

Fluorescent Imaging With Indocyanine Green During Laparoscopic Cholecystectomy in Patients at Increased Risk of Bile Duct Injury

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Abstract

Background. Although rare, injury to the common bile duct (CBD) during laparoscopic cholecystectomy (LC) can be reduced by better intraoperative visualization of the cystic duct (CD) and CBD. The aim of this study was to establish the efficacy of early visualization of the CD and the added value of CBD identification, using near-infrared (NIR) light and the fluorescent agent indocyanine green (ICG), in patients at increased risk of bile duct injury. **Materials and Methods.** Patients diagnosed with complicated cholecystitis and scheduled for LC were included. The CBD and CD were visualized with NIR light before and during dissection of the liver hilus and at critical view of safety (CVS). **Results.** Of the 20 patients originally included, 2 were later excluded due to conversion. In 6 of 18 patients, the CD was visualized early during dissection and prior to imaging with conventional white light. The CBD was additionally visualized with ICG-NIR in 7 of 18 patients. In 1 patient, conversion was prevented due to detection of the CD and CBD with ICG-NIR. **Conclusions.** Early visualization of the CD or additional identification of the CBD using ICG-NIR in patients with complicated cholecystolithiasis can be helpful in preventing CBD injury. Future studies should attempt to establish the optimal dosage and time frame for ICG administration and bile duct visualization with respect to different gallbladder pathologies.

Keywords

image-guided surgery, surgical education, simulation

Introduction

Laparoscopic cholecystectomy (LC) has become the standard surgical treatment for patients with symptomatic cholecystolithiasis¹⁻⁴ and today is one of the most frequently performed procedures in general surgery.^{5,6} Although laparoscopy improves postoperative outcomes compared with open surgery, bile duct injury is a rare but serious and persistent complication. The classic injury occurs when the common bile duct (CBD) is mistaken for the cystic duct (CD), resulting in (partial) CBD resection.⁷ Bile duct injury is associated with high morbidity rates, prolonged hospital stay, challenging and extensive surgery, and a significant negative impact on quality of life even 10 years after the event.⁸ Therefore, it is now strongly advised that the critical view of safety (CVS) must be met prior to clipping of any tubular structure.⁹ However, and despite the widespread implementation of CVS, recent literature suggests that bile duct injury still occurs in 0.26%

to 0.7% of procedures.¹⁰⁻¹⁵ In addition, conversion to an open procedure is indicated in cases where CVS cannot be reached, with reported conversion-to-open rates in LC presently around 2.6% to 10%.¹⁶⁻¹⁸ Conversion is often due to unclear (biliary) anatomy associated with a wider range of conditions including acute cholecystitis, acute biliary pancreatitis, bleeding in Calot's triangle, fibrotic shrunken gallbladders due to previous infection, gallstones in Hartmann's pouch, a short cystic duct, Mirizzi's syndrome, or abnormal biliary anatomy.¹⁷⁻²⁰

Although the intraoperative cholangiogram (IOC) was introduced in open cholecystectomy for diagnostic and

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therapeutic reasons, use of the procedure in LC also helps prevent bile duct injury by allowing real-time imaging of the bile ducts. However, the routine use of IOC in LC is controversial due to a number of drawbacks including significantly increased operating time, added costs, requirement for cannulation of the bile duct with a concomitant increased risk of bile duct injury, radiation exposure, misinterpretation and the need for additional equipment and trained personnel.^{13,21-23} IOC is therefore not part of the standard operative procedure in every country. More recently, extensive investigation of fluorescent image-guided surgery has shown that the technique can improve the identification of certain anatomic structures. A number of studies have demonstrated that real-time fluorescent imaging, using indocyanine green (ICG) (ICG-Pulsion, Pulsion medical Systems AG, Munich, Germany) in combination with a near-infrared (NIR) camera, is a viable approach to real-time fluorescent identification of the bile ducts in uncomplicated cholecystolithiasis,²⁴⁻³⁸ and without the disadvantages of IOC. Although real-time fluorescent imaging has clear potential in the enhanced visualization of the CBD in patients at risk for bile duct injury, the majority of the studies published to date actually excluded patients with acute cholecystitis, biliary pancreatitis, cholangitis, increased risk of common bile duct stones, and conversion to an open procedure. These patients in particular would potentially derive the greatest benefit from intraoperative identification of the CD and CBD, and improved imaging would help in the move toward safe LC.

