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Indocyanine green: The guide to safer and more effective surgery

Fransvea P *et al.* Indocyanine green in abdominal surgery

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Abstract

In this editorial we comment on the article by Kalayarasan and co-workers published in the recent issue of the *World Journal of Gastrointestinal Surgery*. The authors present an interesting review on the use of indocyanine green fluorescence in different aspects of abdominal surgery. They also highlight future perspectives of the use of indocyanine green in mini-invasive surgery.

Indocyanine green, used for fluorescence imaging, has been approved by the Food and Drug Administration and is safe for use in humans. It can be administered intravenously or intra-arterially.

Since its advent, there have been several advancements in the applications of indocyanine green, especially in the surgical field, such as intraoperative mapping and biopsy of sentinel lymph node, measurement of hepatic function prior to resection, in neurosurgical cases to detect vascular anomalies, in cardiovascular cases for patency and assessment of vascular abnormalities, in predicting healing following amputations, in helping visualization of hepatobiliary anatomy and blood vessels, in reconstructive surgery, to assess flap viability and for the evaluation of tissue perfusion following major trauma and burns. For these reasons, the intraoperative use of indocyanine green has become common in a variety of surgical specialties and transplant surgery.

Colorectal surgery has just lately begun to adopt this technique, particularly for perfusion visualization to prevent anastomotic leakage. The regular use of indocyanine green coupled with fluorescence angiography has recently been proposed as a feasible tool to help improve patient outcomes. Using the best available data, it has been shown that routine use of indocyanine green in colorectal surgery reduces the rates of anastomotic leak.

The use of indocyanine green is proven to be safe, feasible, and effective in both elective and emergency scenarios. However, additional robust evidence from larger-scale, high-quality studies is essential before incorporating indocyanine green guided surgery into standard practice.

Key Words: Indocyanine green; Colorectal surgery; Fluorescence-guided surgery; Gastrointestinal surgery; Hepato-biliary surgery; Pancreatic surgery; Surgical oncology

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Core Tip: Indocyanine green is a sterile, anionic, water-soluble molecule, which was approved for clinical use in 1959 by the Food and Drug Administration. After intravenous injection, indocyanine green rapidly bounds to plasma lipoproteins. When injected outside blood vessels (e.g., into the normal tissue close to tumors), indocyanine green binds to proteins, reaching the nearest lymph node usually within 15 minutes. The intraoperative usage of indocyanine green has become common in a variety of surgical specialties and transplant surgery. By observing the signal using a fluorescence imaging video system, surgeons can visualize and assess organ perfusion intraoperatively while making adjustments in real-time.

INTRODUCTION

"In brightest day, in blackest night, no evil shall escape my sight. Let those who worship evil's might. Beware my power – Green Lantern's light!" so recited the oath of Green Lantern, a comic book superhero from the 1940s.^[1] And indeed, indocyanine green is an effective light that facilitates surgical work.

One of the cardinal rules of surgery is "never cut what you can't see", and, when sight does not discriminate, other senses often come to the rescue. In minimally invasive surgery, the absence of direct contact and two-dimensional vision constantly put this axiom to the test. The identification of structures that must be removed (tumor tissue, lymph nodes, *etc.*) from others that must be spared (nerves, vessels, bile ducts, *etc.*) is of fundamental importance in daily surgical practice. Sometimes, even with full sensorial assistance, this differentiation is extremely difficult, hence the constant search for diagnostic and imaging systems that can provide useful information in real time and guide the surgeon in what we can define as "augmented reality". ² The introduction of fluorescence-guided surgery for breast cancer sentinel node biopsy using indocyanine green by Kitai *et al*^[2] has ushered in a new era in general surgery, marked by image-guided procedures. Over the last 5 years we have been witnessing its re-evaluation, thanks also to its role in surgery, where it represents the anatomical navigation system with the highest potential.^[3]

Fluorescence is based on the following principle: a contrast medium (fluorophore), injected intravenously, submucosally, subserously or intradermally, depending on the purpose of the study, following the absorption of a light source at 700-900 nm, becomes fluorescent emitting radiation at a wavelength of approximately 800 nm; these are captured and filtered through a series of filters and a dedicated optical system, allowing only the highlighted image to be displayed. Applied in surgery, this principle leads to the visualization of anatomical structures that are otherwise not visible when the light source has a wavelength that falls within the visible light spectrum (390-700 nm).

