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Intraoperative Laparoscopic Near-Infrared Fluorescence Cholangiography to Facilitate Anatomical Identification: When to Give Indocyanine Green and How Much

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Abstract

Recent technological advances have enabled real-time near-infrared fluorescence cholangiography (NIRFC) with indocyanine green (ICG). Whereas several studies have shown its feasibility, dosing and timing for practical use have not been optimized. We undertook a prospective study with systematic variation of dosing and timing from injection of ICG to visualization. Adult patients undergoing laparoscopic biliary and hepatic operations were enrolled. Intravenous ICG (0.02-0.25 mg/kg) was administered at times ranging from 10 to 180 minutes prior to planned visualization. The porta hepatis was examined using a dedicated laparoscopic system equipped to detect NIRFC. Quantitative analysis of intraoperative fluorescence was performed using a scoring system to identify biliary structures. A total of 37 patients were enrolled. Visualization of the extrahepatic biliary tract improved with increasing doses of ICG, with qualitative scores improving from 1.9 ± 1.2 (out of 5) with a 0.02-mg/kg dose to 3.4 ± 1.3 with a 0.25-mg/kg dose ($P < .05$ for 0.02 vs 0.25 mg/kg). Visualization was also significantly better with increased time after ICG administration (1.1 ± 0.3 for 10 minutes vs 3.4 ± 1.1 for 45 minutes, $P < .01$). Similarly, quantitative measures also improved with both dose and time. There were no complications from the administration of ICG. These results suggest that a dose of 0.25 mg/kg administered at least 45 minutes prior to visualization facilitates intraoperative anatomical identification. The dosage and timing of administration of ICG prior to intraoperative visualization are within a range where it can be administered in a practical, safe, and effective manner to allow intraoperative identification of extrahepatic biliary anatomy using NIRFC.

Keywords

infrared fluorescence, intraoperative cholangiography, biliary anatomy, intraoperative guidance

Introduction

Clear delineation of biliary anatomy is of paramount importance to hepatobiliary surgery. This is especially important because gains in surgeon skills and experience are leading to more complex hepatic and biliary operations being performed laparoscopically.[1] Furthermore, laparoscopic cholecystectomy continues to be one of the most commonly performed surgical procedures in the United States.[2] Intraoperative cholangiography (IOC) has been the gold standard for decades despite logistical difficulties that lead to its low use. Whether IOC limits the rate or severity of bile duct injury remains controversial.[3,4] What is certain is that conventional fluoroscopic

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cholangiography is time and resource intensive and exposes patients and staff to radiation.

To meet the need for techniques to facilitate safe intraoperative identification of biliary anatomy, new technologies using near-infrared (NIR) fluorescence have been developed.[5,6] This technology uses indocyanine green (ICG), a NIR fluorescent dye, which has been used for angiography[7] and the measurement of global liver function for decades.[8] ICG is a fluorescent dye with absorbance and fluorescence in the NIR range. Its almost complete hepatobiliary elimination means that it is excreted in the bile and is not subject to enterohepatic recirculation, thus making it a promising contrast agent for biliary visualization. The development of devices that allow the visualization of ICG fluorescence and the overlaying of that image with the conventional white light image facilitate its practical use in the operating room. However, the dosage and timing of the intravenous administration of ICG relative to the operative procedure still requires optimization to ensure reliable images. Prior studies have used doses ranging from 2.5 to 20 mg, regardless of patient weight, and the timing of injection has ranged from 24 hours prior to the operation to immediately after induction of anesthesia.[6,9] Furthermore, the studies reporting the use of near-infrared fluorescence cholangiography (NIRFC) to date have yet to utilize a device approved by the US Food and Drug Administration (FDA). In this study, we used an FDA-approved NIR laparoscopic imaging system designed to visualize ICG fluorescence to assess the optimal timing and dosage of ICG administration prior to intraoperative visualization of the biliary tract in patients undergoing laparoscopic hepatic or biliary operations.

