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Dose and administration time of indocyanine green in near-infrared fluorescence cholangiography during laparoscopic cholecystectomy (DOTIG): study protocol for a randomised clinical trial

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ABSTRACT

Background One of the most severe complications in laparoscopic cholecystectomy (LC) is intraoperative bile duct injury (BDI). Despite its low incidence, the medical implications for the patient can be serious. Besides, BDI can also generate significant legal issues in healthcare. Different techniques have been described to reduce the incidence of this complication, and near-infrared fluorescence cholangiography with indocyanine green (NIRFC-ICG) is one of the latest additions. In spite of the great interest aroused by this procedure, there are currently great disparities in the usage or administration protocols of ICG.

Methods and analysis This is a randomised, multicentre, per-protocol analysis, open clinical trial with four arms. The estimated duration of the trial is 12 months. The aim of the study is to analyse whether there are differences between the dose and administration ICG intervals to obtain good-quality NIRFC during LC. The primary outcome is the degree of identification of critical biliary structures during LC. In addition, different factors will be analysed that may have an influence on the results of this technique.

Ethics and dissemination The trial will be conducted according to the recommendations for Clinical Trials in the Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects and the recommendations of the Spanish Agency of Medicines and Medical Devices (AEMPs) for clinical trials. This trial was approved by the local institutional Ethics Committee and the AEMPs. The results of the study will be presented to the scientific community through publications, conferences or other means.

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Trial registration number NCT05419947.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Randomised clinical trial that attempts to find differences in the visualisation rates of extrahepatic biliary structures with different doses and administration intervals of indocyanine green (ICG).
⇒ Future possibilities to create a protocol and generalise adequate doses and administration intervals for ICG.
⇒ However, only four arms are assessed (the most common ones found in the literature), and there are multiple possible combinations.
⇒ Subjective visual assessment of the targets.

INTRODUCTION

Symptomatic cholelithiasis has a major worldwide impact, with prevalence rates of up to 20%. Regardless of the related-symptoms or complications, the gold standard treatment is the laparoscopic cholecystectomy (LC).[1 2] One of the most severe complications is bile duct injury (BDI). Although its incidence is <1%, BDI is associated with increased morbidity and mortality, poorer quality of life, increased health costs and medicolegal consequences.[3] One of the main factors in BDI is the misidentification of biliary anatomy,[4] related to anatomic variability and inflammatory changes after complicated cholelithiasis.

One of the techniques that have been developed to avoid BDI is near-infrared fluorescence cholangiography with indocyanine green (NIRFC-ICG). Although this technique has been widely assessed over the last years, currently there are still significant differences in the ICG administration protocols.

The aim of the study is to analyse the differences between the doses and administration intervals of ICG to achieve an optimal visualisation of the extrahepatic biliary anatomy during LC.

METHODS AND ANALYSIS

Objectives

Primary endpoint

Analysing whether there are differences between different doses (fixed or weight-adjusted doses) and ICG administration intervals for an optimal visualisation of biliary anatomy during NIRFC-LC.

Secondary endpoints

- Analysing the influence of the body mass index (BMI) on the results of NIRFC-LC.
- Analysing the influence of the previous biliary disease (biliary colic, choledocholithiasis, cholecystitis, pancreatitis, cholangitis) and previous liver disease (fatty liver, hepatitis, cirrhosis), on the results of NIRFC-LC.
- Analysing the influence of the surgery (elective/early/delayed) on the results of NIRFC-LC.
- Analysing the influence of previous biliary interventions (endoscopic retrograde cholangiopancreatography (ERCP), percutaneous cholecystostomy, endoscopic ultrasound-guided gallbladder drainage) on the results of NIRFC-LC.
- Analysing the influence of the different laparoscopic imaging systems on the results of NIRFC-LC.
- Analysing the rate of intraoperative and postoperative complications related to NIRFC-LC.
- Analysing the impact of NIRFC-LC on general surgeons and their subjective assessment of the procedure.

Design

Prospective, randomised, phase IV, open, multicentre and parallel study with four arms (two doses and two administration intervals). The distribution of the patients is 1:1:1:1. The framework of the study has been designed to observe differences between doses and the time of ICG administration in NIRFC-LC. We adhere to the Standard Protocol Items for Randomized Trials (SPIRIT).[5] The SPIRIT 2013 Checklist is provided in online supplemental file 1.

Study scope

The institutions which participated in the study were the Hospital Universitario de Salamanca and the Hospital Universitario Germans Trias i Pujol. They are both academic medical hospitals in Spain.