This study therefore sought to evaluate whether ICG-NIR facilitates earlier identification of the CD compared with conventional white light imaging in patients with complicated cholecystolithiasis. Furthermore, we also attempted to determine if ICG-NIR contributes to the additional identification of the CBD compared with conventional imaging in these cases.

Materials and Methods

Patients

All consecutive patients attending the outpatient clinic or the emergency room of the VU Medical Centre Amsterdam who met the inclusion criteria were asked to participate.

Inclusion criteria were the following: age 18 years and older, scheduled for LC after complicated gallstone disease as indicated by an acute or chronic cholecystitis, biliary pancreatitis, percutaneous gallbladder drainage, choledocholithiasis without signs of CBD stones at surgery or after endoscopic retrograde cholangiopancreatography (ERCP).

Exclusion criteria were the following: isolated symptomatic cholelithiasis, iodine allergy, hyperthyroidism,

hypothyroidism and use of listed medication interfering with hepatic ICG uptake as mentioned in the "Summary of Product Characteristics" (SPC) of ICG-Pulsion (anti-convulsive medication, cyclopropane, bisulphate connections, sodium bisulfite haloperidol, diamorphine, pethidine, morphine, nitrofurantoin, opium alkaloids, phenobarbital, phenylbutazon, probenecid, metamizole, rifamycin, methadone, or heroin). The study protocol was carried out in accordance with the Declaration of Helsinki, approved by the institutional ethics committee of the VU University Medical Centre Amsterdam and registered in the Dutch Trial Registration register (NTR 4680).

Indocyanine Green

Indocyanine green is a fluorescent contrast agent with a peak emission of 830 nm when assessed with NIR light. Following intravenous injection, ICG becomes protein-bound and is excreted exclusively by the liver into the bile without entering the enterohepatic circulation.³⁹⁻⁴¹ ICG is pharmacologically inactive, is not metabolized, and has been successfully and safely used in the assessment of liver function, arterial microcirculation, tissue perfusion, ophthalmic imaging, and imaging of the bile ducts during uncomplicated cholecystolithiasis.

Near-Infrared Laparoscopic Camera

The NIR camera used for this study was developed by Olympus (Olympus, Tokyo, Japan). A filter was designed to fit a rigid 0° laparoscope with a 10 mm diameter (Olympus, Tokyo, Japan). Using a lever, the image from the laparoscopic camera can be switched from conventional laparoscopic imaging to NIR imaging. The excitation barrier filter only admits light with a wavelength above 800 nm. Using the NIR camera, all fluorescent structures are displayed in green against a black (non-fluorescent) background. The NIR camera system in conjunction with ICG-enhanced fluorescence has already been used during a number of laparoscopic procedures including LC and sentinel lymph node imaging in colorectal cancer.^{28,42,43}

Surgical Procedures

Patients were scheduled and prepared according to the standard preoperative protocol for elective or acute LC, depending on the indication for surgery. In the operating room, directly after the time-out procedure and induction of general anesthesia, patients received an intravenous bolus of 0.2 mg/kg ICG diluted in water for intravenous injection. During the cholecystectomy, a conventional laparoscopic camera (EndoEye, Olympus, Tokyo, Japan) and a NIR camera (Olympus, Tokyo, Japan) were used

and the image modes were switched during the surgical procedure. The NIR scope was used at set points during surgery (further referred to as “look”) to visualize the fluorescent bile ducts, in particular the CD and the CBD. The first look performed in all patients, attempt to visualize the fluorescent bile ducts (first look) after incising the peritoneal fold in the hilus of the gallbladder and before dissection of Calot’s triangle. If the CD could not be visualized at the start of dissection, a second look with the NIR scope followed at an early point during dissection but before skeletonizing of structures. In all patients, a third look with the NIR laparoscope was performed when CVS was reached with conventional imaging, to identify fluorescent bile ducts. Bile ducts, visualized by either NIR or conventional white-light imaging, were identified by the operating surgeon, the assisting surgeon and the attending investigator. The visualized structures and time of observation were noted on the case record form. The LC was performed in accordance with Dutch protocols, including achievement of CVS. An IOC was not performed since this is not part of standard LC in the majority of the hospitals in The Netherlands, including our hospital. After surgery, patients recovered on the surgical ward and were discharged according to standard post-operative procedures.