Methods

Patients

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, and institutional review board approval was obtained. Informed consent was obtained for all participants. Patients were eligible for enrollment if they were older than 18 years and were scheduled for a laparoscopic hepatic or biliary operation at the Ronald Reagan UCLA Medical Center. Patients with a history of adverse reactions or known allergy to ICG, iodine, or iodine dyes were excluded. Pregnant and/or lactating patients were also excluded. Participants received a baseline assessment. Demographic information, including age, gender, ethnicity or race, body mass index, American Society of Anesthesiologists class, preoperative diagnosis, liver function, and complete medical history, was collected. Patients were assigned to a group to determine the timing of ICG administration and a cohort to determine the dosage of ICG. Three patients were planned for each group/cohort for the first pass. Additional patients were enrolled into the group/cohorts as necessary to obtain more data for analysis. Specifically, each case was reviewed by the principal investigator to assess for the case difficulty (inflammation, adhesions, scarring, periportal fat, etc). Participants were added to various cohorts to ensure equitable distribution of such cases throughout.

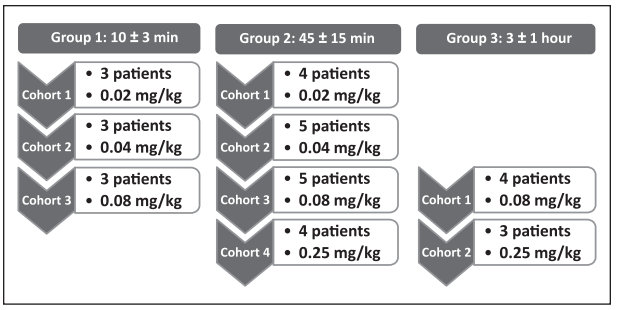

Figure 1. Design of the study listing the protocol according to which patients were assigned to a specific dose and timing of administration of indocyanine green.

NIRFC Device

During the surgical procedure, the PINPOINT Endoscopic Fluorescence Imaging System (Novadaq Technologies Inc, Ontario, Canada) was used. This device enables the surgeon to simultaneously see real-time, high-definition visible-range and NIR fluorescence videos and to superimpose them. It is currently approved by the FDA for the visual assessment of blood flow in vessels and tissue perfusion.[10] Essentially, it is a standard laparoscopic device with an added excitation laser at 805 nm running at 20 Hz and a filter set to allow for visualization of the ICG fluorescence.

NIRFC Technique and Assessment

ICG was administered intravenously by the study coordinator or the anesthesiologist at the following doses: 0.02, 0.04, 0.08, and 0.25 mg/kg. The timing of the injection also systematically varied: 10 ± 3 minutes, 45 ± 15 minutes, and 3 ± 1 hours prior to anticipated visualization (Figure 1). At the completion of each case, a qualitative assessment was determined by examining the quality of the intraoperative visualization of the extrahepatic biliary tree (being able to identify and distinguish the common bile duct, the common hepatic duct, and the cystic duct from the surrounding structures and from each other) on a scale of 1 to 5 (1 = *no improvement/identification not confirmed*; 2 = *marginally improved*; 3 = *sufficiently improved*; 4 = *well improved*; 5 = *greatly improved/*

Table 1. Selected Characteristics of Patients Enrolled (n = 37).

Characteristics		Values
Age (years)	Median	62
	Range	19-85
Gender	Male	17 (45.9%)
	Female	20 (54.1%)
Physiological MELD	Median	7.5
	Range	6-20
BMI (kg/m^2)	Median	25.7
	Range	18.3-46.6
Child-Pugh score	A	30 (81%)
	B	7 (19%)
	C	0 (0%)
Platelet count (×10^3/μL)	Median	216
	Range	65-498
Operative indication	Acute cholecystitis	9 (24%)
	Chronic cholecystitis	5 (13.5%)
	Liver mass	18 (49%)
	Other	5 (13.5%)

Abbreviations: BMI, body mass index; MELD, model for end-stage liver disease.