Study population

Inclusion criteria

- Age>18 years.
- Self-sufficiency.
- Scheduled LC indication:
  - Surgery for gallstone disease.
  - Surgery for gallbladder polyps.
  - Surgery for gallbladder adenomyomatosis.
- Indication of early LC (<72 hours for admission with acute cholecystitis or biliary colic).
- Delayed urgency LC.
- Understanding the information.
- Signature of the informed consent (online supplemental file 2).

Exclusion criteria

- Age <18 years.
- Disability.
- Pregnancy or lactation.
- Chronic kidney disease (stage>IIIb).
- Previous adverse reactions to ICG.
- Previous adverse reactions to ICG excipients.
- Previous adverse reactions to iodinated contrast agents.
- Functional thyroid disorders.
- Emergency gallbladder surgery.
- Initial laparotomy surgery.
- Previous suspicion of gallbladder cancer.
- Inability to understand the information about the study.
- Refusal to participate in the study.

Interventions

All the patients included in the study will undergo LC with intraoperative NIRFC through intravenous administration of ICG (Verdye (Diagnostic Green GMBH, Achheim-Dornach, Germany)). The administration protocols of this drug will be divided according to the dose and time interval until surgery, as detailed below (figure 1):

- **Dose**: two groups—2.5 mg fixed dose or weight-adjusted dose (0.05 mg/kg).
- **Administration time**: two groups—on admission (>3 hours before surgery) and during the anaesthesia induction (15–30 min before surgery).

Surgery will be conducted based on the criteria for safe LC. The surgeons who will perform this technique have wide experience in the treatment of symptomatic gallstone disease and hepatobiliary disorders. Different imaging systems will be used according to each hospital: 1688 Advanced Imaging Modalities (AIM) 4K Platform (Stryker), IMAGE1 S 4U-LINK/RUBINA, OPAL1 NIR/ICG (Karl Storz-Endoskope) and VISERA ELITE II OTV-S300 (Olympus).

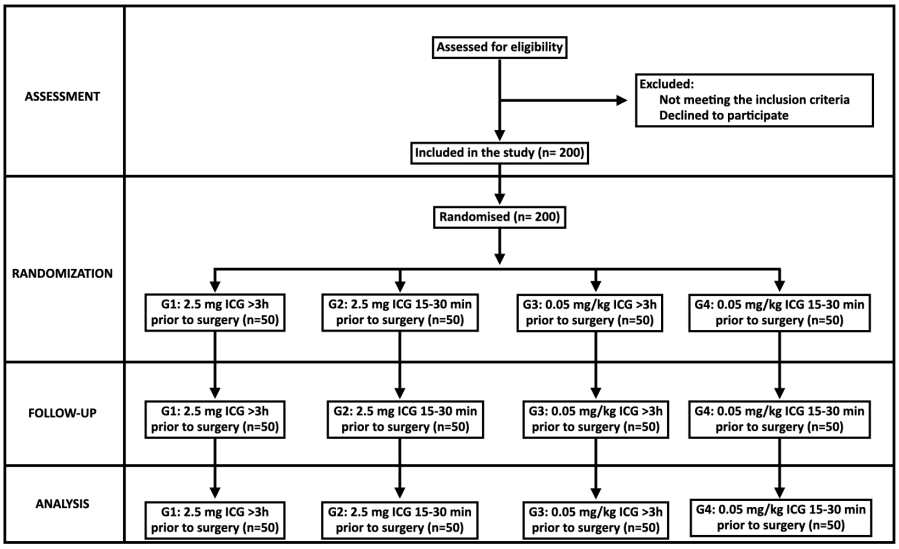
Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Results

In order to assess the differences between the four treatment groups (primary endpoint), the following target variables will be applied:

1. Visualisation of biliary structures prior to the dissection of the hepatocystic triangle (yes/no):
   - Cystic duct (CD)
   - Common bile duct (CBD)
   - CD–CBD junction
   - CD–gallbladder junction
   - Common hepatic duct.



G1: Group 1, G2: Group 2, G3: Group 3, G4: Group 4, ICG: Indocyanine green

Figure 1 Flow chart for participant eligibility, interventions, assessments and follow-up.

- Anatomical variations.