Statistical Analysis

Data were analyzed using SPSS software (SPSS version 20.0; IBM Corp, Armonk, NY). Continuous data are expressed as the median (minimum-maximum). The Mann-Whitney *U* test was performed to determine the statistical significance between groups with and without bile duct visualization with ICG-NIR. Results were considered statistically significant when $P < .05$.

Results

Following receipt of oral and written informed consent, 20 patients scheduled for LC were included in the study. The group included 13 males and 7 females, with a mean age of 65 (range 26-82) years and a mean body mass index (BMI) of 25.45 (range 16.8-38.0) kg/m². Two patients required early conversion to an open procedure due to dense adhesions as a result of acute cholecystitis. One of these patients had already undergone percutaneous gallbladder drainage and ERCP. Both patients were excluded from further analysis (Table 1).

Eighteen patients were included in the analysis (Table 2). Three patients suffered from biliary pancreatitis, one of whom had a complicated history of necrotizing biliary pancreatitis with renal failure and neuropathy, resulting in a prolonged stay at the intensive care unit before surgery (patient 1). Seven patients were diagnosed with

Table 1. Patient Characteristics (N = 20).

Male:Female	13:7
Age, years, median (min-max)	65 (26-82)
Body mass index, kg/m ² , median (min-max)	25.45 (16.8-38.0)
ASA (American Society of Anesthesiologists)	
I	7
II	10
III	3
Conversion	2

acute cholecystitis. Seven patients were diagnosed with choledocholithiasis, of whom one had undergone a prior magnetic resonance cholangiopancreatography (MRCP; patient 2), 4 patients a single ERCP (patients 3, 6, 7, 16), 1 patient 2 ERCPs (patient 10), and 1 patient 3 ERCPs (patient 14) before surgery.

The average time between injection of ICG and the first look with the NIR camera was 30 (range 20-72) minutes. At first look, the CD was observed in 3 of 18 patients using conventional white-light imaging and in 4 of 18 with ICG-NIR (Table 2). In 1 patient, the CD could be visualized with both conventional white light and ICG-NIR imaging. The CBD was visible in 2 of 18 patients using ICG-NIR. These structures could not be visualized with white light at this time point (Table 2).

In the remaining 11 patients, no bile ducts could be visualized at first look. In the protocol a second look was planned for these patients early in dissection but before skeletonizing of structures. As CVS was reached quickly after the first look in 5 of the 11 patients, a second look was performed in just 6 patients. At second look, the CD could be visualized with both imaging modalities in 1 of 6 patients, and visualized only with conventional white light in a further 2 patients. In 2 patients, the CD and CBD could be visualized only with ICG-NIR. In the final patient (patient 14), anatomy was unclear with white light. Visualization of the CD and CBD with ICG-NIR during second look aided the surgeon and prevented conversion to an open procedure.

Overall, CVS was reached 51 (range 10-117) minutes after ICG injection. At CVS, the CD could be identified in all 18 patients using conventional white light, whereas the CBD could be identified in only 3 of 18 patients. Using ICG-NIR imaging, the CD was identified in 13 of 18 patients, and the CBD could be identified in 7 of 18 patients, all of whom also showed a fluorescent cystic duct (Table 3).

When comparing patients with a cystic duct of common bile duct identified by ICG-NIR at CVS to patients in whom no fluorescent bile ducts were identified at CVS, no differences were apparent with regard to age, BMI, or duration of symptoms before surgery (Table 4). Average

Table 2. Identification of the Cystic Duct (CD) and Common Bile Duct (CBD) by Conventional Imaging and ICG-NIR During Laparoscopic Cholecystectomy.

No	Diagnosis	First Observation		Second Observation		CVS	
		Conventional imaging	ICG-NIR	Conventional Imaging	ICG-NIR	Conventional Imaging	ICG-NIR
1	Biliary pancreatitis	-	CD + CBD	x	x	CD	CD + CBD
2	Choledocholithiasis ^a	-	-	CD	-	CD	CD + CBD
3	Choledocholithiasis ^b	-	-	x	x	CD	CD + CBD
4	Acute cholecystitis	-	-	-	-	CD	-
5	Acute cholecystitis	-	CBD	x	x	CD	CD + CBD
6	Choledocholithiasis ^b	-	-	x	x	CD + CBD	CD + CBD
7	Choledocholithiasis ^b	CD	CD	x	x	CD	CD
8	Acute cholecystitis	-	CD	x	x	CD	CD
9	Acute cholecystitis	-	-	CD	-	CD	-
10	Choledocholithiasis ^c	-	-	CD	CD + CBD	CD + CBD	CD + CBD
11	Cholangitis	CD	-	x	x	CD	CD
12	Acute cholecystitis	-	-	x	x	CD	CD
13	Acute cholecystitis	-	-	x	x	CD	-
14	Choledocholithiasis ^d	-	-	-	CD+CBD	CD + CBD	CD + CBD
15	Biliary pancreatitis ^b	CD	-	x	x	CD	-
16	Choledocholithiasis ^b	-	-	-	-	CD	-
17	Acute cholecystitis	-	CD	x	x	CD	CD
18	Biliary pancreatitis	-	-	x	x	CD	CD