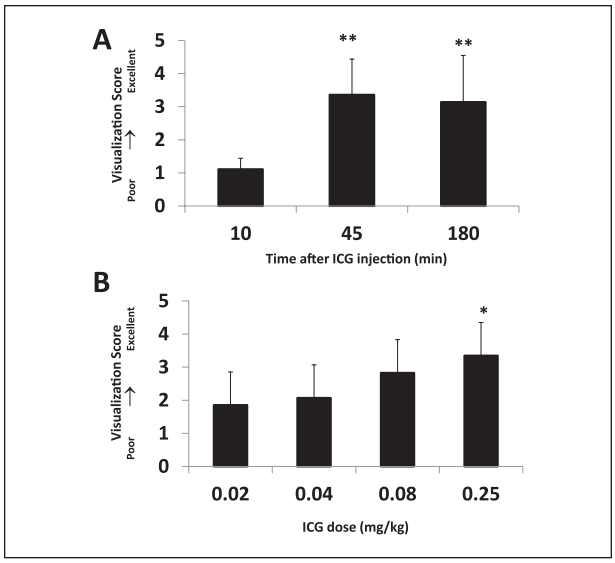

Figure 2. Qualitative evaluation of the visualization of the biliary anatomy. The visualization score as affected by timing of indocyanine green (ICG) injection (A) or dose of ICG (B). *P <.05 for 0.02 mg/kg; **P <.01 for 10 minutes.

exceeds expectations). The assessment was performed by the operating surgeon who was blinded to the dose and the timing of ICG administration. Quantitative assessment was performed using ImageJ (US National Institutes of Health, Bethesda, MD; http://imagej.nih.gov/ij/) by dividing the fluorescence intensity signal of the common bile duct by that of the surrounding fat or liver.

Statistical Analysis

All statistics were calculated with JMP Pro 11.2 (SAS Institute Inc, Cary, NC) using a Student's *t*-test to compare data across groups. Results have been provided as the mean ± SD. Unless otherwise stated, P values <.05 were considered significant.

Results

Study Participants

Participant characteristics are detailed in Table 1 and were representative of standard patients undergoing laparoscopic liver or biliary procedures. Of the 37 participants, 20 were women. Three were enrolled but did not receive ICG because of unavailability of the laparoscope (n = 2) or conversion to an open operation prior to planned ICG administration (n = 1). These patients were excluded from the analysis. The median age was 62 (range = 19 to 85) years. The median body mass index (BMI) was 25.7 (range = 18.3 to 46.6) kg/m^2. The operative procedures included laparoscopic cholecystectomy (n = 13), laparoscopy followed by open cholecystectomy (n = 1), laparoscopic bile duct exploration (n = 2), laparoscopic partial liver resection (n = 6), and laparoscopy followed by open liver resection (n = 11). There were no adverse events resulting from the use of ICG or the PINPOINT system. No cases required standard fluoroscopic IOC.

Qualitative Assessment

Almost immediately after intravenous administration, ICG fluorescence was readily visible in the liver. In the group with the shortest time interval between ICG administration and visualization, the visualization was poor and significantly worse than that for the longer time points (1.1 ± 0.3 out of a possible 5 at 15 minutes; 3.4 ± 1.1 at 45 minutes; 3.1 ± 1.4 at 3 hours; P < .01 for 45 minutes and 3 hours vs 15 minutes; Figure 2A). Whereas the scores were recorded only at the designated times, observing the entire length of the operation showed that it took approximately 20 minutes following IV injection of ICG to be able to see it flow into the common hepatic duct in all patients; the fluorescence of the common duct remained visible until the completion of all cases (up to 5 hours after the ICG injection). (A video clip demonstrating the visualization of NIRFC is available online at http://sri.sagepub.com/supplemental.) The qualitative visualization score at 45 minutes was the highest but not significantly different from the longest time point at 180 minutes. The effect of the dose was less pronounced. Given enough time, a dose as low as 0.02 mg/kg was

