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Review Article

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Indocyanine Green (ICG) / Near-infrared Fluorescent (NIRF) Imaging and Its Applications in Pediatric Surgery

Aydın Şencan, PhD

Manisa Celal Bayar University, Faculty of Medicine, Department of Pediatric Surgery, Manisa-TÜRKİYE

ABSTRACT

Recently, fluorescent guided surgical procedures have been increasingly used in pediatric surgery and urology. This method is based on the principle that fluorochrome molecules produce radiation at a different wavelength when exposed to laser or near-infrared light of a certain wavelength. Thus, both the vascularization - perfusion of the tissues can be evaluated and the contrast difference in the tissue allows tissues to be distinguished. Today, fluorescent guided surgical procedures are performed with indocyanine green (ICG) and near-infrared fluorescence (NIRF) imaging systems. This technology is used for various purposes such as determining the intersegmental planes of lungs during the operation, imaging the bile ducts, determining the borders of tumors, metastases, and ischemic tissue, evaluating the perfusion of the anastomotic lines. Many surgical procedures are performed more safely and quickly owing to ICG/NIRF imaging.

The aim of this article is to summarize the basic features of the ICG/NIRF imaging method, use in pediatric surgery and urology, advantages, limitations, and our experimental experience on this subject in the light of the literature.

Key words: indocyanine green, near-infrared, florescence, pediatric surgery, pediatric urology

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Aydın Şencan
Manisa Celal Bayar University, Faculty of Medicine, Department of Pediatric Surgery, Manisa-TÜRKİYE

aydin.sencan@yahoo.com.tr
ORCID: 0000-0002-8892-4907

Introduction

When fluorescent molecules are excited by laser or near-infrared, they absorb electromagnetic energy of a certain wavelength and then emit some of this energy at a different wavelength. Thus, a form of radiation is formed (fluorescence) that allows substances to be distinguished. Indocyanine green (ICG) molecule is a water-soluble tricarbocyanine dye that fluoresces when excited with near-infrared (NIR) light [1]. After excitation, the electrons of fluorochrome molecules move to a higher energy level and while returning to their former level, the energy is emitted in the form of photons and becomes visible at a certain wavelength [2] (Figure 1). ICG was first developed for painting photographs during World War II, and in 1957 the Mayo Clinic used ICG in liver and heart function testing. The use of the drug was approved by the FDA in 1959 [3].

ICG/NIR fluorescence imaging requires a special camera that emits NIR light at a wavelength of 600-900 nm and a special optical system that detects the light emitted from the ICG. The ICG is excited at a wavelength of 778-806 nm and the fluorescence emission reaches a maximum at 832 nm. At this level, the tissue diffusion depth is approximately 15 mm [4,5]. The radiation detected by the optic is transmitted to the monitor with a special software, providing a high-resolution image that can distinguish the tissues [3,6]. By integrating firefly software into the ICG/NIRF technology, the system can be controlled by the robot console [7,8].

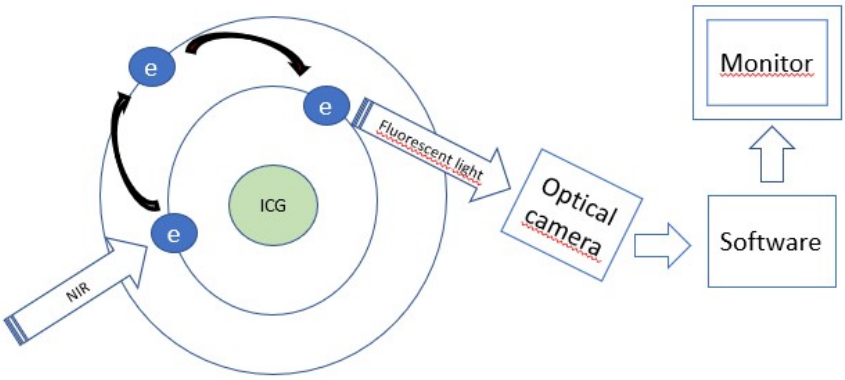

Figure 1. As a result of the near-infrared excitation of the indocyanine green molecule, the fluorescent luminescence emerging during the movement of the orbiting electrons and the transfer of the luminescence captured by a special optical camera to the monitor.

