analyses were performed using GraphPad Prism 6 software (GraphPad Software). Parametric and nonparametric data are presented as mean ± standard deviation (SD) or median (range).

RESULTS

The study design is shown in Figure 1. The indication to perform a subtotal parathyroidectomy in the 13 patients was HPT of renal origin in 6 patients and primary HPT (HPT1) in 7 patients. One patient (patient 4) with renal

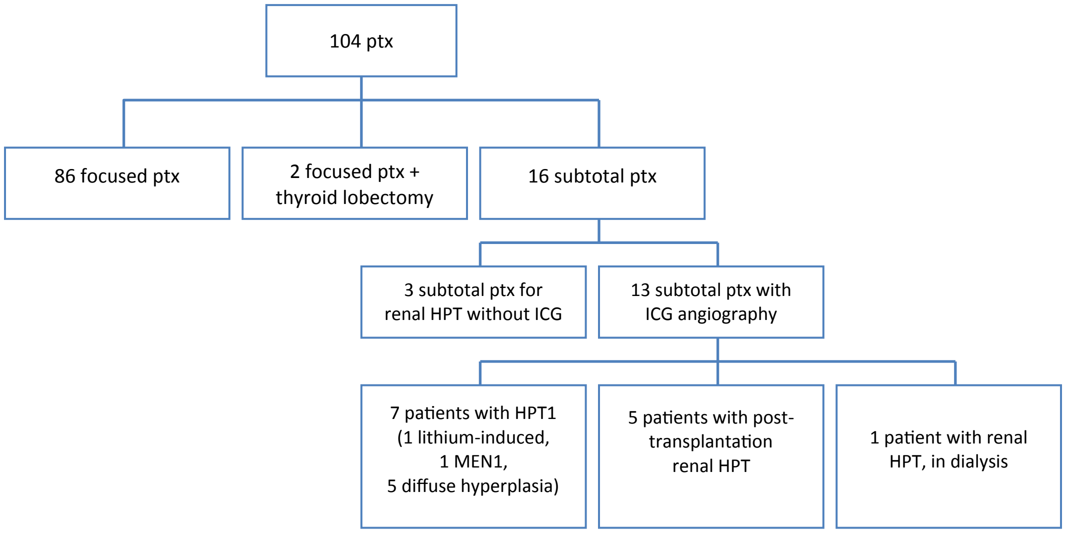

Figure 1. Design of the study. HPT, hyperparathyroidism; ICG, indocyanine green; MEN, multiple endocrine neoplasia; Ptx, parathyroidectomy.

HPT underwent total thyroidectomy during the same procedure, and 2 had a thyroid lobectomy (patients 9 and 10). Characteristics of the patients are summarized in Table 1.

Preoperative imaging using MIBI scintigraphy and ultrasound was performed in every patient, except patient 1, who underwent only ultrasound because of claustrophobia. Intraoperatively, the 4 parathyroid glands were visualized in every patient, and histopathologic analysis confirmed the parathyroid origin of the resected tissue. Undergoing subtotal parathyroidectomy procedures, 10 patients had 3½ glands removed and 3 patients had 3 glands removed. Of these resected parathyroid glands, 91.7% were hyperplastic; of those, 31.1% were nodular as well, and 4 glands were normal (8.3%).

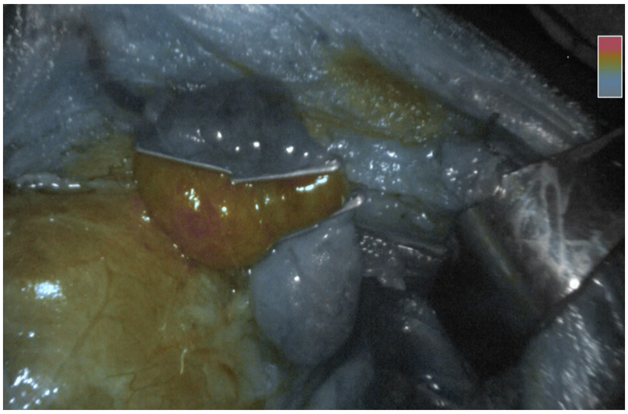

Figure 2. Virtual parathyroid gland reduction with applied clips, showing good perfusion of the remnant between clips during indocyanine green angiography, as seen in red-orange on the color scale.