Indocyanine green, developed by Kodak in 1955 for photographic studies and approved just a year later for medical purposes, compared to methylene blue and sodium fluorescein, the other two ⁶ fluorescent contrast agents currently approved by the Food

and Drug Administration and the European Medicines Agency, is the one with the best chemical-physical characteristics for use in fluorescence-guided surgery. Indocyanine green is a water-soluble tri-carbocyanine dye extensively utilized for evaluating cardiac output, hepatic function, liver blood flow, and performing ophthalmic angiography, demonstrating a high level of safety, with rare adverse events occurring at dosages below 0.5 mg/kg. Following intravenous injection, indocyanine green promptly binds to plasma lipoproteins, exhibiting a plasma half-life of 3–5 minutes and biliary excretion within 15–20 minutes. When exposed to light with a wavelength of 800–810 nm in the near-infrared spectrum, indocyanine green becomes fluorescent and can be detected with specific cameras. This technique facilitates the real-time and precise identification of anatomical structures and allows for the assessment of local blood flow during surgical procedures.^[4, 5] Augmented reality, enhancing conventional human senses by accurately locating anatomical structures and providing real-time functional information based on indocyanine green's fluorescent properties, holds significant potential as a transformative tool in the field of surgery.^[6-10]

One of the characteristics of near-infrared fluorescence is the ability to penetrate deeply into tissues, without causing cellular damage; furthermore, unlike ultraviolet light, it does not present natural background fluorescence. At present the penetration power is approximately 1-2 cm, but, with the help of more powerful fluorophores (with a higher "contrast-to-background ratio") and special filters, this value could be increased. In addition to the Firefly Imaging System, there are other devices for near-infrared fluorescence, which differ in specific technical characteristics and the use of different light sources. Examples of systems for open surgery are the Photodynamic Eye, used in many Japanese reports, FLARE (from which m-FLARE was later deviated, an experimental model for minimally invasive surgery), developed in Boston, the HyperEye Medical System - HEMS, designed by Sato's Japanese team for the evaluation of grafts in cardiovascular surgery, the French Fluobeam 800, the American FDPM Imager and the German IC-View by Pulsion Medical. In minimally invasive surgery the most widespread model is the PINPOINT, based on SPY Fluorescence Imaging

technology, which allows both pure fluorescence visualization and one superimposed on natural light. Other companies have instead created prototypes that derive from already existing models, for example Olympus proposes a variation of the well-known Viscera Laparoscopic system for near-infrared fluorescence, while Storz has modified its Photodynamic Diagnostic D-Light. Of the aforementioned, only Photodynamic Eye, PINPOINT, Fluobeam, IC-View and the D-Light P system are currently on the market.^[12-16]

In this issue of *World Journal of Gastrointestinal Surgery*, Kalayarasan and co-workers^[9] present an interesting review on the use of indocyanine green fluorescence in different aspects of gastrointestinal, hepatobiliary, and pancreatic surgery. The authors' goal is to write a narrative review that outlines previous contributions, limitations, and research opportunities for future studies in gastrointestinal subspecialties. We agree with the authors that the findings of the present review would be useful for scholars and practitioners to explore and advance this exciting field of abdominal surgery.

PROS AND CONS OF USE IN ELECTIVE ABDOMINAL SURGERY

There are multiple applications of indocyanine green in gastrointestinal surgery. Indocyanine green⁴ fluorescence imaging is a promising technique in minimally invasive gastric cancer surgery.^[7, 17] Intraoperative fluorescence angiography with indocyanine green is feasible and safe and allows to assess gastric perfusion before performing upper gastrointestinal anastomoses.^[18-20] The evaluation of tissue perfusion reduces the risk of gastro-jejunal or esophago-jejunal anastomotic leakage and duodenal dehiscence, which are worrisome complications of oncological gastric surgery^[21], negatively impacting the short- and long-term prognosis of patients.

Several studies demonstrated the usefulness of indocyanine green fluorescence lymphography in performing⁴ sentinel lymph node mapping associated to endoscopic or laparoscopic resection of early gastric cancer, and lymphatic mapping in order to simplify lymphadenectomy during minimally invasive surgery and increase the number of harvested lymph nodes.^[22, 23] It is useful to remember that lymph nodes

dissection is a fundamental curative aspect in the surgical treatment of advanced gastric cancer.^[24, 25] Furthermore, some studies reported the possibility to identify gastric cancer peritoneal carcinomatosis through antibody or liposomal labelled indocyanine green.^[26] The applications of indocyanine green in colorectal surgery are significant and continually advancing. Its uses include perfusion assessment, intraoperative visualization of the ureter, identification of sentinel nodes and visualization of lymphatic drainage. It has also been used for localizing and assessing peritoneal and hepatic metastases.^[27-29]

