Low vs Standard Dose Indocyanine Green in the Identification of Biliary Anatomy Using Near-Infrared Fluorescence Imaging: A Multicenter Randomized Controlled Trial

NCT04942665

12/9/2021

1. Title:

- Low dose ICG for near-infrared fluorescence imaging of biliary tract

2. Investigators:

- Ali Zarrinpar, MD, PhD (PI)
- Tyler Loftus, MD (co-PI, PI proxy)
- Alexandra Ladd, MD (co-Investigator)
- Haley Stone (co-Investigator, medical student)
- Curtis Warren (Study Coordinator)

3. Abstract:

We have a series of surgical cases in which we have been able to achieve excellent intraoperative biliary visualization with a greatly decreased (50-200X fold lower) dose of ICG than the previously published dose. Furthermore, this decreased dose was visible in about 15-20 minutes from the time of injection with low liver background fluorescence, a significant improvement that would make its utilization in the operating room more practical. We hypothesize that a lower dose will allow adequate visualization of the extrahepatic biliary tree, including the cystic, common hepatic, and common bile ducts. Confirmation of this hypothesis would mean that a lower dose of ICG can be administered on the same day of surgery in order to augment real-time intraoperative localization of the extrahepatic biliary tree, thereby providing a safe, feasible, and cost-effective strategy for the surgical treatment of liver disease.
We intend to test our hypothesis with the following specific aims:
Aim: To compare the efficacy and utility of a low dose ICG (0.05 mg) protocol with a previously published dose (2.5 mg) in imaging the extrahepatic biliary tract.

4. Background:

Near-infrared fluorescence (NIRF) imaging after an intravenous injection of indocyanine green (ICG) allows for the intraoperative identification of biliary anatomy. ICG binds to plasma proteins and emits light with a peak wavelength around 830nm when illuminated with near-infrared light. ICG is exclusively excreted by the liver, and biliary excretion lasts from several minutes to 24 hours post-injection (1). NIRF imaging has been shown to be a safe, easy, fast, cost-effective strategy for delineating biliary anatomy because it decreases the risk of bile duct injury and does not require radiation (2)(3)(4). Research from our group, among others, has shown that visualization of the extrahepatic biliary tract is adequate at a dose on the order of 2.5 mg administered at least 15 minutes prior to visualization (5).

Since the advent of NIRF, imaging technology has improved, with increasing sensitivity and improved intraoperative displays. Whether these improvements have resulted in increased sensitivity and utility has not yet been demonstrated, nor has the possibility of whether improved technology has decreased either the dose required for adequate visualization or the time interval prior to optimal visualization.

5. Specific Aim:

To compare the efficacy and utility of a low dose ICG (0.05 mg) protocol with a previously published dose (2.5 mg) in imaging the extrahepatic biliary tract.

6. Research Plan:

Current standard of care for this service is to administer 2.5 mg of ICG preoperatively to patients before surgical bile duct visualization. If there is any further need for anatomic information, then a combination of ultrasound and X-ray cholangiography is used. For this study, adult patients scheduled to undergo a laparoscopic hepatic or biliary operation will be randomized to two groups 1) low dose (0.05 mg) or 2) standard dose (2.5 mg) of ICG preoperatively on the day of surgery. Patients with a history of adverse reactions or known allergy to ICG, iodine, or iodine dyes will be excluded. Pregnant and/or lactating patients will also be excluded. Participants will receive 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, will be collected. Case difficulty will be graded by the primary surgeon based on standardized criteria (https://pubmed.ncbi.nlm.nih.gov/29956029/). The PINPOINT Endoscopic Fluorescence Imaging System (Stryker Corporation, Kalamazoo, Michigan) will be 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 intraoperative near-infrared fluorescence imaging. Essentially, it is a standard laparoscopic device with an added excitation laser at 805 nm and a filter set to allow for visualization of ICG fluorescence. The visualization of the biliary tree will be recorded.

Low dose or standard dose ICG will be administered by the anesthesiologist as guided by the study coordinator at the beginning of the case. The operating surgeon will be blinded to the dose given. At two points during the operation (1- prior to the dissection of the biliary tract and 2- upon completion of the dissection and establishment of the critical view of safety), a *qualitative assessment* will be made by the primary surgeon based on 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/exceeds expectations). The recorded visualization will also be assessed by a blinded independent surgeon who will use the same scale. A quantitative assessment will also be performed on the recorded visualization 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. These quantitative measurements will allow an independent measure of duct visualization. Both quantitative and qualitative scores will be compared to determine whether there are significant differences between the doses. A total of thirty patients (15 in each arm) will be required for more than a 90% power to detect a difference in the duct-to-liver ratio of 0.2 between the two groups, given an alpha of 0.05 and a standard deviation of 0.15. These estimates are based on our previously published results. (5)

