Fluorescence Imaging Using Indocyanine Green Dye in the Pediatric Population

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OBJECTIVES Fluorescence imaging using indocyanine green (ICG) allows for the intraoperative mapping of the vascular supply of various tissue beds. Although generally safe and effective, rare adverse effects have been reported including anaphylactoid reactions. The current study retrospectively reviewed our experience the intraoperative administration of ICG to pediatric patients.

METHODS The anesthetic records of patients who received ICG over a 2-year time period were retrospectively reviewed and demographic, surgical, and medication data retrieved. Objective intraoperative data before and after the administration of ICG were also recorded. These included heart rate, systolic and diastolic blood pressures, oxygen saturation, and peak inflating pressure.

RESULTS The study cohort included 100 patients with a median age of 12 years (9.5 ± 7.4 years) and the median weight being 44.5 kg (45.9 ± 36.9 kg). ICG was administered intravenously to all patients. In all cases, 2.5 mg/mL ICG solution was used, with a median dose of 1.1 mL (1.79 ± 1.8 mL). Eight patients received more than 1 dose of ICG, with no adverse respiratory or hemodynamic effects related to its use.

CONCLUSIONS ICG fluorescence is an important imaging modality that can be safely used as an intraoperative adjunct to various surgical procedures in the pediatric population.

ABBREVIATIONS BP, blood pressure; HR, heart rate; ICG, indocyanine green; NIR, near-infrared; PIP, peak inflating pressure

KEYWORDS anesthesia; fluorescent dye; indocyanine green; pediatric

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Introduction

Fluorescence imaging is a relatively new and rapidly evolving modality used in the intraoperative setting to delineate the vasculature, lymphatic drainage, or demarcate between tumor and normal tissue.^{1–3} Indocyanine green (ICG), a fluorescence agent, is a water-soluble dye with a peak spectral absorption and emission at 800 to 810 nm in the blood or plasma. ICG has been used clinically since 1956 for angiography, to measure cardiac output or cerebral blood flow, evaluate hepatic function, and assess regional blood flow assessment.^{4–7} After intravenous administration, the dye is bound by plasma proteins, remaining intravascular, thereby allowing blood vessels to be visualized when the tissue is illuminated and observed at appropriate wavelengths of light. In recent studies, its clinical application has been tested in the treatment of cancer, laparoscopic procedures, and reconstructive colorectal and vascular surgeries.^{6,7} Currently, there are limited data available regarding its use, dosing, and adverse effect profile in the pediatric population. We retrospectively reviewed our experience with the intraoperative use of ICG in pediatric patients. Dosing guidelines and

potential adverse effects are discussed with recommendations for the appropriate care of pediatric patients.

Materials and Methods

As a retrospective chart review, the need for informed consent was waived. The hospital pharmacy database was queried, and patients who had received intraoperative ICG over a 2-year period were identified. The electronic medical records were reviewed and the perioperative administration of ICG confirmed. The data retrieved included demographic data consisting of age, weight, gender, and associated comorbid conditions. Additional data included the preoperative diagnosis, the surgical procedure, and indication for the use of ICG. Data related to ICG included the dilution (mg/mL), amount of ICG administered (mg/kg), number of doses administered, duration of time over which the ICG was administered, and adverse effects related to the dye.

To identify potential adverse hemodynamic or respiratory effects, objective intraoperative data before and after the administration of ICG were recorded including heart rate (HR), blood pressure (BP) including systolic BP and diastolic BP, oxygen saturation, and peak inflat-

Table 1. Suggested Dosing Guidelines for ICG

Weight	Volume of ICG to Administer	Concentration (mg/mL)
Skin and soft tissue procedures		
Weight $\geq$ 25 kg	Weight (kg)/20 = mL	2.5
Weight < 25kg	Weight (kg)/5 = mL	0.5
Colorectal procedures		
Weight $\geq$ 25 kg	Weight (kg)/27 = mL	2.5
Weight < 25 kg	Weight (kg)/10 = mL	0.5
Robotic cases (including cholecystectomy, pyeloplasty, and gastric sleeve)		
Weight $\geq$ 10 kg	1 mL	2.5
Weight < 10 kg	1.25 mL	2.5

ICG, indocyanine green

ing pressure (PIP). The data after the administration of ICG were recorded at 5, 10, and 15 minutes, respectively. HR and BP data were evaluated based on the 5th and 95th percentiles for age. Oxygen saturation less than 95% or a PIP greater than 30 cmH₂O was considered abnormal. The need to treat hemodynamic changes with an anticholinergic agent (i.e., atropine or glycopyrrolate) or a vasoactive agent (i.e., epinephrine or phenylephrine) and the need to treat respiratory changes with albuterol were noted.

