Utility of Indocyanine Green Fluorescence Imaging for Intraoperative Localization in Reoperative Parathyroid Surgery

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Abstract

Background. Due to the variations in anatomic location, the identification of parathyroid glands may be challenging. Although there have been advances in preoperative imaging modalities, there is still a need for an accurate intraoperative guidance. Indocyanine green (ICG) is a new agent that has been used for intraoperative fluorescence imaging in a number of general surgical procedures. Its utility for parathyroid localization in humans has not been reported in the literature. Results. We report 3 patients who underwent reoperative neck surgery for primary hyperparathyroidism. Using a video-assisted technique with intraoperative ICG fluorescence imaging, the parathyroid glands were recognized and removed successfully in all cases. Surrounding soft tissue structures remained nonfluorescent, and could be distinguished from the parathyroid glands. Conclusions. This report suggests a potential utility of ICG imaging in intraoperative localization of parathyroid glands in reoperative neck surgery. Future work is necessary to assess its benefit for first-time parathyroid surgery.

Keywords
indocyanine green, ICG, hyperparathyroidism, parathyroid glands, fluorescence imaging

Introduction

Localization of parathyroid glands in primary hyperparathyroidism is important in minimizing dissection, shortening operative time, and enabling minimally invasive approaches. Despite advances in preoperative imaging, the sensitivity of sestamibi (MIBI) scans is around 50% and ultrasound 70% for primary hyperparathyroidism. Accurate localization is even more critical in reoperative surgery due to the presence of significant scar tissue in the neck.

Some modalities such as methylene blue (MB) dye injection and aminolevulinic acid (ALA) imaging have been described to aid in the identification of parathyroid glands. However, due to postoperative neurologic complications associated with MB, and requirement for an extensive photosensitization preparation for ALA, the use of these techniques has been restricted. Radioguided parathyroidectomy has also been used for intraoperative localization. However, due to the radiation exposure risk, the lack of reproducibility of results, and confusion with uptake from thyroid nodules, its use has been limited.

One evolving modality is indocyanine green (ICG) imaging, whose utility has been described in various surgical procedures including robotic cholecystectomies, laparoscopic cholecystectomies, colorectal resections, living-donor nephrectomies, kidney autotransplantation, inguino-iliac/obturatory lymph node dissection, and various oncologic procedures. However, its utility in reoperative parathyroidectomy is unknown. The aim of this report is to describe the utility of ICG imaging in reoperative parathyroid surgery.

Case Presentations

Case 1

All of the cases were performed as part of an institutional review board–approved prospective study evaluating the...
utility of intraoperative ICG imaging in endocrine surgical procedures. In the first case, a 68-year-old Caucasian male was found to have primary hyperparathyroidism when he was investigated for kidney stones and osteoporosis. His serum calcium was 11.6 mg/dL (normal range = 8.5-10.5 mg/dL), parathyroid (PTH) 119 pg/mL (normal range = 15-65 pg/mL), and phosphorus 3.5 mg/dL (normal range = 2.5-4.5 mg/dL). His 24-hour urine calcium was 268 mg (normal range = 100-300 mg/24 h), and a 24-hour urine creatinine of 1080 mg. He had a remote history of thyroid cancer (papillary and follicular) in 1977, which was treated with thyroidectomy modified radical neck dissection. On exam, he had incision scars in his neck from the previous surgical procedure. Surgeon-performed neck ultrasound showed the surgical absence of thyroid glands bilaterally, and a hypoechoic density in the right central neck, measuring 0.90 × 0.30 × 0.92 cm (Figure 1A). This structure was biopsied with fine-needle aspiration under ultrasound guidance. PTH assay from the biopsy was 10,978 pg/mL, and cytology confirmed the presence of parathyroid tissue. Sestamibi-iodine subtraction scan showed an uptake involving the same tissue in the right paratracheal region (Figure 1B). With these findings, he was consented for a focal parathyroid exploration using intraoperative ICG dye localization.

**Surgical Procedure.** The patient was placed supine on the operating table with the neck slightly extended and positioned on a beanbag. The procedure was carried out under general endotracheal anesthesia. After performing percutaneous ultrasound, a 5-cm incision was made approximately 1 to 2 cm above the sternal notch. The platysma was divided and the central neck was entered between the strap muscles.

Then, a video-assisted ICG imaging technique was used for parathyroid localization. The patient was injected with 5 mg of intravenous (IV) ICG. Using the Novadaq (Ontario, Canada) fluorescence imaging system, the parathyroid gland adenoma was recognized by its intense green fluorescence on video monitor. The gland was visualized within 2 minutes of injection, and the fluorescence persisted for 20 minutes (Figure 2). The surrounding structures, such as muscles and soft tissues, were much less fluorescent and the parathyroid adenoma could be easily distinguished. The patient was given a total of 10 mg of IV ICG, in 2 separate injections during the case. Under fluorescence imaging guidance, the right parathyroid adenoma measuring 1.1 × 1.0 × 0.8 cm was removed (Figure 3), part of which was cryopreserved. Frozen section revealed hypercellular parathyroid gland tissue.