Preparation, administration routes and dosage of ICG:

The current form of ICG is in powder form. Reconstitution should be done with distilled water. There is a risk of precipitation when used with saline or Ringer's Lactate solution. Some sources recommend dilution with albumin if it is to be used for the identification of tumors draining into the sentinel lymph node. ICG bounded to albumin accumulates in the first lymph node and a better image is provided [9].

ICG can be given intravenously, subcutaneously, or directly into the tissue. The route of administration of ICG varies according to the target organ to be imaged. It is administered intravenously to visualize tissue vascularization, to determine the boundaries of ischemic or hypoxic tissues, or to determine the anatomical boundaries of tumors. ICG remains in the vascular system by binding to plasma proteins when administered intravenously. The plasma half-life of ICG is 3-5 minutes for the first 15-20 minutes after injection and is excreted unchanged from the body via the biliary tract [3,10]. If the sentinel lymph node detection or lymphatic mapping is intended, it is administered directly into the tissue. In this case, ICG binds to lipoproteins and reaches the nearest lymph node within minutes and regional lymph nodes within 1-2 hours [9]. If imaging of a structure with lumen such as the ureter is desired, the images are obtained by injecting diluted ICG into a catheter to be inserted into the ureter [9,11–13].

There is no fully standardized dose of ICG yet. There are dose applications ranging from 0.5 to 5 mg/kg in various ICG/NIRF imaging studies in the literature. The dose of ICG is usually expressed as 2 mg/kg. It is recommended that the maximum dose should not exceed 2 mg/kg in children. It has been reported that doses of 80 mg/kg and above are lethal in rats [9].

Side effects of ICG are very rare. It can be used safely even in newborn babies [14]. In a study conducted with 100 pediatric patients under 12 years of age, no side effects of ICG were observed on hemodynamics and respiratory system [15]. However, it may cause allergic reactions (sodium iodine allergy) at a rate of 0.05% due to its content. Therefore, its use is not recommended in patients with hyperthyroidism and autonomic triode adenoma [16].

Clinical applications and advantages of indocyanine green/near-infrared fluorescent (ICG/NIRF) imaging

ICG/NIRF imaging is important in the evaluation of vital anatomical structures in abdominal surgery, especially in colorectal, esophageal, gastric, and bariatric surgery, and determining the vascularity or perfusion level of the tissue or anastomosis line. It can also be used to determine the boundaries of bowel ischemia due to necrotizing enterocolitis or other pathologies. Recently, it has been increasingly used in bile duct surgery [3,6,7,9,10,14,17,18]. In a meta-analysis, 4 studies (45 patients, 18 newborns) using ICG/NIRF imaging in pediatric gastrointestinal system surgery were reviewed. In this study, It was reported that ICG/NIRF imaging was more useful than the conventional method in determining the blood flow of the anastomotic line and bowel resection margins and it was also emphasized that ICG/NIRF imaging can be used safely in newborns. The authors observed subcutaneous dye retention which disappeared in 2 weeks in only one newborn as a complication [14].

The unchanged biliary excretion of ICG enables real-time visualization of the extrahepatic bile ducts. Intraoperative real-time imaging of structures such as the common bile duct and cystic duct makes the operation safer, especially when performing cholecystectomy in obese patients [17,18]. In fluorescent cholangiography, images obtained by superimposing fluorescent light on standard white light (RUBINA technology) provide great convenience to the surgeon in identifying anatomical variations [19]. ICG/NIRF imaging is also useful in determining the level of micro bile ducts that show bile flow in the hilar region in patients with biliary atresia [3,20]. In a study, it was shown that open micro bile ducts can be better determined with ICG/NIRF in patients with biliary atresia. In this study, it was determined that bowel anastomosis make to the porta hepatis including the open micro bile ducts, decreased the blood bilirubin levels significantly more than the control group [20].