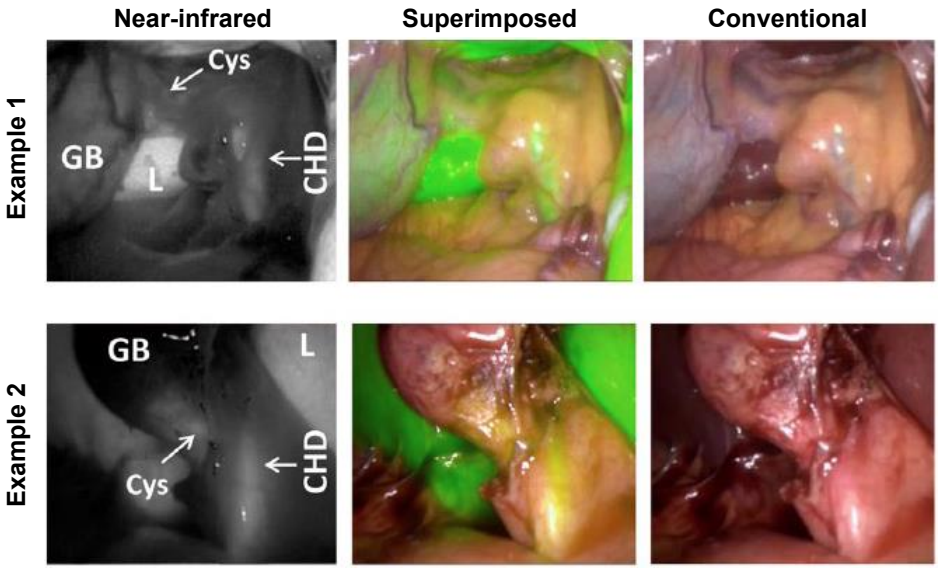

Figure 1. Representative examples of intraoperative images of biliary tract. GB, gallbladder; L, liver; CHD, common hepatic duct; Cys, cystic duct. (Zarrinpar *et al, Surgical Innovation* 2016)

Patients who are not able to provide informed consent and have a history of sensitivity or allergy to shellfish, ICG, or iodine will be excluded from the study.

Randomization: Identical envelopes will be made with a card marked either standard or low dose to be chosen in blocks of four. At the time of enrollment, an envelope will be selected at random from a box and the subject will be assigned to the corresponding arm. This envelope will then be discarded to allow for equal numbers in each group.

For the purposes of the study, the recorded videos will be stored on a secure local server with access limited only to the study team. This will allow them team to perform the image analysis and related calculations. At the end of the study, the videos will be deidentified and maintained for possible future research.

7. Possible Discomforts and Risks:

Using a lower dose of ICG may lead to poorer visualization of the anatomy during surgery compared to the standard dose. The surgeons, however, routinely use other methods of visualization during surgery (such as ultrasound or x-rays) that would decrease the risks of poor visualization during the operation. The most commonly reported adverse reactions to ICG are typically mild and included pruritus, shortness of breath, and nausea. Less commonly reported events include bronchospasm (a condition wherein muscles lining the airways of the lungs constrict or tighten, reducing airflow), laryngospasm (a spasm of the vocal cords that temporarily makes it difficult to speak or breath), low blood pressure, and cardiac arrest. IVs are routinely used by clinicians and they are considered to be low risk.

8. Possible Benefits:
Decreasing the dose of ICG may lead to better visualization of the anatomy during surgery and also it may decrease the risk of side-effects.

9. Conflict of Interest:

The investigators have no real or potential conflict of interest with regard to this research project.

10. Data Safety and Monitoring Plan

10.1 Data Integrity and Safety Committee

This protocol summary will include a minimum of the following:
• The UF IRB assigned protocol number, protocol title, PI name, data coordinator name or primary study coordinator, regulatory coordinator name, and statistician
• Date of initial UF IRB approval, date of most recent consent UF IRB approval/revision, date of UF IRB expiration, study status, and phase of the study, study target accrual and study actual accrual.
• Protocol objectives with supporting data and list of number of study participants who have met each objective.
• Intraoperative measures
• Summary of toxicities and protocol deviations.
• Summary of any recent literature which may affect the safety or ethics of the trial.

10.2 Site Monitoring

10.3 Principal Investigator Responsibilities
As part of the responsibilities assumed by conducting this study, the Principal Investigator (PI) agrees to maintain and have available for monitoring adequate case records (accurate source documents and CRFs) for the subjects treated under this protocol.

The PI will be primarily responsible for monitoring of adverse events, protocol violations, and other immediate protocol issues. The study coordinator will collect information on subjects enrolled through the use of electronic or paper adverse event (AE) forms, CRFs, and Informed Consent forms.

10.4 Interim Analyses & Stopping Rules
As a phase II feasibility study, our goal is to establish clinical and operative expectations around the use of low-dose IV ICG. Given the standard use of standard dose IV ICG, we are not concerned about safety, so a phase I study or safety run-in of low dose ICG is not felt to be needed. However, we will monitor and record any AEs related to the IV ICG administration in both arms of the study.

Given the published safety data on intraoperative use of ICG, we do not anticipate any safety issues between the standard and low dose ICG, but will monitor AEs related to ICG administration in real time. A pre-planned stopping rule for safety is not needed.