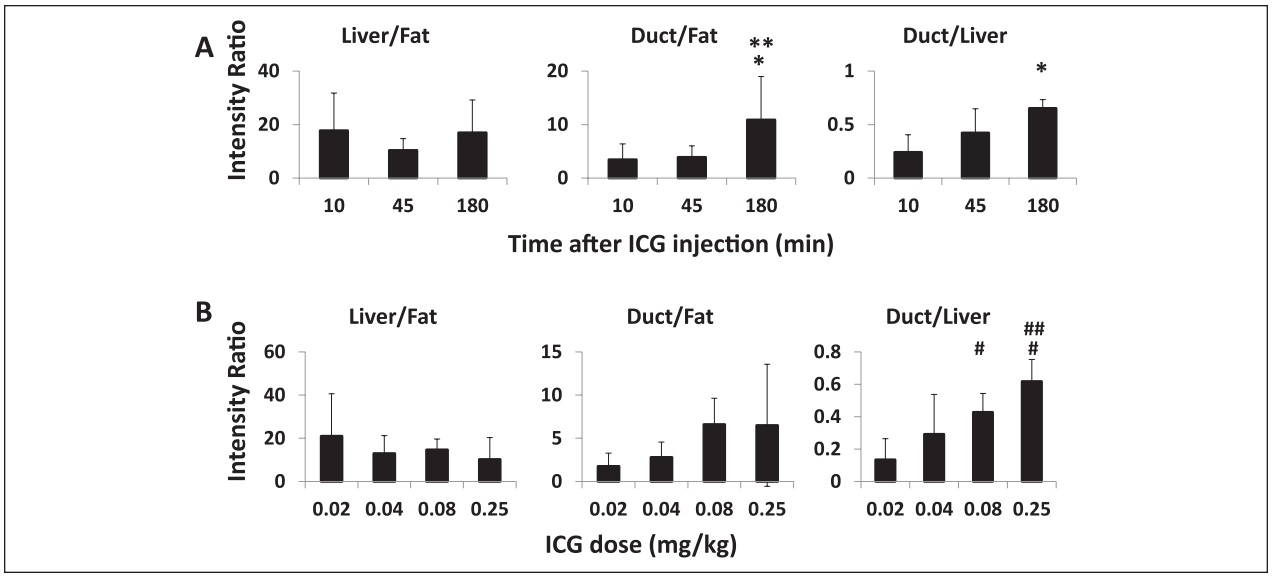

Figure 3. Quantitative evaluation of the visualization of the biliary anatomy. The intensity ratios as affected by timing of indocyanine green (ICG) injection (A) or dose of ICG (B). *P < .01 for 10 minutes; **P < .01 for 45 minutes; #P < .01 for dose 0.02 mg/kg; ##P < .01 for dose 0.04 mg/kg.

effective in allowing visualization of the biliary anatomy. However, there was a trend toward improved visualization scores with higher ICG doses (1.9 ± 1.2 with a 0.02-mg/kg dose; 2.1 ± 1.3 with a 0.04-mg/kg dose; 2.8 ± 1.6 with a 0.08-mg/kg dose; and 3.4 ± 1.3 with a 0.25-mg/kg dose; P < .05 for 0.02 mg/kg vs 0.25 mg/kg; Figure 2B). There was no correlation with BMI (2.8 ± 1.4 for BMI <30 kg/m^2; 2.4 ± 1.4 for BMI >30 kg/m^2; P = .54).