The mean duration of surgery was 112.8 ± 28.9 minutes, and performing the ICG angiography increased duration of the procedure by 3.0 ± 2.3 minutes. The median length of stay was 3.0 days (24 hours to 8 days [for social reasons]). None of the patients presented with postoperative complications such as hemorrhage or recurrent laryngeal nerve palsy. Overall median follow-up was 4.1 (0.8 to 13.4) months.

In all patients, the parathyroid remnant that was best perfused was selected according to ICG angiography. In 1 patient (patient 7), the selected parathyroid remnant was first identified by ICG angiography to be not well perfused, so another gland was chosen for subtotal resection, after additional ICG control.

Two patients (patients 5 and 8) needed IV calcium supplementation according to our protocol: 1 patient with HPT1 associated with multiple endocrine neoplasia type 1 (MEN1) was discharged 24 hours after surgery and had to be readmitted for paresthesia with hypocalcemia at 1.81 mmol/L; the other patient with renal HPT experienced asymptomatic hypocalcemia in the immediate postoperative setting. For both patients, treatment by IV calcium infusion was stopped after 48 hours.

At postoperative day (POD) 1, 4 patients presented a low PTH level (<1.1 pmol/L). At POD 10, PTH was measurable in all patients, indicating that the parathyroid remnant was well functioning, except in 1 patient who had a PTH value of 0.9 pmol/L, with a hypercalcemia of 2.84 mmol/L (patient 3). At follow-up, corrected calcium levels and PTH levels were in the normal range for all patients, according to their pathology (Table 1). Furthermore, at last follow-up, PTH levels decreased 70.7% ± 22.5% compared with preoperative levels.

DISCUSSION

This study shows that ICG angiography is feasible in patients undergoing subtotal parathyroidectomy and that parathyroid remnant perfusion correlates with postoperative gland function. At follow-up, corrected calcium levels were within normal range (all patients recovered from their HPT) and none presented with hypoparathyroidism.

Primary HPT is due to a single adenoma in 80% to 85% of patients and is multiglandular (either multiple adenoma or diffuse hyperplasia) in 15% to 20% of the patients. In HPT1 associated with MEN1 and renal HPT, all parathyroid glands are usually involved.[15,16]

A search for all 4 parathyroid glands is generally recommended for patients with sporadic HPT1 and negative or discordant imaging, with lithium-induced HPT1, with HPT1 associated with MEN1, and with renal HPT. Subtotal parathyroidectomy or total parathyroidectomy with or without auto-transplantation is usually recommended for patients with diffusely enlarged parathyroid glands in HPT1 and in renal HPT.[17,18] In our center, we perform subtotal parathyroidectomy for all patients having diffuse parathyroid disease. Usually, the most normal looking gland is left in place or used for subtotal resection; the other 3 glands are resected. Visual evaluation of the remnant is based on the coloration and morphology of the gland, which is a subjective decision.