In general, dosing was guided by pharmacy and departmental protocols (Table 1). The total dose (cumulative for the case if multiple doses were administered) was set at $\leq$ 2 mg/kg. ICG was mixed with the 10 mL pH balanced solution supplied in the package and used within 6 hours of reconstitution. The protocol and dosing varied based on the type of procedure (Table 1). The ICG was injected rapidly into the lumen of the vein as quickly as possible followed immediately by a 10-mL bolus flush of normal saline.

Results

The study cohort included 112 doses of ICG administered to 100 patients, ages ranging from 5 days to 31 years. The median age was 12 years (9.5 ± 7.4 years), and the median weight was 44.5 kg (45.9 ± 36.9 kg). The demographic data of the study cohort are listed in Table 2. Surgical procedures are listed in Table 3. Procedures on the gastrointestinal tract included laparoscopic cholecystectomy ($n = 56$) and colorectal surgery ($n = 30$). The latter included sagittal anorectovaginourethroplasty, transanal pull-through for Hirschsprung's disease, perineal reconstruction, and exploratory laparotomy. Renal procedures ($n = 5$) included 1 case each of bladder exstrophy repair, heminephrectomy, nephrectomy, cystoscopy, and pyeloplasty. The remaining procedures ($n = 9$) included thoracotomy, retinal photocoagulation with vitrectomy, lymphangiography, and surgical debridement with skin grafting.

ICG was administered intravenously to all patients. In all cases, 2.5 mg/mL ICG solution was used and diluted to the final concentration before intravenous administration. The median dose was 1.1 mL (1.79 ± 1.8 mL). Eight patients received more than 1 dose of ICG with the maximum number of doses being 5. Postoperatively, renal function tests were measured in 27 patients. No values were outside the normal for age with the median blood urea nitrogen and creatinine being 7.5 and 0.4 mg/dL, respectively. Five patients have elevated liver function tests including aspartate aminotransferase and alanine aminotransferase prior to the administration of ICG. In 5 other patients, liver function tests were measured postoperatively, and these values are listed in Table 4.

Hemodynamic and respiratory variables before and after the administration of ICG are outlined in Table 3. There were no adverse respiratory or hemodynamic effects related to the use of ICG. Hemodynamic variables were not less than the fifth percentile for age and did not exceed the 95th percentile for age at any

Table 2. Demographic Data for the Study Cohort

Cohort Characteristics	Result
Patients, N	100
Age, yr, (mean $\pm$ SD)	12 (9.5 ± 7.4)
Weight, kg, (mean $\pm$ SD)	44.5 (45.9 ± 36.9)
Sex, n (%)	
Male	33 (33)
Female	67 (67)
Type of surgery, n	
Laparoscopic cholecystectomy	56
Colorectal	30
Renal	5
Others	9

Table 3. Patient Characteristics Before and After Administration of ICG*

Characteristic	Before ICG Administration	After ICG Administration		
		5 min	10 min	15 min
HR, beats/min	106 (106 ± 23.9)	102 (104 ± 24.5)	102 (103.7 ± 26.7)	102 (103.5 ± 24.2)
Systolic BP, mm Hg	92 (92.1 ± 18.4)	91 (90.9 ± 17.3)	91 (93.2 ± 18.7)	90 (93.7 ± 20.5)
Diastolic BP, mm Hg	53 (53.6 ± 16.2)	51 (52.7 ± 15.3)	53 (53.6 ± 15.4)	53 (55.9 ± 18.8)
SpO ₂ , %	99 (96.8 ± 10.9)	99 (98.6 ± 1.8)	99 (98.9 ± 1.2)	99 (98.9 ± 1.2)
PIP (cmH ₂ O)	16 (16.9 ± 7.5)	16 (17.1 ± 3.9)	16.5 (17.5 ± 3.6)	17 (17.6 ± 3.7)

BP, blood pressure; HR, heart rate; PIP, peak inspiratory pressure; SpO₂, peripheral pulse oximeter

* Data presented as the median (mean ± SD).

time point. No patient required treatment with an anticholinergic agent, a vasoactive agent, or an agent to bronchospasm.

Discussion

ICG was developed for near-infrared (NIR) photography by Kodak Research laboratories in 1955 and approved for use clinically in the adult population in 1956. Since then, its applications have been expanded to include fluorescent imaging, retinal angiography, vitreoretinal surgery, assessment of liver function, surgical oncology, assessment of burn wound severity, and clinical imaging of the lymphatic system.^{4–7} Its use has expanded to include the pediatric population; however, to date, reports have been largely anecdotal regarding both its use and its adverse effect profile. Some of the recent reports have demonstrated its successful application in the pediatric population (Table 5).^{8–13}

The primary intent of our current study was to retrospectively review our general use and dosing practices with the intraoperative administration of ICG to pediatric patients over a 2-year period. Over this period, 112 doses of ICG were administered to 100 patients for procedures including laparoscopic cholecystectomy, colorectal surgery, and renal procedures. Administration of ICG intraoperatively in the aforementioned procedures helped in visualization and identification of the biliary tree, demonstrated perfusion of colonic segments and pelvic structures, and also aided in the identification of pulmonary nodules for resection. In all cases, 2.5 mg/mL ICG solution was used and diluted to the final concentration before intravenous administration. Eight patients received more than 1 dose. No adverse effects on hemodynamic or respiratory function related to the use of ICG were noted.

