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ORIGINAL ARTICLE

Image-guided laparoscopic cholecystectomy using indocyanine green fluorescence cholangiography: what is the optimal time of administration?

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ABSTRACT

Introduction: Near-infrared (NIR) fluorescent cholangiography (FC) using indocyanine green (ICG) in laparoscopic cholecystectomy (LC) has been used as a technique for real-time visualization of bile ducts for approximately ten years; however, no standard protocol has been determined. This study aimed to determine the optimal time of administration of ICG.

Material and methods: In this prospective study, patients ($n = 30$) indicated for LC were divided into two groups. The first group received ICG 1 h before anesthesia at a dose of 0.1 mg/kg (1 h group), whereas the other group received ICG immediately after anesthesia with the same dose (0 h group).

Results: The rates of identification of the cystic duct (CD) and common bile duct (CBD) using NIR FC before and after dissection of Calot's triangle were comparable between the two groups. The fluorescence intensity ratios of CD/Liver and CBD/Liver were significantly higher in the 1 h group (2.2 vs. 0.49 and 2.1 vs. 0.38, respectively, $p < .001$) with minimal background liver fluorescence interference in the 1 h group.

Conclusions: The study illustrates that administration of ICG 1 h before surgery with a dose of 0.1 mg/kg allows superior visualization of the extrahepatic bile ducts with minimal fluorescence interference from the background liver.

Abbreviations: BDI: bile duct injury; BMI: body mass index; CBD: common bile duct; CD: cystic duct; CHD: common hepatic duct; CVS: critical view of safety; FC: fluorescent cholangiography; FI: fluorescence intensity; GB: gallbladder; ICG: indocyanine green; IOC: intraoperative cholangiography; LC: laparoscopic cholecystectomy; NIR: Near-infrared; WL: white light

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Indocyanine green; near-infrared fluorescence cholangiography; cholecystectomy; laparoscopic

Introduction

Laparoscopic cholecystectomy (LC) is the standard approach for the treatment of benign gall bladder (GB) diseases and one of the most frequent surgical procedures performed worldwide [1]. Bile duct injury (BDI) after LC is rare with an incidence of 1%, but it is associated with significant morbidity and repeated surgical interventions [2,3]. The main cause of BDI is the anatomical variations and misinterpretation of cystic and common bile ducts during surgery [4]. To reduce the risk of BDI, several techniques have been recommended, such as the principle of critical view of safety (CVS) and intraoperative cholangiography to visualize the biliary tree [1,5].

The risk of BDI through imaging of the biliary tree during LC is reduced with intraoperative radiographic cholangiography (IOC); however, it is associated with several pitfalls that limit its use, such as exposure to radiation, requirement for training and expertise in the technique, time consumption, and the likelihood of the technique of cannulation of the cystic duct (CD) to cause BDI itself [2,6,7].

Fluorescent cholangiography (FC) using indocyanine green (ICG) represents a better real-time imaging alternative to IOC because it is less invasive and easy to interpret, and it does not expose the staff to radiation [4]. Several studies have reported the role of FC in the identification of the biliary anatomy and prevention of BDI [1,7–9]. However, those studies used different doses of ICG, which were administered at different times either after induction of general anesthesia or before surgery (up to 24 h) [2,4,10,11].

The standard protocol of ICG administration that could achieve high fluorescence in the bile ducts with low background liver fluorescence is still being

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studied [4]. Therefore, the aim of this study was to evaluate FC during LC using an ICG dose of 0.1 mg/kg at two different dosing times either immediately after induction of general anesthesia or 1 h before surgery.

Material and methods

Study population

This prospective study was approved by the Ethics Committee of Alexandria University and included 30 consecutive patients who underwent elective LC for symptomatic cholelithiasis with the aid of ICG FC. Patients with any contraindications to ICG, such as renal impairment, iodine/ICG allergy, and pregnancy, were excluded from the study. Informed consent was obtained from all patients.

Indocyanine green administration

Patients were divided into two groups; the first group received ICG 1 h before anesthesia (1 h group), and the other group received ICG after induction of general anesthesia (0 h group). ICG, 25 mg (Verdye, Diagnostic Green, Aschheim-Dornach, Germany), was suspended in 10 ml sterile water and injected at a dose of 0.1 ml/kg for every patient.