ICG/NIRF imaging provides convenience to the surgeon in oncological surgery, especially in the identification of tumors and lymphomas located in the liver, retroperitoneum, and in the detection of metastases. In addition, this technique is also used in clinical practice for the detection of sentinel lymph nodes and lymphatic mapping in malignant tumors [3,21]. The increase in vascular permeability and the disruption of lymphatic drainage in tumors cause stasis of ICG in the tumor tissue and thus the tumor tissue can be separated from the healthy tissues more easily [21]. ICG/NIRF imaging is also effective in identifying nodules 1 cm below the pleural surface of the lung. For this procedure, it is sufficient to inject ICG directly around the lesion [21]. Recently, it has been reported that ICG/NIRF imaging is useful in determining the boundaries of pediatric renal tumors. In a study, renal tumors have been localized by ICG/NIRF in eight pediatric patients and a nephron-sparing surgical procedure was performed successfully. In this study, the authors observed that the normal kidney gave increased fluorescence signal (inverse signal pattern) compared to tumor-containing areas [22].

ICG/NIRF imaging can also be used to determine intersegmental planes in thoracic surgery and leak points in ductus thoracic injuries [23,24]. In a study, it was reported that in 10 newborn patients with chylothorax, in the ICG-guided thoracoscopic intervention, the leak point was clearly detected and primarily sutured, and the patients were successfully treated [24].

In recent years, ICG/NIRF imaging has also been widely used in the field of pediatric urology. It has been reported to be particularly useful in the evaluation of tissue blood supply and perfusion in duplex kidney surgery, varicocele (imaging of enlarged vessels), and testicular torsion [3,6,10–13].

ICG/NIRF imaging is a good option for determining the boundaries of functional and non-functional kidney poles in patients scheduled for partial nephrectomy.

First, ICG is given iv to evaluate the hilar vessels of the kidney and the vascular structures associated with the non-functioning kidney. After ligation of the vascular structures of the non-functioning kidney, ICG is given again as bolus and iv. Thus, the boundaries of the perfused functioning kidney and the non-perfused non-functioning kidney become clearly visible. This ICG/NIRF images provide great convenience to the surgeon during the operation [6,13]. Esposito et al. have performed laparoscopic partial nephrectomy in 22 children with dysfunctional duplex kidneys. ICG/NIRF imaging was used in 12 of these patients while standard technique was used in the other10 patients, and the results have been compared. The authors emphasized that the operative time was shorter in the ICG/NIRF group, the postoperative early residual renal cyst was less developed, and there was no complication (The authors have observed one surgical complication in the standard technique [13].

ICG/NIRF imaging can be used in varicocele surgeries, especially in making lymphatics visible (varicocele surgery that preserve lymphatics) by injecting ICG as a single dose directly into the testis. The fluorescence starts within 20-40 seconds after the injection and keeps on about 15 minutes. ICG is superior to isosulfan blue in varicocele surgery. Because it is technically more difficult to inject isosulfan blue into dartos, and a blue color may remain in the scrotum for several days after administration, and the patient's urine may be blue. If ICG is given iv, artery and veins of the testis can also be determined according to the sequence of imaging. This provides an advantage in varicocele surgeries which protects the testicular artery [3]. Esposito et al. applied ICG directly into the testis in 30 men with varicocele who underwent the laparoscopic Palomo technique and reported that ICG/NIRF imaging guided varicocelectomy was successful in preserving the lymphatic ducts [6]. Later, the same researchers reported that they performed robotic varicocele surgery that preserved lymphatics under the guidance of ICG/NIRF [7].

Rarely, ureteral injuries may occur during colorectal surgical procedures. ICG/NIRF imaging can be used to prevent ureteral injury during such major interventions. A ureteral catheter filled with diluted ICG is inserted into the ureter with the aid of a cystoscope and the tip of the catheter is closed. The ureter becomes visible with the NIR camera due to the fluorescence emitted by the ICG inside the catheter so, the risk of injuring the ureters during the operation is prevented [2,9].