Abbreviations: CVS, critical view of safety; ICG, indocyanine green; NIR, near-infrared; -, not visible; x, no second look performed.

^aMagnetic resonance cholangiopancreatography.

^bEndoscopic retrograde cholangiopancreatography.

^cTwo times endoscopic retrograde cholangiopancreatography.

^dThree times endoscopic retrograde cholangiopancreatography.

Table 3. Bile Duct Imaging With Conventional and Indocyanine Green Near-Infrared (ICG-NIR) Imaging at Each "Look."

	Look 1 ^a	Look 2 ^b	Look 3 ^c
No. of patients	18	6 ^d	18
Time after ICG injection, minutes, median (min-max)	30 (20-72)	70 (28-91)	51 (10-117)
Bile duct imaging	7	4	18
Conventional imaging			
Cystic duct (CD)	3	3	18
Common bile duct (CBD)	0	0	3
No visualization of bile ducts	15	3	0
ICG-NIR imaging			
Cystic duct (CD)	4	2	13
Common bile duct (CBD)	2	2	7
No visualization of bile ducts	13	4	5

^aAfter incising the peritoneal fold in the hilus of the gallbladder and before dissection of Calot's triangle.

^bAfter the first look before skeletonizing of structures and only performed if the cystic duct could not be visualized at the first look.

^cWhen critical view of safety was reached with conventional imaging.

^dA second look was planned in 11 patients but performed in just 6 patients. In 5 patients, critical view of safety was reached quickly after the first look before a second look could have been performed.

total operating time was 82.5 (range 45-128) minutes, and this did not differ between patients with and without fluorescent bile duct imaging (Table 4). Time between ICG injection and first look).

Time between ICG injection and first look and the time between injection and CVS were also comparable between groups. This suggests that there were no significant differences in terms of difficulty of

Table 4. Characteristics of Patients With and Without ICG-NIR Imaging of the Bile Ducts at CVS.

	ICG-NIR Identification	No ICG-NIR Identification	P
No. of patients	13	5	
Age, years, median (min-max)	65 (39-82)	65 (26-73)	.964
BMI, kg/m ² , median (min-max)	25 (16.8-32.4)	25.6 (19.4-33.0)	.750
Diagnosis			
Cholecystitis acuta	4	3	
Biliary pancreatitis	2	1	
Choledocholithiasis	6	1	
Cholangitis	1	0	
Time symptoms to operation, days, median (min-max)	75 (2-714)	2 (2-238)	.213
First look, minutes, median (min-max)	30 (20-72)	42 (23-57)	.750
CVS, minutes, median (min-max)	49 (25-117)	60 (10-101)	.892
Operating time, minutes, median (min-max)	75 (45-128)	90 (50-120)	.892

Abbreviations: CVS, critical view of safety; ICG, indocyanine green; NIR, near-infrared.

the surgical procedure between the patients with and without ICG-NIR bile duct imaging.

No bile duct injuries occurred in the cohort and no other complications arose. In addition, no anatomical variations of the biliary tree were identified.

Discussion

This study was designed to assess the practicality and usefulness of ICG-NIR in early identification of the CD and the additional imaging of the CBD, compared with conventional white-light imaging, during LC in patients with complicated cholecystolithiasis. Fluorescent imaging of the CD was possible in the majority of the cases at CVS, and improved the identification of the CBD compared to conventional white-light imaging. In 1 patient, it was even possible to prevent conversion by detecting the CD and CBD with ICG-NIR before CVS was reached. However, we should emphasize that the number of patients included in the study was small and earlier CD identification by ICG-NIR was only possible in a few of these patients. Second, overall visualization rates of the CD and CBD with NIR fluorescence were much lower than the visualization rates described for uncomplicated cases of cholecystolithiasis.²⁴⁻³⁸