Laparoscopic fluorescence imaging system

LC was performed using a high-definition laparoscopic fluorescence imaging system (Karl Storz GmbH & CO. KG, Tuttlingen, Germany). The system provides two separate modes: the conventional white light mode (WL mode) and fluorescence mode (ICG mode) without the possibility of overlay of the two modes. However, switching between the modes is easy and rapid through buttons on the camera head.

Assessment of fluorescence intensity

A quantitative assessment of FC was performed using Image J software, version 1.53a (National Institutes of Health, USA) [12,13]. The mean fluorescence intensities (FI) of the regions of interest (CD, CBD, and background liver) were measured; then, the ratios of CD/Liver and CBD/Liver were calculated.

Statistical analysis

Gpower software version 3.0.10 was used to calculate the sample size depending on the following parameters: $\alpha = 0.05$, power of study = 80%, and difference in means (δ) of FI, based on a previous study; it should be equal to or more than 12 patients in each group [4]. Categorical data were expressed as numbers and percentages and compared using the chi-squared test or Fisher's exact test, as appropriate. Meanwhile, continuous variables were presented as medians and interquartile ranges and compared using the Mann–Whitney *U*-test. p-Values < .05 were denoted statistical significance. All statistical analyses were performed using SPSS Statistical Package for the Social Sciences (version 25.0; IBM Corp., Armonk, NY, USA).

Table 1. Perioperative characteristics of patients of both groups.

	1h Group ($n = 15$)	0h Group ($n = 15$)	p
Age (years)*	41 (36–55)	45 (28–55)	.96
Female gender, *n* (%)	12 (80)	14 (93)	.28
BMI (Kg/m^2) *	35 (30–43)	37 (30–41)	.59
Laboratory Parameters			
Hb (mg/dl)*	12.5 (11.5–13)	12 (11.6–13)	.90
PT-INR*	1 (0.96–1.02)	0.97 (0.92–1)	.16
T. Bil (mg/dl)*	0.5 (0.3–0.75)	0.5 (0.4–0.6)	.96
ALP (U/l)*	80 (65–111)	74 (49–90)	.26
ALT (U/l)*	21 (16–23)	22 (18–31)	.26
AST (U/l)*	19 (17–26)	21 (17–24)	.58
GB Ultrasound, *n* (%)			
Thickened wall (>4 mm)	6 (40)	4 (27)	.44
Contracted GB	2 (13)	1 (7)	.54
Impacted stone in the GB neck	2 (13)	1 (7)	.54
GB stones > 2.5 cm	1 (7)	2 (13)	.54
Multiple GB stones	9 (60)	10 (67)	.71
Operative parameters			
Operative time (min)*	35 (30–40)	40 (30–40)	.56
Blood loss (ml)*	10 (10–30)	30 (20–30)	.06

*Data are presented as medians and interquartile range.
ALP: alkaline phosphatase; ALT: alanine transaminase; AST: aspartate transaminase; BDI: bile duct injury; BMI: body mass index; GB: gallbladder; Hb: hemoglobin; HBV: hepatitis B virus; HCV: hepatitis C virus; INR: international normalized ratio; T. Bil: total bilirubin.

Results

This study included 30 patients who underwent LC for symptomatic cholelithiasis. Patients' characteristics are summarized in Table 1. No significant differences were found between the two groups regarding age, gender, body mass index (BMI), laboratory parameters, or the ultrasonographic features of the GB. The operative time and intraoperative blood loss were comparable between the two groups. Neither BDI nor other postoperative complications occurred, and all patients were discharged on the day of surgery or the next morning. There were three difficult cases of LC with severe adhesions in the 1 h group and four difficult cases of LC with marked fibrosis in Calot's triangle in the 0 h group, but no patient required conversion to open surgery.

Identification of biliary structures using FC

Before dissecting the Calot's triangle, the CD and CBD were identified using FC in 93% and 87% of cases, respectively, in the 1 h group and 67% and 53% of cases, respectively, in the 0 h group with no significant difference. However, after the achievement of CVS and removal of all fat and fibrous tissues in the Calot's triangle, the visualization of the CD and CBD by FC was improved reaching 100% and 93% of cases in the 1 h group and in 80% and 60% of cases in the 0 h group, as presented in Table 2.