We think that ICG/NIRF imaging may also be useful in the management of testicular torsion, which has not been described in the literature before. To confirm this hypothesis, we evaluated tissue blood supply and perfusion with ICG/NIRF imaging at the 4th hour of torsion and reperfusion in an experimental rat testicular ischemia-reperfusion model [25]. While ICG/NIRF images did not show blood flow and tissue perfusion during torsion (Figure 2), tissue perfusion partially returned after detorsion and at the 4th hour of reperfusion [25]. We think that intraoperative ICG/NIRF imaging can be used in clinical practice in cases with testicular torsion and will help the surgeon to decide on orchiopexy or orchiectomy. The saving of the intraoperative ICG/NIRF images especially in forensic cases may be important because of it is evidence of perfusion and vascularization in testicular torsion.

ICG/NIRF imaging provides a great contribution to the surgeon when intraoperative evaluation of tissue perfusion is required. For example, in pathologies that may result in severe ischemic necrosis of the intestine,

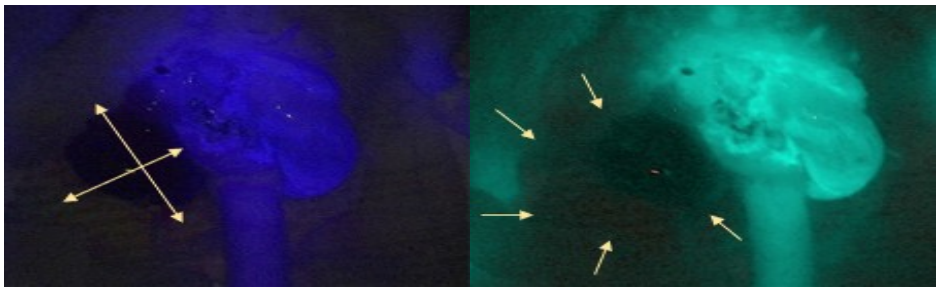

Figure 2. Two different modes of ICG/NIRF image of torsioned testis in an experimental animal (rat). It is seen that there is no blood supply and perfusion in the torsioned testicles (Arrows indicate the borders of the torsioned testis).

such as necrotizing enterocolitis, it shows the ischemic borders of the tissue more clearly, and the surgeon decides more accurately on the resection boundaries of the intestine.

Intraoperative evaluation of the perfusion of the anastomotic suture line in esophageal replacement surgery may change the management of the operation. Intraoperative evaluation of the perfusion of the upper and lower anastomotic suture lines is important, especially in colon replacement surgery. Another pathology that ICG/NIRF imaging will contribute to the surgeon is testicular torsion. The evaluation of testicular tissue vascularization and perfusion after testicular detorsion may facilitate the surgeon to decide on orchiopexy or orchiectomy [3,9,14,26,27].

In an experimental study in which we performed open and robotic augmentation ileo-cystoplasty in pigs, we evaluated the tissue perfusion of the ileo-cystoplasty anastomosis line with ICG/NIRF imaging and concluded that open or laparoscopic assisted robotic operation did not change the thickness of the ischemic zone in the anastomosis line. In addition, the formation of ileo-cystoplasty by suturing a single layer or double layer did not make a statistical difference in the ischemic zone at the anastomosis line. This study is important in terms of showing that ICG/NIRF imaging is applicable and useful in evaluating the blood supply of the anastomotic line in complicated reconstructive surgeries (Figure 3) [26].

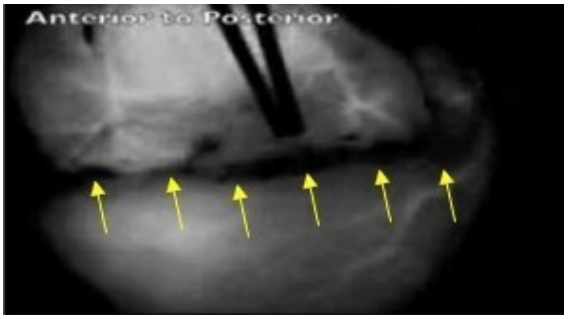

Figure 3. The evaluation of blood supply and perfusion of the ileo-cystoplasty anastomotic line with ICG/NIRF imaging in a pig who underwent a monolayer bladder-to-bowel anastomosis with robot-assisted laparoscopic surgery (Arrows indicate the non-perfused anastomotic line).