Quantitative Assessments

Quantitative analysis of the images obtained during the study was also performed. To do so, we measured the intensities of the fluorescent images in the liver parenchyma, the bile duct, and surrounding fat tissue. The quantitative measurements were performed to allow an independent measure of duct visualization. Presumably, increased fluorescence in the duct compared with surrounding fat should correlate with better identification because it would mean that it is brighter than the fat in which it may be encased. Because ICG fluorescence is quite high in the liver for a prolonged period of time, we measured the duct to liver ratio to better understand the timing of decrease in liver fluorescence compared with increased duct fluorescence. A higher duct to liver ratio would also be preferred if NIRFC were to be used for hilar dissection because the duct may be obscured by a high level of liver fluorescence.

The calculated intensity ratios are presented in Figure 3. The general trend of improved duct-to-fat and duct-to-liver ratios were similar to that in the qualitative assessment. The duct-to-fat ratio was highest after 180 minutes (10.9 ± 8.1 vs 3.5 ± 3.0 at 15 minutes; P < .01), and there was a trend toward improved duct-to-fat ratio with increasing ICG dose. Additionally, the duct-to-liver ratio was highest in the longer time points (0.65 ± 0.08 vs 0.24 ± 0.2 at 15 minutes; P < .01) and the higher doses (0.13 ± 0.13 with a 0.02-mg/kg dose; 0.29 ± 0.25 with a 0.04-mg/kg dose; 0.43 ± 0.12 with a 0.08-mg/kg dose; and 0.62 ± 0.14 with a 0.25-mg/kg dose; P < .01 for 0.08 mg/kg and 0.25 mg/kg vs 0.02 mg/kg). There was no correlation of any of the variables with BMI.

Discussion

This study confirms the feasibility of NIRFC during laparoscopic surgery. Although the numbers of participants in the study was small, it nevertheless serves to show the timing and dosage of ICG necessary for intraoperative identification of extrahepatic biliary anatomy. The common hepatic duct was visualized by NIRFC in all patients regardless of BMI, bilirubin, Child-Pugh classification, or MELD score. Some examples of the images obtained are shown in Figure 4 and in the video available online. Correct identification of the anatomy was confirmed by subsequent surgical dissection. The duct-to-fat and duct-to-liver ratio was highest at the longer time points (180 minutes), in agreement both with the subjective assessment of the visualization and with previous reports.[9] Nevertheless, we found that intravenous injection of low doses of ICG with little lead time, as brief as 25 to 30 minutes, facilitated identification of the extrahepatic

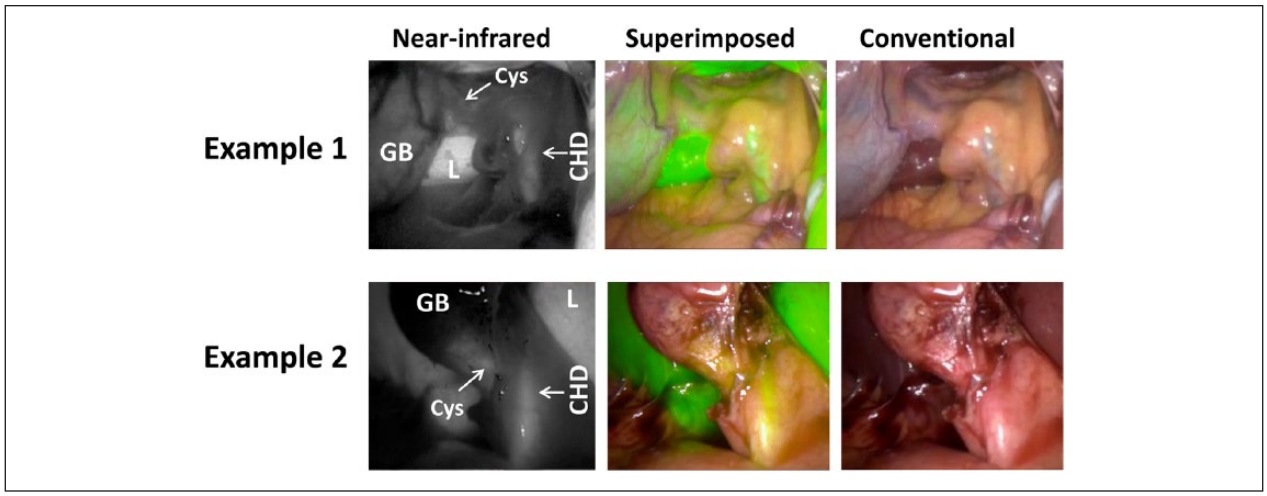

Figure 4. Representative examples of intraoperative images.
Abbreviations: GB, gallbladder; L, liver; CHD, common hepatic duct; Cys, cystic duct.