Intraoperative intact PTH level decreased from a preexcision level of 119 pg/mL to 25 pg/mL, 10 minutes after excision. On postoperative day (POD) 1, serum calcium was 9.5 mg/dL, PTH was 25 pg/mL, and phosphorus was 3.5 mg/dL. He was discharged home uneventfully on POD 1. At 2 week follow-up her calcium was 9.3 mg/dL, PTH was 44 pg/mL, and phosphorus was 3.4 mg/dL.
Case 2

A 68-year-old Caucasian female presented with persistent primary hyperparathyroidism, after a failed 4-gland parathyroid exploration in 2005 at an outside institution. Her calcium and PTH levels did not normalize after her initial neck exploration involving removal of both lower parathyroid glands, which were normocellular on final pathology. She did not have any history of radiation exposure to her head and neck, or family history of endocrine disorders. Her past medical history was significant for fat malabsorption and celiac disease. When she presented to our clinic, her calcium was 10.9 mg/dL, PTH 107 pg/mL (normal range = 15 -65), ionized calcium 1.41 mmol/L (normal range = 1.08-1.30), phosphorus 2.1 mg/dL (normal range = 2.5-4.5 mg/dL), vitamin D$_{25}$-OH 27.8 ng/mL (normal range = 31.0-80.0), 24-hour calcium was 123 mg (normal range = 100-300 mg/24 h) with a creatinine of 899 mg. Her office ultrasound was negative for any parathyroid enlargement, but her sestamibi-iodine subtraction scan with IV contrast computed tomography (CT) showed an uptake around the suprasternal notch measuring 0.7 × 0.6 × 0.4 cm in size (Figure 4). She was consented for reoperative neck surgery using intraoperative ICG fluorescence imaging.

Surgical Procedure. The operation was performed with a 5-cm transverse neck incision. By staying in a lateral plane, the central neck was entered. At this point, video assistance was used for ICG parathyroid localization (Figure 5). The patient was initially given 5 mg of ICG, and using the same system, the fluorescence of the tissues was inspected. In 5 minutes, significant fluorescence was identified around the sternal notch, involving the thyro-thymic ligament (Figure 6). With further dissection, a 1.8 × 0.8 × 0.6 cm ectopic parathyroid adenoma was identified within the thymus and excised. This gland displayed a significantly higher intensity of fluorescence compared to the surrounding soft tissues. The patient was given a total of 8.75 mg of IV ICG, in 2 separate injections, during the whole case. A portion of the adenoma was cryopreserved. Frozen section showed hypercellular parathyroid within thymic tissue. Pre-excision intraoperative intact PTH level decreased from 182 to 49 pg/mL 10 minutes after excision. On POD 1, her calcium was 9.4 mg/dL, PTH was 7 pg/mL, and phosphorous was 4.0 mg/dL. She was discharged home uneventfully on POD 1. At 2-week follow-up her calcium was 9.3 mg/dL, PTH was 44 pg/mL, and phosphorus was 3.4 mg/dL.

Case 3

A 62-year-old Caucasian male presented with persistent primary hyperparathyroidism, after a failed unilateral...
after his initial neck exploration, where no parathyroid glands were identified but a left thyroid lobectomy was performed, which revealed microscopic papillary thyroid cancer in final pathology. He did not have any history of radiation exposure to her head and neck, or family history of endocrine disorders. His past medical history was significant for obesity, hypertension, diabetes mellitus, and obstructive sleep apnea. When he presented to our clinic, his calcium was 11.4 mg/dL, PTH 103.5 pg/mL (normal range = 15-65), phosphorus 2.5 mg/dL (normal range = 2.5-4.5 mg/dL), ionized calcium 1.56 mmol/L (normal range = 1.08-1.30), vitamin D$_{25}$-OH 20.9 ng/mL (normal range = 31.0-80.0), and 24-hour calcium was 506 mg (normal range = 100-300 mg/24 h).

Surgeon-performed neck ultrasound showed the surgical absence of thyroid gland on the left side, and revealed a hypoechoic density in the left lower neck, measuring 1.12 ×0.66 cm (Figure 7A). This structure was biopsied with fine-needle aspiration under ultrasound guidance. PTH assay from the biopsy was <60 pg/mL, and cytology was nondiagnostic. However, sestamibi-iodine subtraction scan with IV contrast CT showed an uptake in the left superior mediastinum, in a different location, measuring 1.5 × 1.4 × 0.9 cm in size (Figure 7B). His selective venous sampling also localized to the left lower neck. He was consented for reoperative neck surgery with possible sternal split using intraoperative ICG fluorescence imaging.