The difference in FI between the background liver and bile ducts

The FI of the background liver was higher than that of biliary structures in the 0 h group with CBD/Liver

Table 2. Identification of biliary structures in the two groups.

	1h Group ($n = 15$)	0h Group ($n = 15$)	p
Identification of biliary structures using ICG mode, n (%)			
Before dissection			
CD	14 (93)	10 (67)	.17
CBD	13 (87)	8 (53)	.11
After dissection			
CD	15 (100)	12 (80)	.22
CBD	14 (93)	9 (60)	.08
FI Ratio			
FI CBD/Liver	2.1 (1.8–2.5)	0.38 (0.31–0.43)	<.001
FI CD/Liver	2.2 (2–2.57)	0.49 (0.4–0.63)	<.001

CD: cystic duct; CBD: common bile duct; FI: fluorescence intensity; ICG: indocyanine green.

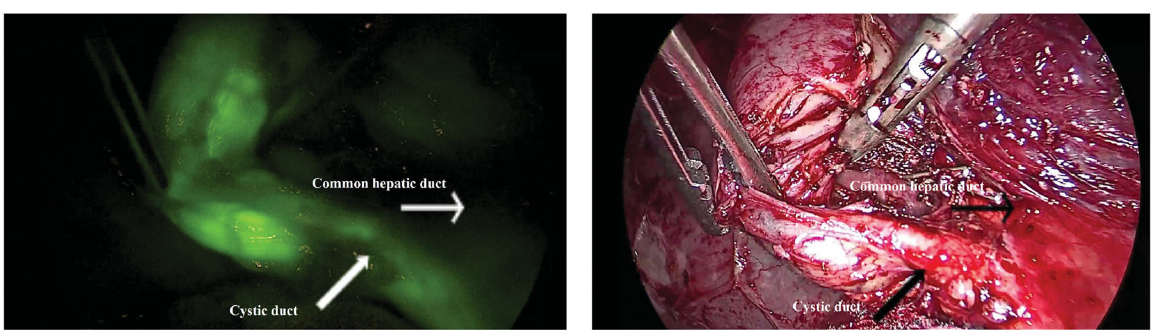

Figure 1. Fluorescence cholangiography using ICG during LC after the achievement of critical view of safety and transection of the cystic artery in the 1 h group.

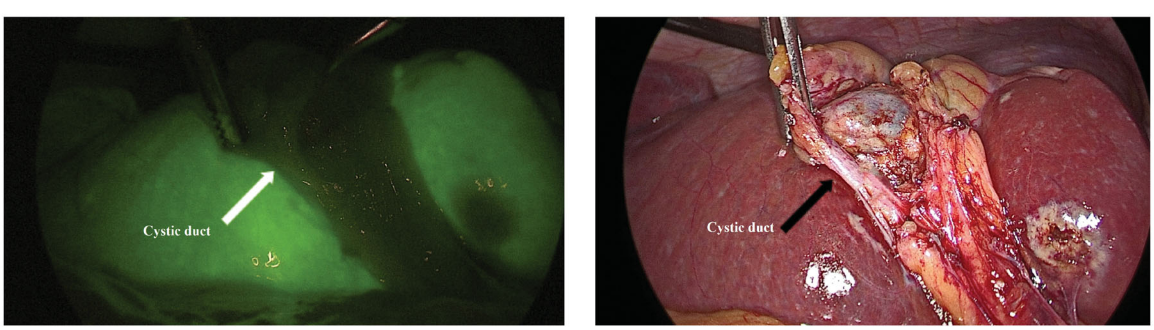

Figure 2. Fluorescence cholangiography using ICG during LC after the achievement of critical view of safety in the 0 h group.