The diminished visualization of the bile ducts with ICG-NIR in the patient population presented here may have been due to severe edema or dense adhesions as a result of an acute or past inflammation or an intervention such as ERCP.^{26,33,34} It is important to bear in mind that the penetration depth of ICG is limited (± 1.0 cm) and is probably insufficient for visualization of the bile ducts when covered by thickened tissue. This phenomenon is also suspected in obese patients (BMI >30 kg/m²), in which case the bile ducts are covered by a fatty peritoneum. In agreement with current literature, we did not find significant differences in BMI in our patients in

relation to successful or unsuccessful imaging of bile duct structures.⁴⁴ We hypothesize that other patient and surgical-related factors, including inflamed tissue, may interfere with and influence the success rate of fluorescence visualization of the bile ducts in complicated cases.

Important unresolved issues regarding the ICG-NIR technique are the large disparities in time intervals to imaging following injection of ICG and the wide variation in dosages. In current literature, the reported timing of ICG injection in uncomplicated cholecystolithiasis varies between 30 and 60 minutes prior to start of surgery until after endotracheal intubation. Whether a prolonged interval (up to 24 hours) improves visualization is not yet known. In terms of dosage, in the present study we used 0.2 mg/kg, which is in the range of a bolus of 2.5 mg in total up to 0.5 mg/kg used in described in current literature. Based on our earlier (satisfactory) results in uncomplicated cases and for logistical reasons, ICG was injected directly after induction of general anesthesia.²⁸ Our final look in all patients at CVS was reached at a median of 51 (10-117) minutes after ICG administration. Bearing in mind the low visualization rates of bile ducts in our study, particularly compared with uncomplicated cases, we presume that dosage and time frame are decisive and crucial for the effectiveness of CD and CBD NIR fluorescence imaging in patients with complicated gallbladder pathologies.

With normal liver function, 95% of ICG is captured by hepatocytes within 15 minutes of injection and excreted into the bile.⁴⁵ In patients with decreased liver function, removal of ICG from blood to bile is delayed. This suggests that earlier injection of ICG could improve detection rates of the CD and CBD in complicated cases. Verbeek et al⁴⁶ have shown, in uncomplicated cases, that optimal visualization of the bile ducts is achieved by injection (10 mg ICG) 24 hours prior to surgery and is due to an increased contrast ratio of CBD versus liver

background. These authors argued that administration of ICG should be performed as early as possible in all patients to allow optimal clearance of the contrast agent from the liver before undertaking NIR fluorescence-assisted LC. However, this regime would be challenging in the case of elective LC and in patients suffering from acute cholecystitis requiring early surgery.

Four studies to date have described (small) patient cohorts in which ICG-NIR bile duct imaging was used in LC due to complicated cholecystitis.^{26,32,33,47} The most complicated cases included in these studies were patients with acute cholecystitis. The CD and CBD visualization rates described in these studies were significantly higher than those found in our study (91.6% to 100% and 72% to 79.1% versus 72% and 38%, respectively). With the exception of patient selection, these studies show no great differences in timing and dosage compared to our study, thus suggesting that patient pathology influences the efficacy of ICG. It is presently unclear whether this phenomenon can be attributed to delayed clearance of ICG from blood to bile due to decreased liver clearance, as described above. Therefore, future studies should attempt to establish optimal dosages and timeframes for ICG administration and bile duct visualization, taking into account both the various gallbladder pathologies and feasibility in daily surgical practice.

Conclusion

NIR fluorescence-assisted LC has the potential to become a standard surgical procedure. Early visualization of the cystic duct and additional imaging of the CBD may increase safety in LC and might offer an alternative to the intraoperative cholangiogram in patients with an increased risk of CBD injury. In contrast to the ease and efficiency of CD and CBD detection by fluorescent imaging in uncomplicated cases, gallbladder pathology appears to create a much more challenging and complex situation. Further research is needed to optimize techniques, dosage, timing, and patient selection in order to establish whether ICG-NIR can help prevent and manage bile duct injury, and whether there is a place for routine use of fluorescent imaging in those patients at increased risk of bile duct injury during LC.

Authors' Note

Olympus (Olympus, Tokyo, Japan) provided the prototype NIR camera used in this trial. Results of the study were presented orally at the 23th International EAES Congress, June 3-7, 2015, Bucharest, Romania.

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Declaration of Conflicting Interests

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