ICG is a negatively charged, water-soluble, tricarboxyanine dye available pharmaceutically in a stable dry form. To preserve its spectral effects, it must be dissolved in distilled water.^{14,15} The intense fluorescent property of ICG is a result of its binding to the lipids of lipoprotein complexes in plasma proteins and confinement to the vascular compartment. ICG has no known metabolites and is excreted primarily through the liver

into the bile after being transported by glutathione S-transferase.^{16,17} ICG is a fluorescence agent with a peak spectral absorption and emission at 800 to 810 nm in the blood or plasma. The principle of fluorescence imaging is to illuminate the tissue of interest with light at the excitation wavelength and observe it at longer emission wavelengths. ICG operates at NIR wavelengths, at which tissues appear more translucent, thus providing information on deeper lying blood vessels and tissues. ICG is the only clinically approved dye for NIR fluorescence imaging.^{5–7,18}

ICG has been shown to be a relatively safe dye with a low incidence of adverse effects. It is not metabolized after injection and is almost exclusively excreted by the liver into bile. Although the dye has been shown not to cross the placenta, studies on fetal toxicity are limited. ICG contains iodine, and therefore should be avoided in patients with a history of iodine allergy. Although rare, anaphylactoid reactions have been reported, with reports of death.^{19–21} ICG has also been shown to artifactually cause transient alteration of oximetric detection of arterial hemoglobin oxygen saturation and oxyhemoglobin percentage.²²

Conclusion

ICG fluorescence is an important imaging modality that can be a useful intraoperative adjunct during various surgical procedures. It has been used to delineate

Table 4. Hepatic Function Tests for the 5 Patients Who Had the Analysis Performed

AST (IU/L)*	ALT (IU/L)*
19	38
32	30
64	73
56	28
21	30

ALT, alanine aminotransferase; AST, aspartate aminotransferase; IU, international units

* Reference range was between 15 and 50 IU/L.

† Reference range was ≤ 40 IU/L.

Table 5. Reports on the Application and Use of ICG in the Pediatric Population

Reference	Cohort Demographics	Summary of Intraoperative Care and Outcome
Fernández-Bautista ⁸	Five pediatric patients for varicocele ligation, nephrectomy, cholecystectomy, and aortocoronary fistula closure.	Surgical dissection facilitated by the use of ICG. No adverse systemic effects.
Calabro ⁹	Twenty-nine patients, 6–18 yr of age, operated for laparoscopic cholecystectomy.	ICG fluorescent cholangiography was used intraoperatively to define the extrahepatic biliary anatomy and the bile ducts. Average surgical time was reduced by 16 min with use of ICG.
Esposito ¹⁰	ICG was used in 46 minimally invasive surgical procedures in children and adolescents.	Varicocele repairs (n = 30), cholecystectomies (n = 5), tumor excisions (n = 3), nephrectomies (n = 3), partial nephrectomies (n = 2), and lymphoma excisions (n = 3). ICG solution was administered intravenously in all cases except for varicocelelectomy in which it was injected into the testicle. The ICG injection was performed intraoperatively in all cases except for cholecystectomy in which it was injected 18 hr prior to the procedure. No adverse or allergic reactions to ICG were reported.
Quintero ¹¹	A prospective study of 48 patients <18 yr of age with ALF.	ICG-PDR was measured to assess hepatic function every 24 hr until ALF resolution, liver transplantation, or death. The ICG-PDR was found to successfully predict the evolution of pediatric patients with ALF and improve their categorization.
Esposito ¹²	Retrospective review of 215 children undergoing laparoscopic cholecystectomy over a 25-yr period.	ICG-enhanced fluorescence technology was adopted intraoperatively in 15 cases to visualize and identify the gallbladder and biliary tree. The operative time after its implementation was reported to decrease by 17 min.
Yamamichi ¹³	Three pediatric patients with hepatoblastoma.	ICG fluorescence imaging used intraoperatively in all 3 cases to help visualize the anatomy and guide tumor resection. The technique allowed identification of nodules as small as 3 mm.

ALF, acute liver failure; ICG, indocyanine green; PDR, plasma disappearance rate

the bile ducts during laparoscopic cholecystectomy, to monitor hepatic function during acute liver failure, to guide tumor resection of hepatoblastoma and thoracic malignancies, for intraoperative angiography, nephrectomies, lymph node intraoperative identification of metastasis, and assessment of blood vessel patency during vascular surgeries.^{8–13}

ARTICLE INFORMATION

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Ethical Approval and Informed Consent This study was approved by Institutional Review Board at Nationwide Children's Hospital. Given the nature of this study, the project was exempt from HIPAA authorization, assent, and/or parental permission.

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