Indocyanine green fluorescence angiography in parathyroidectomy for primary hyperparathyroidism

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INTRODUCTION: *Primary Hyperparathyroidism (PHPT) is a systemic pathology caused by an excessive secretion of parathyroid hormone. Parathyroidectomy is the treatment of choice in PHPT, and the success of surgery is based on precise localization of the abnormal parathyroid gland. Preoperative diagnosis makes use of imaging techniques and functional examinations, however these are insufficient in some cases for the precise location of the pathological gland. Therefore the need arises for an intraoperative localization technique.*
MATERIALS AND METHODS: *We have retrospectively analyzed 20 consecutive patients with PHPT undergoing parathyroidectomy from April 2019 to September 2021, and divided them in two groups, in base of the use of Indocyanine Green (ICG) fluorescence during the surgery.*
RESULTS: *Of the twenty patients considered in the two groups, all received a preoperative ultrasound evaluation, while second level examinations were reserved for the more difficult cases, with small volume parathyroid adenomas. In the group where the fluorescence method was employed, fluorescence was especially useful in doubtful cases, allowing easier identification of the parathyroid adenoma and consequently a reduction of time and operatory risks. In two procedures using Indocyanine green, a fluorescence signal was weak.*
CONCLUSIONS: *ICG represents a convenient and safe way to detect parathyroid adenomas. We found that ICG fluorescence was very useful in all patients with non-localizing preoperative imaging studies. However further investigation is needed, to demonstrate how ICGfluorescence could be a useful localization method during parathyroid surgery.*

KEY WORDS: Endocrine surgery, Indocyanine green, Parathyroid surgery

Introduction

Hyperparathyroidism arises in case of one or more parathyroid glands become overactive, causing elevated serum levels of parathyroid hormone (PTH) and leading to hypercalcemia. Diagnosis is based on serum calcium and parathyroid hormone levels. Patients may be asymptomatic or have variable intensity symptoms, including muscle aches, difficulty sleeping, bone pain, depression, and headache.
Hypercalcemia is most often caused by a Primary Hyperparathyroidism (PHPT) which is a systemic pathology caused by an excessive secretion of parathyroid hormone by one parathyroid gland, corresponding to parathyroid adenoma in approximately 85% of patients. Hyperplasia of two or more glands occurs in less than 15% of cases, while parathyroid carcinoma occurs in less than 1% of cases [1].
Parathyroidectomy is the treatment of choice in PHPT, and the success of surgery is based on precise localization of the abnormal parathyroid gland. Knowing the exact location of the hyperfunctioning gland already in the preoperative phase allows an efficient and targeted dissection, reducing operating times, avoids the need for exploration of the four glands and decreasesthe risk of bilateral recurrent laryngeal nerve injury and other complications [2].
This is possible thanks to the combination of US and other instrumental findings, such as 99Tc-scintigraphy, Computed tomography (CT) or magnetic resonance imaging (MRI) [3]. Neck Ultrasound and Biphasic

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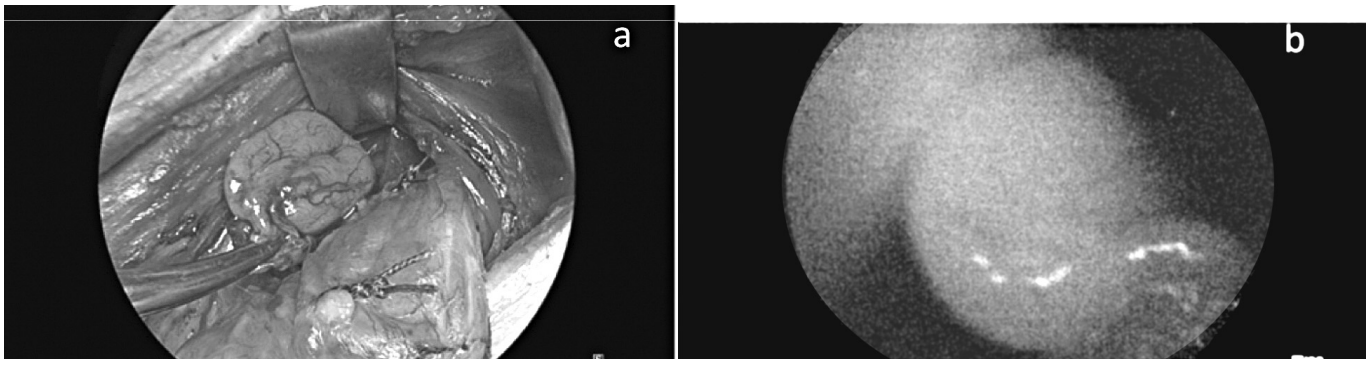

Fig. 1: ICG fluorescence angiography showing a parathyroid adenoma. (A) The bright light image of the operating field, (B) Fluorescent mode.