A useful application of indocyanine green for perfusion assessment is in the evaluation of anastomotic leakage. Anastomotic leak rates vary depending on the type of surgery. The incidence of this fearful postoperative complication can reach up to 19%. There are multiple factors that contribute to anastomotic dehiscence in colorectal surgery.^[30] In any type of gastrointestinal surgery, however, for an appropriate healing process to occur it is necessary that the anastomosis, be it between the esophagus and jejunum, gastrojejunal, entero-enteric or colorectal, is well vascularized and free of tension.^[31] Indocyanine green can be used to intraoperatively assess anastomotic perfusion.^[27, 32, 33] Traditionally, the correct preparation of an anastomosis is based on the absence of tension, a correct surgical technique and adequate tissue perfusion, which is evaluated by the surgeon on weak subjective parameters such as active bleeding from the section margins, manual perception of arterial flow at the mesenteric level and the absence of color change of the viscera. Evaluating these indicators can be misleading.^[34-37] For example, a cyanotic appearance of the bowel may be due to a transient venous insufficiency which does not compromise the vitality of the intestine, while an early arterial occlusion may be colorless; just as the absence of mesenteric pulsation may be due to a spasm or temporary hypoperfusion while an intestine already in ischemic involution may still present peristaltic activity. As Karliczek *et al* demonstrated for the first time in a prospective study, the operator's clinical judgment has low sensitivity, low specificity and diagnostic accuracy is not associated with the degree of preparation;^[37] in fact, there is no significant difference between the predictive

ability of the teacher and the student. Furthermore, if it is true that the greater the number of risk factors the greater the probability of developing an anastomotic leakage, the absence of the aforementioned does not exclude this eventuality *a priori*. An example of the surgeon's lack of predictive power is the attribution of a lower risk to patients with a protective ileostomy when it is proven that the aforementioned does not reduce the probability.^[30]

The percentages of anastomotic leakage described are high, especially considering the consequences this entails, so much so that they deserve the title of "the most painful and painful complication of gastrointestinal surgery".^[34] In this category of patients, morbidity, the probability of being subjected to a surgical procedure again, the length of hospitalization, 30-day and long-term mortality, and worse anorectal compliance are significantly higher. If you look at the economic side, Turrentine and co-workers estimated that a surgical hospitalization complicated by anastomotic leakage costs double that of a standard hospitalization for the same procedure.^[38] Unfortunately, despite almost a century of studies on risk factors and surgical techniques, the pathogenesis of anastomotic dehiscence is not yet fully understood. It certainly has a multifactorial etiology, attributable partly to the patient, partly to the surgeon and partly to the disease (which led to the operation).^[34]

³ Evidence for the impact of intraoperative fluorescence angiography in reducing anastomotic leakage after colorectal anastomosis is growing. The procedure provides information on tissue perfusion that may help prevent the leakage. Intravenous indocyanine green is safe with no related adverse events observed in the literature.

However, several studies have been carried out, especially in recent years, on fluorescence. This technique presents all the characteristics required by an ideal test for the evaluation of intestinal viability: availability, manageability, easy use, accuracy, high sensitivity and specificity, objectivity, reproducibility and cost-effectiveness. Kudzus and co-worker in 2010 presented the first retrospective study on the use of fluorescence in colorectal surgery in humans. Using IC-View, the authors compare over four hundred patients undergoing resection for neoplastic disease in the period 1998-

2008, noting a reduction in the reoperation rate for anastomotic leakage of 4%. The advantage of near-infrared fluorescence is especially noticeable when analyzing the most susceptible subgroups, reporting a reduction in the risk of surgical revision of 64% in patients over seventy undergoing elective surgery, with a significant reduction in the average hospital stay.^[35] Sherwinter *et al* suggests instead a transanal approach for the evaluation of the viability of the colonic, rectal and perianastomotic mucosa. Using an introducer of his own invention, following intravenous administration of 2.5 mg of indocyanine green, he uses the Pinpoint laparoscopic system to perform intraoperative sigmoidoscopy in twenty patients undergoing laparoscopic anterior rectal resection for benign and malignant pathology.^[39, 40] Out of four who present anomalous intestinal perfusion under near-infrared fluorescence, only in two cases is a protective ileostomy performed (in one case because the anastomosis is ultralow and in another because it presents clinical characteristics "in white light" compatible with a picture of hypovascularization). While the latter do not present complications during follow-up, the two cases considered "well vascularized" in white light show signs and symptoms of anastomotic leak and are treated with CT-guided drainage for a perianastomotic collection. Although the analysis is based on qualitative assessments and the sample is small, the author agrees that the Pinpoint represents a rapid, safe and useful system for the transanal evaluation of perianastomotic mucosal perfusion.^[40]