Given the pilot and feasibility aspects of this study such that a primary efficacy difference is not being targeted along with the relatively small numbers of patients and short enrollment period, a stopping rule for efficacy is not appropriate.

11. References

1. Ishizawa T, Tamura S, Masuda K, Aoki T, Hasegawa K, Imamura H, et al. Intraoperative fluorescent cholangiography using indocyanine green: a biliary road map for safe surgery. J Am Coll Surg. 2009 Jan;208(1):e1–4.

2. Dip F, Roy M, Lo Menzo E, Simpfendorfer C, Szomstein S, Rosenthal RJ. Routine use of fluorescent incisionless cholangiography as a new imaging modality during laparoscopic cholecystectomy. Surg Endosc. 2015 Jun;29(6):1621–1626.

3. Matsui A, Tanaka E, Choi HS, Winer JH, Kianzad V, Gioux S, et al. Real-time intra-operative near-infrared fluorescence identification of the extrahepatic bile ducts using clinically available contrast agents. Surgery. 2010 Jul;148(1):87–95.

4. Ishizawa T, Bandai Y, Ijichi M, Kaneko J, Hasegawa K, Kokudo N. Fluorescent cholangiography illuminating the biliary tree during laparoscopic cholecystectomy. Br J Surg. 2010 Sep;97(9):1369–1377.

5. Zarrinpar A, Dutson EP, Mobley C, Busuttil RW, Lewis CE, Tillou A, et al. Intraoperative Laparoscopic Near-Infrared Fluorescence Cholangiography to Facilitate Anatomical Identification: When to Give Indocyanine Green and How Much. Surg Innov. 2016 Aug;23(4):360–365.

6. Aoki T, Yasuda D, Shimizu Y, Odaira M, Niiya T, Kusano T, et al. Image-guided liver mapping using fluorescence navigation system with indocyanine green for anatomical hepatic resection. World J Surg. 2008 Aug;32(8):1763–1767.

7. Inoue Y, Arita J, Sakamoto T, Ono Y, Takahashi M, Takahashi Y, et al. Anatomical Liver Resections Guided by 3-Dimensional Parenchymal Staining Using Fusion Indocyanine Green Fluorescence Imaging. Ann Surg. 2015 Jul;262(1):105–111.

8. Ishizawa T, Fukushima N, Shibahara J, Masuda K, Tamura S, Aoki T, et al. Real-time identification of liver cancers by using indocyanine green fluorescent imaging. Cancer. 2009 Jun 1;115(11):2491–2504.

9. Kudo H, Ishizawa T, Tani K, Harada N, Ichida A, Shimizu A, et al. Visualization of subcapsular hepatic malignancy by indocyanine-green fluorescence imaging during laparoscopic hepatectomy. Surg Endosc. 2014 Aug;28(8):2504–2508.

10. Gotoh K, Yamada T, Ishikawa O, Takahashi H, Eguchi H, Yano M, et al. A novel image-guided surgery of hepatocellular carcinoma by indocyanine green fluorescence imaging navigation. J Surg Oncol. 2009 Jul 1;100(1):75–79.

11. Lim C, Vibert E, Azoulay D, Salloum C, Ishizawa T, Yoshioka R, et al. Indocyanine green fluorescence imaging in the surgical management of liver cancers: current facts and future implications. J Visc Surg. 2014 Apr;151(2):117–124.

12. Satou S, Ishizawa T, Masuda K, Kaneko J, Aoki T, Sakamoto Y, et al. Indocyanine green fluorescent imaging for detecting extrahepatic metastasis of hepatocellular carcinoma. J Gastroenterol. 2013 Oct;48(10):1136–1143.

13. van der Vorst JR, Schaafsma BE, Hutteman M, Verbeek FPR, Liefers G-J, Hartgrink HH, et al. Near-infrared fluorescence-guided resection of colorectal liver metastases. Cancer. 2013 Sep 15;119(18):3411–3418.

14. Qi B, Crawford AJ, Wojtynek NE, Holmes MB, Souchek JJ, Almeida-Porada G, et al. Indocyanine green loaded hyaluronan-derived nanoparticles for fluorescence-enhanced surgical imaging of pancreatic cancer. Nanomedicine. 2018 Jan 9;14(3):769–780.

15. Imamura H, Sano K, Sugawara Y, Kokudo N, Makuuchi M. Assessment of hepatic reserve for indication of hepatic resection: decision tree incorporating indocyanine green test. J Hepatobiliary Pancreat Surg. 2005;12(1):16-22. doi: 10.1007/s00534-004-0965-9

16. Hope-Ross M, Yannuzzi LA, Gragoudas ES, Guyer DR, Slakter JS, Sorenson JA, Krupsky S, Orlock DA, Puliafito CA. Adverse reactions due to indocyanine green. Ophthalmology. 1994 Mar;101(3):529-33. doi: 10.1016/s0161-6420(94)31303-0.