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Defining the ideal dose of indocyanine green dye for the identification of biliary structures during surgical treatment to remove the gallbladder

Submission date
06/05/2022

Recruitment status
No longer recruiting

Registration date
30/05/2022

Overall study status
Completed

Last Edited
21/07/2023

Condition category
Digestive System

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Cholecystectomy is a surgical procedure to remove the gallbladder: a small organ that sits below the liver on the upper right side of the abdomen. The gallbladder collects and stores bile, a digestive fluid produced by the liver. The gallbladder is connected to the liver and the bowel through small tubes that allow bile flow (biliary ducts or biliary tree). In case of common benign pathology like gallstones (cholelithiasis) and polyps (adenomyomatosis) the gallbladder should be removed. The cholecystectomy is commonly performed by inserting a video camera and surgical tools through four small incisions to see inside the abdomen and remove the gallbladder (laparoscopic cholecystectomy). It is a common surgical procedure, but it can be associated with some complications. The worst complications of cholecystectomy are injuries to the biliary tree. To date, the incidence of bile duct injury during laparoscopic cholecystectomy is about 0.3 %.
Over the last years, several techniques have been introduced into clinical practice to identify bile ducts. One of these techniques allows the identification of biliary structures after the administration of a green fluorescent dye called indocyanine green (ICG; indocyanine green fluorescent cholangiography). Dedicated surgical tools allow the identification of this fluorescent dye during surgery. Scientific studies demonstrated that this technique is better at identifying biliary structures compared to surgical procedures without the dye.
To date, the standard dose and timing of ICG administration for cholecystectomy have not been defined.
About 0.1-0.5 mg/kg of ICG are administered 3-12 hours before surgery. This dose allows visualization of biliary structures with intense green colour (high fluorescence intensity), but it is always associated with intense green colour in the liver parenchyma too (fluorescence hepatic background) with consequent reduction of biliary ducts identification. Recently, some studies tried to assess the correct dose and timing for this procedure, concluding that the ICG should be administered 3-10 hours before surgery. The first limit of this study is to assess a standard ICG dose for all patients, as in order to achieve a good visualization of biliary ducts weight-based dosing has to be defined. Furthermore, for routine clinical practice, administration of ICG several hours before surgery is unpractical, since most of the patients who undergo this surgical

procedure are admitted the same day as surgery.
The primary aim of this study is to define the ideal range of ICG doses that should be administered in order to identify the biliary tree during the surgical procedure. The secondary aims are to define when the fluorescent dye should be administered and how the dye should be prepared for the administration.

Who can participate?
Patients aged 18 years and over requiring gallbladder removal (cholecystectomy) for gallbladder stones (cholelithiasis) or polyps (adenomyomatosis)

What does the study involve?
Participants undergo gallbladder removal with the use of a fluorescent dye injected into a vein before surgery (laparoscopic cholecystectomy with ICG fluorescent cholangiography). The study does not provide any change from the standard surgical procedure, apart from a reduction of the standard fluorescent dye dose. A follow-up visit is performed 30 days after surgery. Surgical procedures are anonymously recorded and images from the procedures are analysed.

What are the possible benefits and risks of participating?
The possible benefit of using a lower dose of the fluorescent dye is achieving a better visualization of the structures that connect the liver, gallbladder and bowel (biliary tree), reducing the risk of injury of these structures that would lead to further procedures. The only risk associated with the fluorescent dye indocyanine green is allergic reactions in patients with an allergy to iodides. Patients with a known allergy to iodides cannot be included in the study.

Where is the study run from?
Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico of Milan (Italy)

When is the study starting and how long is it expected to run for?
September 2020 to April 2022

Who is funding the study?
1. Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico (Italy)
2. Arthrex GmbH (Germany)

Who is the main contact?
1. Ludovica Baldari, ludovica.baldari@policlinico.mi.it
2. Luigi Boni, luigi.boni@unimi.it

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
27

Study information

Scientific Title
Defining the ideal indocyanine green dose for fluorescent cholangiography during laparoscopic cholecystectomy

Acronym
INGreDo

Study objectives
The aim of the study is to define the ideal range of indocyanine green (ICG) doses (mg/kg) that should be administered intravenously in order to perform fluorescence cholangiography during laparoscopic cholecystectomy. The ideal dose is defined by the combination of evidence of high

fluorescence intensity of biliary structures and the absence of fluorescence of the surrounding liver parenchyma.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Ethics approval not required: indocyanine green (ICG) is a dye approved for medical use by the Italian Medicine Agency (AIFA), as well as by the FDA, and is currently used in routine clinical practice for fluorescent cholangiography. ICG fluorescent cholangiography is daily used in every cholecystectomy as it has been demonstrated as able to reduce the number of complications during surgery (Tokyo Guidelines 2018). The study does not involve any change in standard surgical technique. Evaluation of the visualization of biliary structures is performed through surgical video analysis, which is not directly related to the health and illness of the patients. Preliminary consultation with the ethics committee was made and confirmation of not requiring approval was obtained

Study design
Observational case series

Primary study design
Observational

Secondary study design
Case series

Study setting(s)
Hospital

Study type(s)
Other

Participant information sheet
Not applicable

Health condition(s) or problem(s) studied
Benign gallbladder diseases: cholelithiasis, adenomyomatosis

Interventions
The study defines the ideal range of ICG dose (mg/kg), timing of administration and dilution for fluorescent cholangiography and is divided into two parts: the first one identifies the best four ICG doses in a group of 14 patients by applying the bisection method; then these four doses are tested in four groups (four patients for each group) to confirm the defined range of ICG dose; in the second part of the study the ICG dose is tested in a series of 50 consecutive cholecystectomies to confirm the optimal dose, dilution and administration timing.