The potential of fluorescence as a diagnostic means in the evaluation of tissue perfusion in minimally invasive surgery is also underlined by Carus and Dammer, who, reporting an initial experience of forty-nine procedures (45 colorectal anastomoses and 4 sleeve gastrectomy), underlines how in the case of near-infrared fluorescence not convincing that resection of the hypoperfused area is necessary.^[41] Of note is the PILLAR II study,^[42] which evaluates the experience of eleven different american centers in the use of the Pinpoint system in the choice of the proximal section line and in the endoscopic evaluation of the perianastomotic mucosa. Of 147 patients enrolled, 10 (6.8%) underwent a revision of the section margin or anastomosis based on the data provided by near infrared fluorescence; of these none subsequently presented signs or symptoms

of anastomotic leakage. In a patient, whose anastomosis presented characteristics of dubious vascularization in white light, the transanal fluorescence control, with demonstration of adequate perfusion, led the operator not to perform a “protective” stoma, without confirmation during the follow-up of anastomotic complications. The overall anastomotic leakage rate was 1.4%, lower than the average of the values reported in the literature. The doses of indocyanine green administered (varying between 3.5 and 7.5 mg) also differ from other studies.^[42]

The ever-increasing diffusion and usefulness of near-infrared fluorescence is confirmed by the study by Watanabe *et al*,^[43] who, to demonstrate the existence of cases in which there is no anastomosis between the marginal arteries at the level of the rectosigmoid junction, uses fluorescence to identify the optimal section point in all laparoscopic colorectal surgery procedures (119 patients). Spinoglio *et al*^[44] reports the routine use of near infrared fluorescence for the evaluation of tissue perfusion in 128 robotic multiport colorectal resections for benign and malignant pathology. In a series that includes 51 right hemicolectomies, 39 Low and ultra-low rectal resections, 32 Left hemicolectomies and 6 segmental resections of the left flexure, he describes a reliability of the Firefly system of 100% and an anastomotic leakage rate of 0.8%. Degett *et al*^[45] in their analysis of 916 patients demonstrated that angiography with indocyanine green was associated with a reduced risk of anastomotic leakage of 3.3% compared with standard intraoperative methods (8.5%, $P = 0.005$). Blanco-Colino *et al*^[46] showed that fluorescence angiography significantly reduced (OR 0.34; 95% CI 0.16-0.74; $P = 0.006$) the rate of anastomotic leakage in patients undergoing surgery for colorectal cancer.

³ The use of indocyanine green fluorescence angiography instead of standard intraoperative methods to assess anastomotic blood perfusion in colorectal surgery leads to a significant reduction in anastomotic leakage, especially in patients with low or ultra-low rectal resection.^[47-49] A primary limitation of this approach is its subjective nature. To mitigate this concern, recent studies have sought to address it by incorporating software that assesses saturation of the indocyanine green.^[34, 49, 50] However, in order to identify the optimal software for perfusion assessment and to

obtain parameters that are validated, quantifiable and reproducible, further researches on larger and more homogeneous patient populations are necessary.

Regarding hepatobiliary surgery, nowadays, it is crucial in the execution of anatomic liver resections to accurately identify the boundaries of liver segments.^[51-53] Traditionally, hepatic veins have been considered essential for defining these segments, and their mapping is often performed through intraoperative ultrasonography. However, recent emphasis by some authors underscores that major hepatic veins alone are insufficient for guiding anatomic resections due to the three-dimensional irregular shape of liver segments. In this context, the use of indocyanine green fluorescence is emerging as a highly promising navigation tool during liver surgery. It enables real-time three-dimensional identification of both liver neoplasms and segmental boundaries. Moreover, when integrated with preoperative 3D reconstruction and intraoperative ultrasound, it serves as a robust real-time navigation tool, significantly enhancing the precision of liver resections.

Nevertheless, there are limitations in the use of indocyanine green fluorescence in liver surgery. These include a limited penetration depth and reduced reliability in patients with chronic liver disease.^[54-56]

In pancreatic surgery, after intravenous administration, indocyanine green can be rapidly and easily identified in the pancreas when exposed to near-infrared light.^[57-59] This heightened visibility provides a distinct contrast to the organ, especially in comparison to a necrotic tumor with insufficient blood perfusion, such as a solid pseudopapillary neoplasm.