biliary tree for a prolonged period of time, up to 5 hours in our study. Understanding the timing of ICG excretion into the bile and the ability to visualize is very important for the practical use of NIRFC. In one previous study,[9] the timing of injection ranged from 30 minutes to 24 hours prior to the operation with no time points in between. The need for cholangiography cannot always be predicted the day prior to the operation, nor can every patient be administered IV ICG the day before the operation. However, knowing that the administration of ICG in the preoperative holding area or even on patient arrival in the operating room is sufficient means that NIRFC can become more of a routine procedure.

Visualization of NIRFC superimposed on the conventional white light images of the surrounding structures in real time can, therefore, be achieved without a sense of urgency or a time limitation. For the gross identification of the extrahepatic biliary tree, NIRF can obviate extensive portal or biliary dissection as well as the insertion of a cholangiocatheter for the injection of contrast material. It appears to be safe in that no adverse events occurred during the course of this study or in other previous reports.[5,6,9,11] As listed in Table 1, 9 operations were performed for acute cholecystitis, and 5 were performed for chronic cholecystitis. The ducts were distinguishable by fluorescence in all these cases. In the setting of an inflammatory process, just as in the presence of excessive periportal fat, visualization of the extrahepatic biliary system was more difficult than in cases without any portal inflammatory process or fat. Nevertheless, these processes did not prevent NIRFC.

The major limitations of NIRFC include the inability to visualize bile ducts lying in deeper than 5 to 10 mm of fat, tumor, or inflamed tissues or bile ducts that are covered with surrounding organs. This study was not designed to ascertain the ability to visualize small bile duct stones, but the image quality does not seem clear enough to allow this. Finally, high levels of fluorescence of ICG in the liver prevent the visualization of intrahepatic bile ducts.

Nonetheless, NIRFC can quickly establish a roadmap of biliary anatomy in real time superimposed on the standard visual field, thus fulfilling the objectives of IOC in many biliary operations. This technology could offer some advantage in the conduct of safe hepatobiliary surgery. Additional areas that will need further investigation include impact on operative time, cost considerations, and the rate of bile duct injury. Assessment of these end points will require a larger prospective randomized study.

In conclusion, this study provides guidance on the timing and dosing of ICG with respect to anticipated visualization of the biliary tree. NIRFC is practical and effective in delineating extrahepatic biliary anatomy during laparoscopic biliary and hepatic operations, and its use should, therefore, be considered over traditional methods.

Author Contributions

Study concept and design: Ali Zarrinpar, Erik P. Dutson, Darryl T. Hiyama
Acquisition of data: Ali Zarrinpar, Erik P. Dutson, Constance Mobley, Ronald W. Busuttil, Vatche G. Agopian, Areti Tillou, Ali Cheaito, O. Joe Hines, Catherine E. Lewis
Analysis and interpretation of data: Ali Zarrinpar
Writing the manuscript: Ali Zarrinpar
Critical revision of the manuscript: Ali Zarrinpar, Erik P. Dutson, Darryl T. Hiyama, Constance Mobley, Ronald W. Busuttil, Vatche G. Agopian, Areti Tillou, Ali Cheaito, O. Joe Hines, Catherine E. Lewis

Authors' Note

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Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Ali Zarrinpar has previously been a paid speaker for Novadaq Technologies Inc. All other authors have no financial disclosures related to this study. Novadaq Technologies Inc provided the device and funding for this study.

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