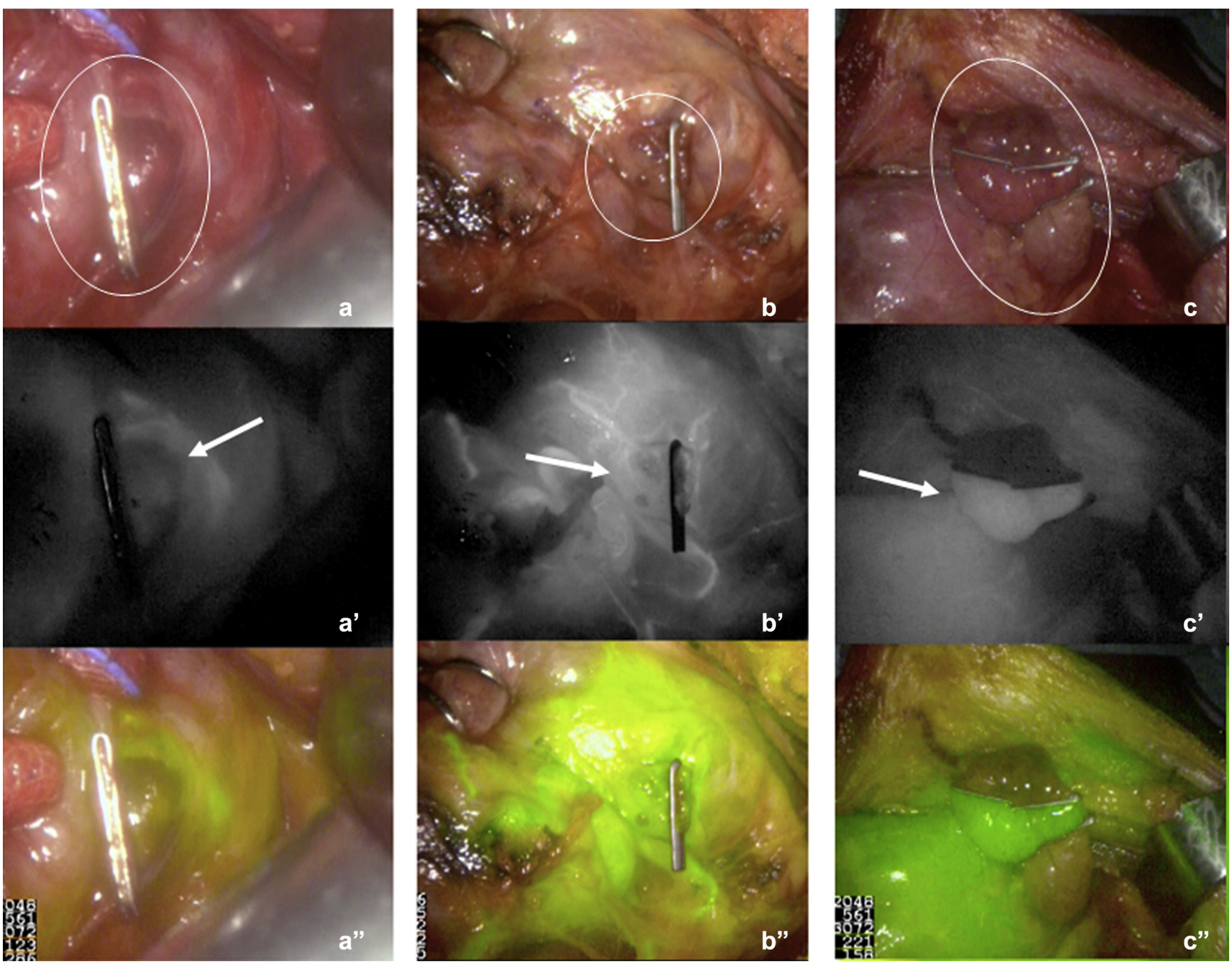

Figure 3. Indocyanine green angiography of (a) a nonperfused, (b) a moderately perfused, and (c) a well perfused parathyroid remnant. a, b, c: Normal views. Circles indicate parathyroid gland. a', b', c': Black and white near infra-red views. Arrows indicate remnant. a", b", c": combined normal and near infra-red views.