Few studies have considered indocyanine based lymph node navigation in pancreatic cancers, which have extremely rich and complex lymph node spread patterns. However, to the current state of knowledge the clinical usefulness of this strategy in pancreatic surgery cannot be assessed.^[58]

An accurate localization of pancreatic tumors is mandatory in minimally invasive procedures and indocyanine green has been employed to pinpoint an intraoperative target, specifically a hypervascularized lesion within the pancreas, representing a

particularly challenging aspect of the surgical procedure.^[60, 61] Interestingly, in a small series of pancreatic neuroendocrine tumors a clear affinity of indocyanine green for neuroendocrine neoplastic cells have been demonstrated.^[62] Moreover, in a study of Oba *et al*^[63], intraoperative indocyanine green was used in combination with ultrasounds to identify radiologically occult liver metastases and other occult metastases in high-risk patients. Furthermore, indocyanine green may be also useful to detect perfusion of the pancreatic remnant in the case of middle segment-preserving pancreatectomy.^[61]

An important issue pertains to the complexity and costs of this technology. A positive feature is that the required training is minimal. The learning curve is extremely rapid. The highest costs are related to the near-infrared fluorescence camera system with appropriate optical devices. The speed with which technological changes and upgrades are occurring and reducing costs make it likely that within the next 5 years, most operating rooms will be equipped with the technology necessary to visualize indocyanine green fluorescence. Once the near-infrared fluorescence camera system is available in a hospital, the additional cost of each surgical procedure using fluorescence imaging will be relatively limited.^[64, 65]

ROLE OF INDOCYANINE GREEN IN EMERGENCY SURGERY

Even if the topic goes beyond the present review^[9], we cannot forget the role of indocyanine green fluorescence in emergency surgery. The studies on the use of indocyanine green fluorescence in the evaluation of trauma patients are still few.^[66] In trauma patients, indocyanine green has been utilized to evaluate the viability of parenchymatous organs, assess tissue impairment related to perfusion in extremity or craniofacial trauma, and reevaluate the vascularization efficacy of surgical procedures.^[67-70] This improves the clinical outcomes of surgery and patient safety.

All the evidence reported above is particularly crucial in acute care settings, where identifying anatomical structures is challenging due to acute inflammation, and compromised blood supply is common in underlying diseases (e.g., acute mesenteric

ischemia, bowel perforation/resection, trauma).^[4, 66] Recent studies suggest that near-infrared imaging using indocyanine green may be beneficial in evaluating ²vascular perfusion at the anastomotic site.^[71, 72]

Similarly, the inflammatory environment is a primary risk factor for biliary injury during cholecystectomy.^[73] The use of indocyanine green fluorescence cholangiography proves to be a valuable technique for visualizing the structures of the biliary tree, particularly the common bile duct, without the need for intraoperative cholangiography.^[74-77]

However, despite fluorescence-based imaging finding applications in various elective surgery fields, there remains a dearth of literature evidence regarding its use in emergency settings. In fact, ¹there is no consensus on the ideal dose, time, and manner of administration nor the indications that indocyanine green provides a genuine advantage through greater safety in trauma surgical settings.

CONCLUSION

We believe that the use of indocyanine green is proven to be safe, feasible, and effective in both elective and emergency scenarios. Several studies confirm that near-infrared fluorescence with indocyanine green is the best imaging system among those currently available to evaluate, in real time, the state of tissue perfusion during minimally invasive surgery. This system reaches maximum effectiveness in robotic surgery, where the magnified stereoscopic vision reduces the known difficulties of advanced laparoscopic surgery. ¹The best-established use of fluorescence imaging is for checking anastomotic stump perfusion in visceral surgery. ¹Some studies, mainly dealing with colorectal and esophageal surgery, have confirmed the usefulness of this technique.

Fluorescence represents an available, handy, easy-to-use, accurate, highly sensitive and specific, objective, reproducible and cost-effective system. Some devices have the disadvantage of not having a quantitative system, but as demonstrated in many studies in the literature, in almost all cases there is a clear discrimination between the ischemic zone and the perfused zone. In addition to the purely clinical data of the reduction in

ischemic anastomotic complications, the enormous economic advantage that would derive from the reduction in the number of re-operations and the average hospital stay should not be underestimated. Given the different quantities of indocyanine green used in various clinical experiences, further studies are essential to standardize the dose necessary to obtain an optimal fluorescence image. It is therefore desirable to increase the diffusion of fluorescence and to establish prospective clinical studies with a larger sample to confirm the present data. However additional robust evidence from larger-scale, high-quality studies is essential before incorporating indocyanine green guided surgery into standard practice.

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