Surgical Procedure. The operation was performed with an 8-cm transverse neck incision. By staying in a lateral plane, the central neck was entered. After dissecting the left carotid artery and the soft tissues around the sternum, video assistance was used for ICG parathyroid localization. The patient

Figure 6. Ectopic parathyroid adenoma under room light (A), under white light (B), and under fluorescence showing the green ICG-9–induced fluorescence of the parathyroid adenoma (C).

Figure 7. (A) Preoperative ultrasound image showing a hypoechoic density in the left lower neck. (B) Tc-MIBI showing uptake in the left superior mediastinum, corresponding to the ultrasound images.
was initially given 5 mg of ICG and using the same system, the fluorescence of the tissues was inspected. In 5 minutes, significant fluorescence was identified around the left mediastinum (Figure 8). After meticulous dissection and sternotomy, a 3.0 × 2.0 × 1.5 cm ectopic parathyroid adenoma was identified and excised. This gland displayed a significantly higher intensity of fluorescence compared to the surrounding soft tissues. The patient was given a total of 8.75 mg of IV ICG, in 2 separate injections, during the whole case. A portion of the adenoma was cryopreserved. Frozen section showed hypercellular parathyroid tissue. Pre-excision intraoperative intact PTH level from left internal jugular vein decreased from 94 to 19 pg/mL 10 minutes after excision. On POD 1, his calcium was 8.5 mg/dL, PTH 10 pg/mL, and phosphorus 2.5 mg/dL. He was discharged home uneventfully on POD 1. At 2-week follow-up his calcium was 9.3 mg/dL, PTH was 38 pg/mL, and phosphorus was 4.3 mg/dL.

Discussion

This report describes a potential utility of ICG fluorescence imaging in parathyroid surgery. To our knowledge, it is the first human study to demonstrate the use of this imaging for intraoperative parathyroid localization. Despite the famous quote from Dr Doppman, “The best localization in parathyroid surgery is the localization of a good endocrine surgeon,”11 there are benefits of localizing studies in primary hyperparathyroidism. The identification of the abnormal glands early on during the exploration can reduce operative time, surgeon anxiety, and also enable the performance of focused explorations. The localization of abnormal parathyroid glands is even more important in reoperative neck surgery due to the presence of significant scar tissue. The 3 cases presented in this report are promising about the utility of this imaging modality for parathyroid surgery.

The advantages of ICG imaging compared to other modalities (MB, ALA, radioguidance) described for intraoperative parathyroid localization include its simplicity and the lack of postoperative neurologic dysfunction.

In this report, we used a video-assisted technique, where a laparoscope was used to detect the fluorescence of the ICG injection. The equipment used was designed for laparoscopic abdominal procedures and hence the laparoscope was longer than desired. A modification in the future would be the production of smaller cameras for neck surgery.

The timing and dosing of ICG administration are of utmost importance for a good visualization. For other operations, the suggested regimens include 4 mg given 15 minutes preoperatively for cholecystectomy and colorectal resection surgeries, and 5 mg given 20 minutes prior to lymphadenectomy surgeries.9 According to our experience, especially the thyroid being absent and away, injection of 3.75 to 8.75 mg during dissection seems to be adequate for reoperative parathyroid surgery. The parathyroid glands take up the dye within 2 minutes and may stay fluorescent up to 20 minutes.

The complications of ICG administration have been extensively studied. As the dye is excreted through the liver immediately via first-pass effect, ICG dye does not seem to have any significant toxic side effects. Rare anaphylactic or urticarial reactions have been reported in patients with or without history of allergy to iodides. In the largest study, the occurrence of these adverse events has...
been reported to be 0.00167% (4/240 000 cases); and in 34 years, 17 adverse reactions has been reported thus far. Since the ICG substance contains 5% of sodium iodine for solubility, the contraindications seem to be iodine allergy and renal insufficiency. Nevertheless, the anesthesia team should be ready to treat allergic reactions.

Suh et al have reported on the utility of ICG as a fluorescent agent for identifying parathyroid glands during thyroid surgery in 3 dogs. Their results have been similar to ours, as they reported that the peak intensity appeared at 50 seconds after injection, with the parathyroid glands losing their fluorescence, but remaining sufficiently fluorescent to be distinguishable.

Indocyanine green binds to plasma lipoproteins and has been used to show perfusion in various studies. We do not know the exact mechanism that is responsible for the parathyroid glands to take up the dye and demonstrate a fluorescent contrast compared to surrounding tissues. However, this may be related to the abundant blood supply of endocrine organs.

In conclusion, we describe a novel technique for video-assisted reoperative parathyroidectomy that may help in identification of the parathyroid pathology in PHP. Our ongoing studies will help understand its utility for first-time parathyroid explorations.

Author Contributions
Study concept and design: Sara Sound, Alexis Okoh, Hakan Yigitbas, Pinar Yazici, Eren Berber
Acquisition of data: Sara Sound, Alexis Okoh, Hakan Yigitbas, Pinar Yazici
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Study supervision: Eren Berber.

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