Scintigraphy 99mTc-MIBI are often used for preoperative evaluation in patients undergoing surgery. SPECT/CT is an additional method matching methods of ultrasound and scintigraphy providing localization of diseased glands. CT and MRI are useful in case of ectopic adenoma, negative result in ultrasonography and scintigraphy or recurring/persistent PHPT [4,5].

The sensitivity of detecting parathyroid glands using these techniques varies widely and can be facility dependent and add significant overall cost. There are some variables, which can counteract the effective preoperative localization of the parathyroid adenoma, such as the small size, the ectopic site or the presence of thyroid nodules. Therefore in these cases identifying the gland, and correctly distinguishing it from other structures such as lymph nodes or adipose tissue can be a challenge [6].

Is useful to be able to use an intraoperative localization method. Aminolevulinic acid and methylene blue have already been proposed in the past but unfortunately, these techniques were found to be inadequate, both for the search of pathological glands and for skin complications, limiting their clinical usefulness [7].

ICG fluoresce angiography might aid intraoperative detecting parathyroid adenoma during parathyroidectomy, and it is already used as a marker to assess blood flow tissues and organs in many medical fields [8]. The wavelength of light required to excite the fluorophore produced by a directly connected near-infrared light source to the camera. This allows immediate assessment and recording of blood flow. As the parathyroid gland is a hypervascular endocrine organ, we theorize that ICG fluorescence angiography will support the localization and resection of parathyroid adenomas.

Materials and Methods

We have retrospectively analyzed 20 consecutive patients with PHPT undergoing parathyroidectomy from April 2019 to September 2021. We divided the entire cohort into two groups, according to a chronological criterion.The first 10 patient underwent surgery without the use of indocyanine (Group 1), on the other hand the last 10 underwent parathyroidectomy with ICG fluorescence angiography (Group 2).

All patients were diagnosed in order to have a preoperative localization with ultrasonography and sestamibi parathyroid nuclear scan, instead CT and MRI have been used in cases where a diagnosis of certainty had not been reached.

Surgery begins with a standard, transverse cervical incision to reach the thyroid lodge. All the patients get a unilateral neckdissection according to the side indicated in preoperative imaging.

A four gland exploration only in doubtful cases was performed.

In the Group 1 the surgery continued with a meticulous and precise search for the suspected lesion without the use of any intro-operative research tool. In the Group 2 immediately after the mobilization of the ipsilateral thyroid lobe, 2.5 mg of ICG dissolved in 10 ml of sterilewater was administered as an intravenous bolus and the fluorescence-capable laparoscope was aimedatthe operative field. Within 1-2 minutes from the injection, exposed parathyroid adenomas exhibited clear fluorescent enhancement (Fig. 1).

If a parathyroid adenoma was not individuated, further dissection was made, and the ICG fluorescence imaging was repeated. After ligation of the vascular pedicle and removal of the gland, a venous sampling was repeated to evaluate the decrease in serum PTH value.

Results

From April 2019 to September 2021 were performed 20 parathyroidectomies for primary hyperparathyroidism. They were chronologically divided into two groups. The first ten (Group 1) underwent traditional parathyroidectomy, the remaining patients (Group 2) were treated with the aid of indocyanine green fluorescence. There were 9 female patients and 11 male patients totally. In