Table 1. Patient Characteristics with Pathology and Laboratory Results

Pt. no.	Age, y	Sex	Pathology	Preoperative Cac	Preoperative PTH	Postoperative POD1 Cac	POD1 PTH	POD10 Cac	POD10 PTH	Follow up Cac	Follow up PTH	Gland in place*	Weight of gland in place, g†	Weight of resected glands, g
1	46	M	Renal HPT − Post transplantation 1990	2.49	33.9	2.35	1.3	2.19	7.6	2.36	4.7	0/0.5/0/0	0.049	1.586
2	70	M	Renal HPT− Post transplantation 2012	2.66	9.6	2.53	0.9	2.84	0.9	2.23	3.0	0/0/0.5/0	0.016	1.755
3	54	F	Goiter + renal HPT− Post transplantation 2013	2.99	13.3	2.29	0.9	2.36	1.6	2.34	3.5	0/0.5/0/0	0.038	0.389
4	38	F	Renal HPT − Post transplantation 1999	2.58	46.4	2.54	1.5	2.55	1.2	2.19	13.6	0/0/0/0.5	0.036	1.990
5	65	F	Renal HPT − Post transplantation 2001	2.72	7.3	2.39	1.2	2.73	1.8	2.36	4.7	0/0/0.5/0	0.032	2.550
6	62	M	HPT 2 under dialysis	2.29	106.0	1.93	8.0	2.17	11.0	2.24	3	0.5/0/0/0	0.025	3.080
7	24	F	HPT1 MEN1	2.57	30.9	2.24	0.9	1.96	4.4	2.07	5.8	0/0/0/0.5	0.015	3.790
8	67	F	HPT 1 − Lithium	2.72	17.6	2.39	2.5	2.27	4.0	2.34	4.4	0.5/0/0/0	0.053	0.581
9	62	F	Goiter + HPT 1	2.53	6.3	2.15	3.0	2.40	4.0	2.27	4	0/1/0/0	0.018	0.410
10	63	F	Goiter + HPT 1	2.56	8.0	2.11	2.0	2.12	5.0	2.38	4.25	1/0/0/0	0.009	1.130
11	50	F	HPT 1	2.65	25.3	2.41	10.0	2.53	12.0	2.41	12	0/0/0/1	0.010	0.468
12	70	F	HPT 1	2.55	13.0	2.39	4.0	2.34	8.0	2.45	9	0.5/0/0/0	0.042	0.639
13	63	F	HPT 1	2.54	8.162	2.37	1.0	2.32	3.0	2.32	6.8	0/0/0/0.5	0.018	0.216
Total‡	56.5 ± 13.7			2.60 ± 0.16	17.6 [6.3 −106]	2.31 ± 0.17	1.5 [0.9 −10]	2.37 ± 0.25	4.96 ± 3.65	2.34 ± 0.13	5.91 ± 3.61		0.028 ± 0.015	1.430 ± 1.15

*Parathyroid gland left in place: 0.5 corresponds to a subtotal resection, 1 when an entire, normal-looking parathyroid gland was left in place. Data show right superior/right inferior/left superior/left inferior.

†(Height × length × width)/2.

‡Total shown in mean ± SD or median [range].

Cac, corrected calcium level in mmol/L; F, female; HPT1, primary hyperparathyroidism; HPT 2, secondary hyperparathyroidism; M, male; MEN1, multiple endocrine neoplasia type 1; POD, postoperative day; PTH, parathyroid hormone level in pmol/L.

The aim of using ICG angiography during subtotal parathyroidectomy is to decrease the risk of permanent postoperative hypoparathyroidism, and ICG angiography confirms that the parathyroid remnant is well perfused, and therefore functional, before proceeding with resection of the other parathyroid glands. If a parathyroid gland that is not well perfused is identified by ICG angiography, another gland can be chosen, which happened in 1 patient in this series. Therefore, surgeons can adapt their decision intraoperatively based on the ICG angiography results, which is a personalized and reproducible evaluation of the vascularization and, therefore, the function of each parathyroid gland.

Intraoperative and early postoperative measurement of PTH is a reliable indicator of global parathyroid function. According to the literature, it is used to evaluate the chance of cure in HPT[3] and to evaluate the risk of postoperative hypoparathyroidism after thyroidectomy.[19-21] However, PTH values cannot be interpreted as the function of an individual parathyroid gland, and usually the results are obtained too late for the surgeon to adapt the surgical procedure. Moreover, one of the main indications of subtotal parathyroidectomy is HPT of renal origin. In this situation, intraoperative PTH decreases more slowly and later than in patients with normal renal function.[22]