2. Visualisation of biliary structures after the dissection ofthe hepatocystic triangle (yes/no):
   - Cystic duct (CD)
   - Common bile duct (CBD)
   - CD–CBD junction
   - CD–gallbladder junction
   - Common hepatic duct
   - Anatomical variations
3. Quality of visualisation of biliary structures before dissection of the hepatocystic triangle (1=poor, 2=sufficient, 3=fair, 4=good, 5=excellent).
4. Quality of visualisation of biliary structures after dissection of the hepatocystic triangle (1=poor, 2= sufficient, 3=fair, 4=good, 5=excellent).
5. Extent to which fluorescence cholangiography wasperceived as useful for the surgery (0=not helpful, 1=moderately helpful, 2=very helpful).
6. Extent to which liver fluorescence background (livertoducts contrast) was perceived as a disturbance(0=absence of disturbance 1=lightly disturbed, 2=disturbed visualisation, but CD–CBD junction was clearly visible before dissection, 3=disturbed visualisationand CD–CBD junction was only visible after dissection, 4=heavily disturbed: it was impossible to correctly visualise biliary structures)

The NIRFC-LC assessment will be performed by the main surgeon during surgery (in the case of a procedure performed by a resident surgeon, the assessment will be carried out by the consultant surgeon of the procedure).

In order to assess the secondary endpoints, the following target variables will be applied:

Preoperative variables

1. Date of birth.
2. Age.
3. Sex (female/male).
4. BMI.
5. Previous liver disease (fatty liver/hepatitis/cirrhosis).
6. American Society of Anesthesiologisth (ASA) physical status classification system.
7. Previous abdominal surgeries (no/bile duct/liver/pancreas/bowel/others).
8. Previous biliary techniques (no/ERCP/percutaneous transhepatic cholangiography).
9. Previous biliary stent (yes/no).
10. History of cholecystitis or cholangitis (yes/no).
11. Previous gallbladder drainage (no/endoscopic ultrasound-guided gallbladder drainage/percutaneous cholecystostomy).
12. Indication for surgery (biliary colic/cholecystitis/choledocholithiasis/cholangitis/pancreatitis lithiasis/gallbladder polyps/gallbladder ademoniomatosis).

Perioperative variables

1. Date and time of admission.
2. Date and time of surgery.
3. Type of surgery (elective/early/ delayed).
4. Grade of cholecystitis in case of early or delayed surgery (according to Tokyo Guidelines 2018).
5. Adverse reactions to ICG (yes /no).
6. Number of trocars (3/4).
7. Laparoscopic imaging system (Olympus/Karl-Storz/Stryker).
8. Laparoscope (30°/0°).
9. Conversion to open surgery (yes/no).
10. Surgical complications (yes/ no).
11. Type of surgical complication (liver injury/gallbladder perforation/right hepatic artery injury/cystic artery injury/bowel injury/others).
12. Surgical time (skin incision to wound closure).

Postoperative variables

1. Hospital stay.

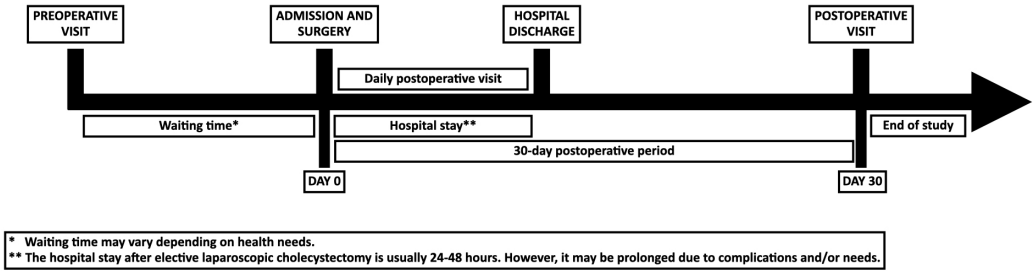


Figure 2 Timeline of the study.

2. Postoperative complications (yes/no).
3. Classification of postoperative complications (Clavien-Dindo classification).
4. BDI (yes/no).
5. Classification of BDI (according to Strasberg classification).
6. Timing of the diagnosis of BDI (during surgery/postoperative period).
7. Treatment of BDI (surgical /radiological/endoscopic).
8. Hospital mortality (yes /no).
9. Mortality at 30 days (yes/ no).
10. Late adverse reactions to ICG (yes/ no).

Timeline

- Preoperative visit: the aim of the study and the protocol are explained to the patient, and informed consent documents are given to the patient.
- In-hospital preoperative visit: the researchers verify that the patient has understood the information and that informed consent forms have been properly signed.
- Daily postoperative visits: these visits will be conducted by the surgery team.
- Follow-up postoperative visit: it will be conducted 30 days after surgery figure 2.

The expected duration of the subject's participation will be 31 days. This includes the preoperative, intraoperative and the 30-day postoperative periods. The end of the clinical trial will take place 30 days after discharge of the last recruited patients in order to analyse morbidity and mortality after 30 days (figure 2).