In another experimental study we conducted in pigs, after excising the extra hepatic bile ducts, we created a duodenal conduit with the help of a stapler and anastomosed the new duodenal conduit to the porta-hepatis. We then evaluated the perfusion of the conduit with ICG/NIRF imaging. Well-perfused areas of the conduit were seen in white color, while poorly perfused areas were observed in black color on monitor. In conclusion, this study showed that ICG/NIRF imaging is an effective method for evaluating intraoperative tissue perfusion (Fig. 4) [27].

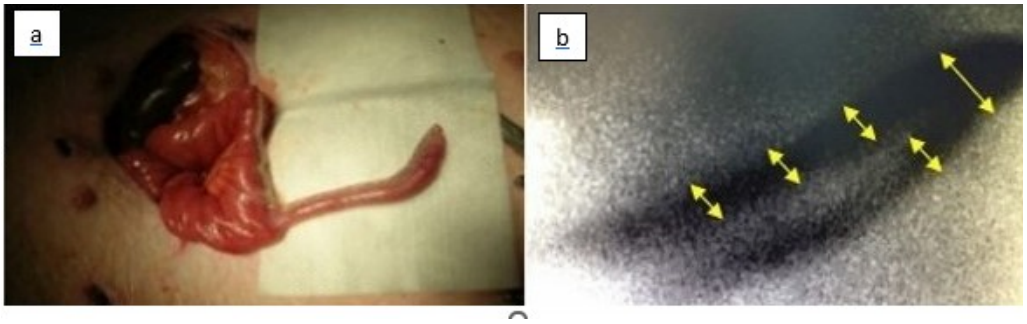

Figure 4. The conduit (a) created from the duodenum of an experimental animal (pig) and ICG/NIRF image of the conduit in black and white mode. The black areas of the conduit indicate regions where the duodenal conduit is not well perfused (Arrows indicate boundaries of non-perfused areas) (b).

Limitations of ICG/NIRF imaging:

ICG/NIRF imaging may be subjective, especially in the evaluation of tissue perfusion because of the intensity of the emitted fluorescent light changes depending on time, and it may not be possible to have a complete idea about the level of tissue perfusion failure. To partially solve this problem, there are some software that perform Fluorescent-Time Curve (FTC) analysis. In addition, patient-specific systemic perfusion variables such as blood pressure and cardiac output may complicate the interpretation of the images [28–30].

The amount of ICG dose given can also affect the brightness level of the images. The non-standardization of the distance between the target organ and the optical camera during ICG/NIRF imaging may lead to misleading results, especially in evaluating tissue perfusion. Moreover, ICG/NIRF imaging technology requires specialized equipment [3, 28–30].

In conclusion, ICG/NIRF imaging is a technology that is becoming increasingly popular in both open and minimally invasive surgical procedures (laparoscopic or robotic) and helps the surgeon in the management of the operation. ICG/NIRF imaging technology is safe, simple, and easy to administer. There is direct evidence that ICG/NIRF imaging is highly beneficial in determining the boundaries of anatomical structures, the evaluation of tissue vascularization and perfusion, and the determining localization of tumors and sentinel lymph nodes. ICG/NIRF imaging technology shortens surgery time and helps protecting vital structures during surgery. Our experimental studies have shown that ICG/NIRF imaging is useful in determining real-time tissue perfusion and ischemic region at the anastomotic line. In addition, our study has showed that ICG/NIRF imaging can assist the surgeon in deciding whether to make orchiopexy or orchiectomy in the testicular torsion model.

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Conflict of Interest

The author declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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