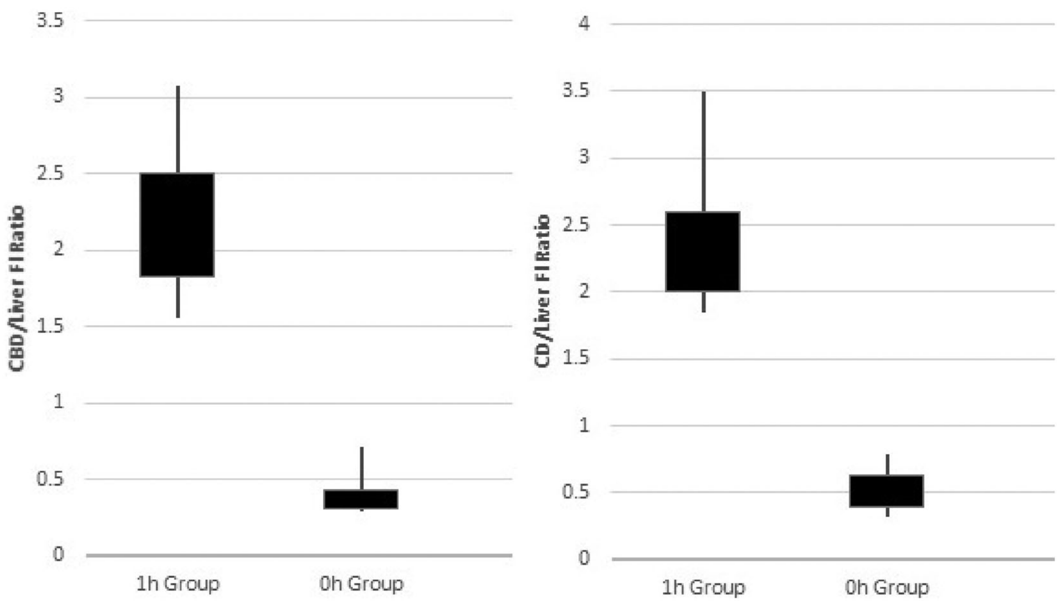

Figure 3. Fluorescence intensity ratios CBD/Liver and CD/Liver in the two groups.

and CD/Liver FI ratios <1 (medians of 0.38 and 0.49, respectively). In the 1 h group, the FI of the background liver was lower than that of biliary structures with CBD/Liver and CD/Liver FI ratios > 1 (medians of 2.1 and 2.2, respectively). The differences in CBD/Liver and CD/Liver FI ratios between the two groups were statistically significant ($p < .001$), as illustrated in Figures 1–3 and Table 2.

Discussion

BDI is a disastrous complication that occurs in approximately 1% of laparoscopic cholecystectomies all over the world, even with the most experienced surgeons [1,13]. Visual misinterpretation of the biliary anatomy during LC plays a major role in the occurrence of BDI, especially in the presence of severe adhesion, inflammation, or biliary anomalies [13,14]. Hence, real-time visualization of the biliary anatomy could potentially reduce the risk of BDI and the rate of conversion to open surgery.

ICG is a fluorescent dye that emits light in the near-infrared spectrum at 830 nm and could penetrate tissues up to 1 cm thick; however, structures deeper than 1 cm are not detectable by near-infrared (NIR) cameras. ICG is the ideal contrast for both fluorescent angiography and cholangiography because it enters the blood vessels by binding to plasma proteins and is totally excreted in the bile. In patients with normal liver function, around 95% of ICG is excreted in the bile within 15 min.

Near-infrared FC using ICG is the only available method for real-time visualization of the biliary anatomy, even before dissection of Calot's triangle and without the need for cannulation of the CD or exposure to radiation. Consequently, this technique enables the surgeon to safely dissect Calot's triangle and achieve a CVS with confidence and without any vasculo-biliary injuries.

Since the first study on the use of FC in LC by Ishizawa et al. [15], several studies have reported that this technique was very efficient in delineation and visualization of the extrahepatic biliary anatomy during LC. Furthermore, they demonstrated that the incidence of BDI, operative time, and rate of conversion to open approach were significantly reduced when ICG was used in LC [16–19]. A recent meta-analysis by Dip et al. [20], which included more than 6000 patients, reported that the incidence of BDI was four times lower, and the incidence of conversion to open surgery was 17 times lower in LC with FC when compared with conventional LC. Its results were attributed to the early and clear delineation of CD and CBD, even before dissection of Calot's triangle, which gave the surgeons more confidence during surgery.