Sample size

In order to estimate the sample size, an annual average of 300 LC was estimated. Assuming a minimum recruitment rate of 50%, a duration of 12 months and the potential loss of patients, we estimated a sample size of 200 patients. Since the primary endpoint is to analyse whether there are differences between doses and administration intervals in the four arms in which categorical variables are measured, the effect of the chosen sample size (n=200) on the statistical contrasts in this type of variables is w=0.25, with a power of ®=0.95 and a cut-off point of significance for the rejection of the null hypothesis of ≤0.05.

Recruitment

The annual rate of LC in the two hospitals in the study is over 300 surgeries per year. In order to recruit 200 in both centres, a review waiting list will be conducted. Patients who meet the inclusion criteria will be given the necessary information and, after signing the informed consent form, will be included in the trial.

Randomisation

The subject's randomisation will be conducted using a computer-generated random number. The electronic case report form (eCRF) will be used to implement a block randomisation method with a sequence of 1:1:1:1. Since this trial has no control group, blinding is not considered. The principal investigator (PI) will have access to the eCRF and will generate the randomisation sequence.

Statistical analysis

The Kolmogorov-Smirnov and Shapiro-Wilk test will be used to study the distribution of quantitative variables. These variables are presented as mean (SD) or median (median absolute deviation) according to their distribution. The relationship between these variables will be measured with Pearson's or Spearman's rank correlation coefficient. The distribution of categorical variables will be studied with frequencies and percentages. χ^2 test, Fisher's exact test, McNemar's test or Cochran's Q test will be used to assess the relationships among categorical variables. In order to analyse the influence that some categorical variables may have on the quantitative variables, ANOVA tests may be performed. Finally, all the statistical information obtained on the relevance of each variable in the study may be used to apply classification tools to the subjects of the study (decision trees, logistic regression, ROC curves).

The procedure used to measure missing data will be the pairwise deletion method. The statistical significance will be established at p values <0.05. All the analyses will be performed with the free software R (V.4.1.2+, R Core Team, Vienna, https://www.R-project.org/) and the interface RStudio (V.1.2.1103+).

The study will not include scheduled intermediate analyses, because a partial analysis of the results will not be conducted. When the data are collected, verified and validated a statistical analysis will be performed according to the instructions established in the protocol. If the analysis

reveals the need for further analyses, this will be stated in the final report of results. All the subjects who received treatment and can be assessed will be analysed.

Data management and monitoring

Data collection, management, and analysis

Study data were collected and managed using REDCap electronic data capture tools hosted at Asociación Española de Cirujanos (AEC; www.aecirujanos.es)[6 7].AEC is a non-profit Scientific and Medical Society focused on General and Digestive Surgery and provides this service free of charge, with the sole aim of promoting independent investigator-driven research. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing (1) an intuitive interface for validated data entry; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

Monitoring

The Data Monitoring Committee (DMC) is appointed by the sponsor, and it includes the clinical trial manager and two clinical trial monitors (one for each centre). The main tasks of the DMC are training all the researchers in the initial visit, checking the veracity of the data, and ensuring protocol compliance with successive visits during the recruiting period. The monitor will supervise the process and contact the centre regularly.

The sponsor will provide instructions and training to the research staff prior to the start of the trial. They will carry out regular monitoring according to the ICH guidelines for GCP. The data will be assessed for protocol compliance and accuracy. The monitors will verify that the trial is conducted, that the data are generated, documented and reported in accordance with the protocol, good clinical practice and any other local applicable regulatory requirements. Direct access to the data will be granted to the PI, monitors, members of the Ethics Committee and the AEMPs and to the necessary authorities, in order to enable monitoring and surveillance of the trial for audit. Auditor's reports will be confidential.

The study interruption criteria are the following:

- Severe adverse events related to drug administration.
- Development of any exclusion criteria within the inclusion period and before surgery.
- Voluntary withdrawal of previously recruited patients.

All the adverse events will be registered in the eCRF. The severity of the event and its relationship with the trial will be assessed according to specific guidelines. Adverse events will be registered after the subject has been randomised. Subjects with adverse events will be monitored by the researcher until they are solved or the patient has been stabilised. The PI must report all severe adverse events within 24 hours.

Annual safety reports will be submitted by the sponsor to the AEMPs, the regional authorities and the Ethics Committee.

Trial Sponsor

Fundación Instituto de Estudios de Ciencias de la Salud de Castilla y León (IESCYL)-Instituto de Investigación Biomédica de Salamanca (IBSAL). Universidad de Salamanca, Salamanca, Spain.