Table I - *Preoperative data. (x2-test and the unpaired t-test two-tailed)*

	Group 1	Group 2	P-value
Male & Female	6 (60%) 4(40%)	5(50%) 5(50%)	0.6530
Age (years) Media(SD) Range	63.8 (±10.1) 50-81	55.5 ((±21.3) 48-80	0.28510
Previous Neck Surgery	0	1(10%)	//
Ultrasonography	10(100%)	10(100%)	//
99mTc-scintigraphy	10 (100%)	9(90%)	//
CT	3 (30%)	2 (20%)	0.6055
MRI	3 (30%)	4 (40%)	0.6392
Preoperative PTH Media(SD) Range	pg/ml 250 (±102.4) 104.5-401.2	pg/ml 245.4 (±112.2) 109.3-375.4	0.9724
Preoperative Calcium Media(SD) Range	mg/dl 13.18(±1.31) 11.3-14.9	mg/dl 12.89(±1.14) 11.3-14.5	0.7602

Table II - *Surgical data (x2-test and the unpaired t-test two-tailed)*

	Group 1	Group 2	P value
Time of surgery (min) Media (SD) Range	92.3 (±22.5) 57-120	80.5 (±18.0) 55-120	0.23785
4 gland exploration	5/10	2/10	0.1595
Correspondence with preoperative diagnostics	9/10	8/10	0.5311
Fluorescent Signal	*	8/10	//

group 1 the mean age was 63.8 years, while in group 2 it was 55.5. Only one patient had previously undergone neck surgery (Zenker's diverticulectomy) and was enrolled in group 2. All patients received ultrasound evaluation, and only one patient did not perform scans in group 2. CT and MRI evaluation were reserved for the most difficult cases with low volume parathyroid adenomas and in all cases in which ultrasonography or sestamibi scan had a no diagnostic certainty (Table I).
Operative times oscillated from 57 to 120 minutes in Group 1, and from 55 to 100 minutes in Group 2, showing an average operative time of 92.3 minutes in Group 1 and 80.5 minutes in Group 2 a difference, not statistically significant, but in favor of the group in which the indocyanine green was used.There was also a reduction in the need to carry out a complete exploration of the four parathyroid glands, in Group 2 thanks to the use of fluorescence which was especially useful in doubtful cases, allowing easier identification of the parathyroid adenoma and consequently a reduction of time and operatory risks. In two procedures using ICG, a fluorescence signal was weak. While the correspondence with the preoperative diagnostic techniques was good in both groups (Table II).
All patients presented a single adenoma during preoperative examinations, and all specimens were sent to the pathology department for histologic analysis; that confirmed the nature adenomatous of the gland. No cases of hyperplasia or carcinoma were found. All patients, had a decrease in their intraoperative PTH level of >50%.

Discussion

The parathyroid glands generally have four elements; occasionally one or more accessory glands may be in the context of the thyroid or thymic parenchyma, or sometimes in the completely ectopic site. They are located laterally and posterior to the two lobes of the thyroid, and the inferior thyroid arteries and the recurrent nerves are useful anatomical landmarks to identify them.
These anatomical notions are indispensable for the surgeon and for the success of the procedure. For years, imaging techniques and preoperative functional tests have been of help that can identify which of the four parathyroid glands is pathological in primary hyperparathyroidism.

However, identifying the exact location of the gland involved still remains a challenge in some cases. This is demonstrated by the fact that, it is still necessary to availconfirmation methods (intraoperative changes in PTH levels and frozen sections) which, nevertheless, can only be performed post surgical and therefore also lengthen the operating times.

These are the assumptions that led to the identification of valid intraoperative detection techniques, as also happens in other surgical fields, including neck surgery and thyroid surgery [9].

Indocyanine green (ICG) is a substance that emits fluorescence after illuminated with light with a near infrared spectrum (750-810 nm). Used for various imaging and cardiological and ophthalmological diagnostic methods, indocyanine green fluorescence is clinically used in surgery to assess the perfusion of tissues and also in hepato-biliary-pancreatic fields.

The parathyroid gland receivesmore blood flow than the adjacent tissue, so it emitsa strong fluorescent signal that demarcates the edges of the gland. Several techniques have been described in order to identify the parathyroid glands during surgery (for example the intraoperative use of a mini gamma camera) [10], the technique based on fluorescence was first described in 2015 in a canine animal model [11], and it is not the only technique described in the literature, in fact, in the past other markers have been proposed such as the aminolevulinic acid,and of methylene blue [7]. However, both methods were not satisfactory both for the lack of real benefits, but also for the onset of some side effects(never occurred with the use of the ICG) [7,12].

The ICG has the advantage of accumulating in the pathological parathyroid glands due to the greater intensity of fluorescence than the surrounding tissue [13,14].