In this study, 4 patients had low PTH levels on POD1 despite a well-vascularized remnant. This immediate postoperative low PTH can be explained by persistent hypercalcemia (due to HPT itself and to the added supplementation, according to our post-parathyroidectomy protocol), parathyroid stunning (dormant glands stunned by long-standing hypercalcemia), or less intensely perfused glands shown with ICG (nonetheless, the best perfused remnant was chosen). This might explain the low PTH secretion in the immediate postoperative setting, followed by a quick recuperation. At POD10, only 1 patient had a low PTH level, but this patient presented with hypercalcemia (patient 3). This can explain the suppressed PTH level, and the hypercalcemia in this patient was probably due to excessive calcium and vitamin D supplementation. This patient had normal calcium (2.24 mmol/L) and PTH levels (3.0 pmol/L) at 4.1 months of follow-up. Many patients will develop hypocalcemia after parathyroidectomy in renal HPT, and in some cases of HPT1.[23] Our ICG angiography technique demonstrates that a well-perfused parathyroid remnant will produce measurable PTH levels and therefore avoid long-term postoperative hypoparathyroidism. However, it does not prevent immediate postoperative hypocalcemia in patients who have severe bone disease and therefore are at risk of developing a hungry bone syndrome after parathyroidectomy.

Our study has some limitations. The laparoscopic system used in this study is expensive. However, ICG angiography equipment can be used and shared by departments for different procedures (visceral, plastic, cardiovascular, and gynecologic surgery), which may decrease the cost per patient. On the other hand, ICG dye is not expensive. The second limitation is the residual fluorescence after the first ICG injection. This renders evaluation after subsequent injections more difficult, although not impossible. To avoid this problem, we apply clips on more than 1 parathyroid gland before ICG angiography and then evaluate the perfusion of those "virtual" remnants (the parathyroid tissue that will be left in place after subtotal resection). Subsequently, the best remnant is chosen before resecting any parathyroid tissue.[13] Further, ICG angiography fluorescence quantification is scored subjectively by the surgeons, which could explain the discrepancy in quantifying the intensity of fluorescence. Nevertheless, the visual difference between a non-perfused gland and a well-perfused gland is clearly apparent in our study (Fig. 3). New technical imaging solutions are currently being developed to help surgeons quantify the intensity of fluorescence by ICG. The function of a parathyroid remnant and its capacity to produce different levels of PTH in the same metabolic conditions like calcium, phosphate, and vitamin D levels, depends on 3 main characteristics: size of the remnant, underlying primary disease, and perfusion of the remnant. A larger remnant will produce more PTH, a remnant in a patient with terminal renal insufficiency will probably produce more PTH than the same size remnant in a patient with sporadic HPT and lastly, a better perfused remnant will produce more PTH. In this preliminary study on 13 patients with HPT of different origin, it was not possible to correlate the quality of the perfusion with the postoperative level of PTH because of the small sample size. However, developing a reliable perfusion scale that could be correlated to postoperative PTH levels is an area for future research.

Our previous study results in 36 patients undergoing thyroidectomy showed a measurable PTH on POD1 in all patients demonstrating at least one well-vascularized parathyroid gland (no patient developed hypoparathyroidism).[9] However, in this previous study, we did not identify all parathyroid glands during the surgical procedure, so it was impossible to guarantee that postoperative parathyroid function was due to the identified well-vascularized parathyroid gland. In this study, all parathyroid glands were identified and 1 remnant was left in place in each patient. Therefore, we conclude that postoperative parathyroid function truly reflects remnant function as evaluated by ICG.

CONCLUSIONS

Our findings suggest a good correlation between parathyroid gland perfusion and postoperative parathyroid function with production of PTH. If these results are validated by future studies, this technique could be used to verify parathyroid vascularization and predict good parathyroid function during parathyroid surgery. This adds a real time tool to assess parathyroid remnant function and assists the surgeon in the intraoperative decision-making process. Finally, our study results might represent a proof of concept of this new technique applicable in thyroid surgery, to predict postoperative parathyroid function.

Author Contributions

Study conception and design: Vidal Fortuny, Sadowski, Triponez

Acquisition of data: Vidal Fortuny, Sadowski, Belfontali, Karenovics, Guigard, Triponez

Analysis and interpretation of data: Vidal Fortuny, Sadowski, Triponez

Drafting of manuscript: Vidal Fortuny, Sadowski, Triponez

Critical revision: Vidal Fortuny, Sadowski, Belfontali, Karenovics, Guigard, Triponez

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