ETHICS AND DISSEMINATION

The trial will be conducted according to the recommendations for Clinical Trials in the Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects and the recommendations of the AEMPs for clinical trials. This study guarantees compliance with the ICH harmonised tripartite guideline for good clinical practice (GCP). This trial was approved by the local institutional Ethics Committee (IRB: Comité Ético de Investigación con Medicamentos-CEIm- del Área de Salud de Salamanca) and the AEMPs.

The patients will be identified with a code. The researcher will inform the patients that the data obtained in the trial will be stored and analysed digitally, in compliance with Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and to Spanish Organic Law 3/2018 of 5 December on Protection of Personal Data.

The PI does not have any interests that may affect the veracity of the data in the clinical trial. Regardless of the results of the study, the sponsor has agreed to present them to the medical community through publications, conferences, or other means.

Dissemination plan

Key message

The clinical trial is seeking participants to analyse the fluorescence cholangiography during LC. The trial is safe, ethical and has the potential to improve the results of LC.

Channels

- Community outreach: informational sessions at local healthcare centres.
- Collaboration with healthcare professionals: work with healthcare professionals such as doctors and nurses to educate them on the trial and encourage them to recommend participation to eligible patients.

Materials

- Presentations to be given at informational sessions.
- Social media posts and online ads to promote the trial and share information.

Implementation

- Schedule informational sessions to promote participation.

- Work with healthcare professionals to educate them on the trial and encourage them to recommend participation to eligible patients.

Evaluation

- Track the number of participants enrolled in the trial.
- Assess the effectiveness of the informational sessions, media advertising and social media outreach (newsletters).
- Make necessary adjustments to the dissemination plan based on the evaluation results.

DISCUSSION

BDI during LC is one of the most severe complications in general surgery. It is associated with high morbidity and mortality rates, need for reinterventions, increased hospital stay and costs, poorer quality of life and legal issues.[3 8–11]

Over the last decades, multiple recommendations have been issued in an attempt to reduce BDI. The best-known one is the Critical View of Safety, published by Strasberg in 1995.[12] This technique is the current standard during safe LC.[13] Other techniques, such as the B-SAFE rule, are still in their implementation stage.[14] One recent approach that combines artificial intelligence and machine learning has been applied to LC to try to improve the safety of the procedure.[15] On the other hand, intraoperative cholangiography (IOC) has been the most frequently used system for the prevention and early detection of BDI, as well as for the diagnosis of choledocholithiasis.[16] However, some of its disadvantages are the use of ionising radiation, its learning curve, the need for prior surgical dissection and other structural problems and needs.[17] In addition, IOC is often performed to rule out a BDI during surgery, rather than to prevent it. In spite of the multiple technical and technological innovations available, there are still cases of BDI during LC.

NIRFC is a recent technique[18] that applies the fluorescent properties and exclusively biliary excretion of ICG to map the extrahepatic biliary tract.[3] ICG has been previously described in cardiology, ophthalmology and hepatology.[19] NIRFC is a fast, real-time visualisation method with a minimal learning curve and no increase in operation times. In addition, it does not require the prior dissection of the hepatocystic triangle and has a lower cost than IOC. However, it is not currently widespread and requires a specific image processing hardware.[17 20]

Recently, NIRFC has shown superiority to LC with white light alone to prevent BDI,[21 22] and a recent meta-analysis estimates that this technique could decrease this complication.[23] There are wide variations in the ICG administration protocols. A correct dose and administration interval are key to achieve an adequate identification of the biliary structures and to reduce the fluorescence emitted by the liver parenchyma, which could be a handicap during the surgery.[24] There are several administration protocols for ICG, either with a fixed dose or with a weight-adjusted dose. The ICG administration intervals also vary widely.[24] Some authors showed lack of liver parenchyma fluorescence when ICG is administered 24 hours before surgery.[25] However, in the context of short-stay surgery, this does not seem to be a viable option. The preliminary results from the IHU-IRCAD-EAES EURO-FIGS reveal several differences in the protocols for preoperative administration of ICG.[26] Therefore, we believe that it is necessary to establish a protocol for the administration of this drug based on the results of randomised clinical trials.

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Contributors JLS is the PI; he designed the study, wrote the protocol and the manuscript. FPA is the PI, he contributed to the design of the study and the protocol. SGM contributed to designed the protocol and write the manuscript. CGS contributed to write the manuscript. RLP is the study manager and he contributed to the review and writing of the protocol. PR-F is the head of Pharmacovigilance and helped write the protocol. JMSS will conduct the statistical analysis of the trial. LMB is the coordinating investigator of the study, helped to design it, write the protocol and he has reviewed the manuscript. All authors approved the final version of the manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

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