Obviously, the ICG does not specifically target the parathyroid parenchyma, and the greatest difficulty is to be able to distinguish the pathological gland from the thyroid tissue as it is also very vascularized, while the difference in signal intensity with respect to adipose and lymph node tissue is evident. The exact mechanism by which the parathyroid glands absorb ICG relative to surrounding tissue is not well known. In the study conducted by DeLong it was suggested that this is related to their significantly increased blood flow compared to the flow in adjacent tissues [1].

We retrospectively analyzed our initial experience with the ICG technique in the intraoperative detection of parathyroid adenomas during parathyroidectomy for PHPT.

We compared two groups, only in one of them we used intraoperative localization using ICG.

We found that ICG fluorescence was very useful in all patients with not very accurate or discordant preoperative imaging studies, often due to the small size of the gland. In these specific cases, identifying the parathyroid gland also intraoperatively can be difficult and lengthy, as it can be confused with lymph node, adipose or thyroid tissue.

In all cases in which ultrasound and sestamibi scan investigations have ensured a precise and correct diagnosis, the use of ICG has not contributed so much in the search for the parathyroid gland as much as in having a rapid, immediate and safety confirmation. However, in the most difficult cases in which the use of second level diagnostic techniques (CT and MRI) was already considered preoperatively, the fluorescence proved to be fundamental in the research and in the identification of the adenoma, after an initial exploration in accordance to the laterality suggested by preoperative diagnostics.

In two patients who did not demonstrate significant fluorescencethe intervention took place regularly according to the traditional technique. In neither case were there any cases of false positives in either group. This has shown how the use of ICG is not essential for the success of the intervention, but represents an excellent aid, to increase the comfort of the intervention, as it constitutes an intraoperative confirmation method, as well as being able to reduce the operating time (not statistically significant in our study).

A possible disadvantage of ICG fluorescence angiography is therefore that for the moment it represents an additional weapon in the hands of the surgeon and cannot replace preoperative diagnostic techniques [15].

However, if this technique were standardized by studies with a broader case series, it could instead replace the intraoperative measurement method of PTH levels, which is more verbose and certainly lengthens the surgical and anesthesia times.

Conclusion

ICG represent a convenient and safeway to detect parathyroid adenomas. Its aptitude tofocus in the parathyroid tissue aids the surgeon during the dissection especially in cases of unsatisfactory preoperative examinations. The fluorescence appears within a few moments after injection,in this way it absolutely does not affect the operating times, on the contrary it reduces them as it facilitates exploration time. However further investigation is needed, to demonstrate how ICG fluorescence angiography could be a useful localization method during parathyroid surgery.

Riassunto

L'iperparatiroidismo primitivo, è una patologia sistemica causata da un'ipersecrezione di PTH, ormone paratiroideo. La paratiroidectomia è l'opzione terapeutica di scelta, e la buona riuscita dell'intervento chirurgico è senza dubbio condizionata da una esatta identificazione della ghiandola paratiroidea patologica. La diag-

nosi preoperatoria si serve di tecniche di imaginged esami funzionali, finalizzati ad una precisa localizzazione, tuttavia in alcuni casi la diagnostica preoperatoria risulta insoddisfacente, determinando allungamento dei tempi chirurgici e incremento morbilità dell'intervento stesso. Su questi presupposti, origina la necessità di un sistema di rilevamento intraoperatorio.
Abbiamo condotto un'analisi retrospettiva, su 20 pazienti sottoposti presso la nostra struttura a paratiroidectomia, per iperparatiroidismo primitivo, in un intervallo temporale da aprile 2019 fino a settembre 2021. I pazienti sono stati suddivisi in 2 gruppi, distinti in relazione all'impiego del verde di indocianina (ICG) come marcatore intraoperatorio. La fluorescenza, è stata registrata con telecamera laparoscopica ad emissione di luce con spettro vicino agli infrarossi.
Questa tecnica, ha rappresentato nel nostro studio un presidio utile e sicuro per il rilevamento degli adenomi paratiroidei. Riteniamo che la sua utilità sia maggiore nei casi, di dubbia localizzazione alla diagnostica preoperatoria. Tuttavia ulteriori studi sono necessari per dimostrare l'utilità di questa metodica.

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