Several studies compared the use of NIR FC versus IOC in LC and found that the duration of surgery was significantly longer in the case of LC with IOC because NIR FC facilitated the surgeon's easy and early detection of bile ducts in the same screen and surgical field, resulting in faster dissection during LC. Moreover, the new NIR devices could overlay ICG and WL modes together, which provide the surgeons with a continuous orientation of the biliary anatomy [20–24].

A systematic review by Lim SH et al. [25], which included 15 studies comparing FC and IOC in LC, found a higher rate of CHD identification while using FC in LC. By contrast, the rates of visualization of CD and CBD were similar between the two techniques. IOC produced biliary images of higher resolution; however, it was associated with a greater incidence of technical failure than FC.

Nevertheless, there are limitations in the ability of ICG FC to visualize CBD stones as in IOC or extrahepatic structures if covered by thickened periductal fat or adhesions (thickness > 1 cm). Osayi et al. [26] found a significant decrease in the rate of detection of the CD junction in obese patients (BMI > 30), and in the same way, Aoki et al. [27] reported poor visualization of bile ducts in obese patients.

Several approaches have been proposed for the dose and timing of administration ICG for FC based on the pharmacokinetics of ICG. [19] The optimal dose and timing of administration of ICG should achieve adequate fluorescence intensity in the extrahepatic biliary structures with low background liver fluorescence, and received wisdom is that the higher the FI in the CBD and CD relative to the background liver FI, the clearer the FC would be [13]. The time of ICG administration varied significantly in the literature, ranging from 24 h before surgery to the time of induction of anesthesia [2,8–10,13,28–30]. By contrast, the dosage of ICG was either a fixed-dose (2.5–20 mg) or according to the bodyweight (0.02–0.5 mg/kg) [2,13,19,31]. In this study, a dose of ICG according to the bodyweight was used as the metabolism of ICG is dependent on it, and a dose of 0.1 mg/kg is sufficient to enable visualization of the extrahepatic bile ducts [4,21].

As the ICG appears in bile minutes after injection, some studies found that administration of ICG at induction of anesthesia provided adequate visualization of the bile ducts [7–9,11]. However, the high FI of the background liver usually interferes with the quality of FC, which is the reason some investigators attempted to administer ICG 24 h before surgery to avoid the interference of the background liver fluorescence [2,10,13]. Matsumura et al. [4] compared two different times of ICG administration – either at induction of anesthesia or one day before surgery. The researchers found that the CBD/Liver FI ratio was <1 if ICG was administered immediately before surgery, whereas it was significantly higher if ICG was administered one day before surgery. Similarly, a study by Verbeek et al. [2] found that 10 mg of ICG administered 24 h before surgery achieved excellent FC with insignificant background liver FI. Nevertheless, the administration of ICG one day before surgery is impractical because most cases of elective LC are admitted to the hospital on the same day of surgery.

In this study, the CBD/Liver contrast ratio was <1 if ICG was administered at the time of surgery, and visualization of the biliary structures was obscured by the background liver contrast. By contrast, administration of ICG 1 h before surgery resulted in a significantly higher CBD/Liver contrast ratio with excellent visualization of the extrahepatic biliary structures and minimal interference from the background liver fluorescence. In the same way, Zarrinpar et al. [31] compared different doses and times of ICG administration and reported that the injection of ICG at a dose of 0.25 mg/kg in 45 min before surgery achieved clear demarcation of bile ducts with the lowest background liver contrast interference. It is evident that the administration of ICG 1 h before surgery is more practical than longer intervals, such as 24 h before surgery, and more suitable for patients with acute cholecystitis, and it does not require admission of the patients one day before surgery.

There are several limitations to this study. First is the small number of patients included in the study and the inability to assess other protocols of ICG administration. Second, the study did not include patients with acute cholecystitis or more complicated cases, such as Mirrizi's syndrome. Lastly, the study did not assess the role of ICG FC in preventing BDI and its impact on the duration of surgery or the rate of conversion to open surgery in comparison with conventional LC.

In conclusion, ICG administration 1 h before LC at a dose of 0.1 mg/kg provides the optimal visualization of the extrahepatic biliary structures with minimal background liver interference.

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Declaration of interest

The authors of this manuscript have no conflicts of interest to disclose.

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