Enrolled patients undergo laparoscopic cholecystectomy with fluorescent cholangiography with intravenous administration of ICG before surgery due to cholelithiasis or adenomyomatosis. Starting from the current ICG dose used in routine clinical practice, the ICG dose is gradually reduced until the identification of good visualization fluorescence into the biliary tree with the absence of fluorescence in the liver parenchyma.

Fluorescence intensity of biliary structures and liver parenchyma is measured through two evaluations:
1. Subjective evaluation by the operating surgeon and ranked as 1(absent), 2 (poor) 3 (medium), 4 (high)
2. Objective evaluation performed using ImageJ software(*) on selected pictures captured on recorded surgical procedures

The evaluation through the ImageJ software is performed:
1. On cystic duct and on common bile duct if visible, in order to define the fluorescence intensity
2. On liver parenchyma: on the left/right side of the infundibulum (next to the cystic duct), in order to define the liver background.

The range of ICG dose is defined by the best balance between the highest fluorescence intensity of biliary structure associated with the lowest liver parenchyma background achievable.

Data obtained by objective evaluation (through the ImageJ software) are used to define the signal to background ratio (SBR) = mean signal of biliary structures fluorescence intensity / mean signal of liver background to strengthen data.

A follow-up visit is performed 30 days after surgery.

Intervention Type
Procedure/Surgery

Primary outcome measure
The definition of the ideal range of ICG dose (mg/kg) for fluorescent cholangiography.
Fluorescence intensity of biliary structures and liver parenchyma is measured through two evaluations twice for each patient during the same surgical procedure (before and after dissection of Calot's triangle):
1. Subjective evaluation by the operating surgeon and ranked as 1 (absent), 2 (poor) 3 (medium), 4 (high)
2. Objective evaluation performed using ImageJ software(*) on selected pictures captured on recorded surgical procedures

Evaluation is performed using the ImageJ software:
1. On cystic duct and on common bile duct if visible, in order to define the fluorescence intensity
2. On liver parenchyma: on the left/right side of the infundibulum (next to the cystic duct), in order to define the liver background.
The range of ICG dose is defined by the best balance between the highest fluorescence intensity of biliary structure associated with the lowest liver parenchyma background achievable.
Data obtained by objective evaluation (through the ImageJ software) are used to define the signal to background ratio (SBR) = mean signal of biliary structures fluorescence intensity / mean signal of liver background to strengthen data.

Secondary outcome measures
1. Best timing for IV ICG administration measured in minutes before surgery. The pre-established administration timing is 1 hour before surgery, and it is eventually modified according to the results of the first part of the study
2. Best dilution of ICG measured in milliliters. Starting from 10 ml dilution with sterile water, it is increased according to the dose identified at the end of the first part of the study

Overall study start date
10/09/2020

Completion date
30/04/2022

Eligibility

Key inclusion criteria
1. Age ≥18 years old
2. Indication for cholecystectomy (gallstones disease; adenomyomatosis)
3. Ability to understand and follow study procedures
4. Having provided signed consent

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
80

Total final enrolment
80

Key exclusion criteria
1. Known allergy to iodides
2. Coagulopathy
3. Pre-existing liver disease
4. Pregnancy
5. Acute cholecystitis
6. BMI ≥40 kg/m²

Date of first enrolment
30/09/2020

Date of final enrolment
28/03/2022

Locations

Countries of recruitment
Italy

Study participating centre
Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico
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Sponsor information

Organisation
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Sponsor type
Hospital/treatment centre

Website
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ROR
https://ror.org/016zn0y21

Funder(s)

Funder type
Hospital/treatment centre

Funder Name
Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico

Alternative Name(s)
Policlinico of Mila, Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico, "Ca' Granda Ospedale Maggiore Policlinico" Foundation, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
Italy

Funder Name
Arthrex GmbH

Alternative Name(s)
Arthrex Medizinische Instrumente GmbH

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
Germany

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal

Intention to publish date
30/09/2022

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Baldari Ludovica (ludovica.baldari@policlinico.mi.it). Each subject provides written consent with knowledge of the procedures involved. Hard copy documents are retained for the duration of the study until data entry. All hard copy documents are kept in a locked cabinet. Data entry (data from image analysis) is completed in an Excel secure database (password protected), which covers all the created case report forms (CRFs). Only de-identified data are used for data analysis. All hard copy documents will be stored for a maximum of 10 years after completion of the study and then they will be shredded upon Sponsor approval. The Principal Investigator will be responsible for data handling and keeping before, during and after the present study.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file	version 1	13/02/2021	29/12/2022	No	No
Results article		20/07/2023	21/07/2023	Yes	No