

Fluorescence versus X-ray cholangiography during laparoscopic cholecystectomy: protocol for a randomised trial

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ABSTRACT

INTRODUCTION: Intraoperative fluorescent cholangiography is a novel non-invasive imaging technique to visualise the extrahepatic biliary tract during laparoscopic cholecystectomy. It has been proven feasible, fast and cost effective. Nevertheless, there is only sparse data on the capacity of fluorescent cholangiography to visualise the biliary anatomy. **METHODS:** Based on a non-inferiority design, patients with complicated gallstone disease are randomised to either intraoperative conventional X-ray cholangiography (reference group, n = 60) or intraoperative fluorescent cholangiography (n = 60). The primary outcome is visualisation of the junction between the cystic duct, the common hepatic duct and the common bile duct.

CONCLUSION: The present study may show that fluorescent cholangiography is as valid for visualisation of important structures of the extrahepatic biliary tract as conventional X-ray cholangiography. This may lead to the introduction of online imaging of the extrahepatic tract during dissection of the gallbladder during cholecystectomy.

FUNDING: none.

TRIAL REGISTRATION: This study was registered with clinicaltrials.gov (No. NCT02344654), with the National Committee on Health Research Ethics (Reg. no. H-15000817) and with the Danish Data Protection Agency (Reg no. AHH-2015-005).

Injury to the biliary duct is a serious complication to laparoscopic cholecystectomy [1, 2]. Biliary duct injury is often caused by misinterpretation of the anatomical structures rather than by insufficient technical skills [3]. Misinterpretation of biliary duct anatomy is probably caused by anatomical variation and/or deformation caused by inflammation and fibrosis.

Several image modalities have been proposed for intraoperative visualisation of the bile duct system [4-6], including routine use of intraoperative X-ray cholangiography [2, 4, 6, 7]. However, the effect of intraoperative X-ray cholangiography to avoid bile duct injury is controversial [8-13].

Intraoperative fluorescent cholangiography is a novel imaging technique. Intravenous indocyanine green (ICG) is used to enhance illumination of the bile duct

structure when near-infrared light is used [14]. The technique offers online switching between normal white light mode (normal vision) and fluorescence mode (Figure 1). Fluorescent cholangiography is non-invasive with no puncture of the biliary structures and does not require X-ray radiation or surgical dissection.

In accordance with other studies [15-17], we recently demonstrated that routine use of intraoperative fluorescent cholangiography is feasible with almost no additional surgical time expenditure and a high success rate (100% (n = 35)) for visualisation of the junction between the cystic duct, the common hepatic duct and the common bile duct [18].

No studies have compared intraoperative X-ray cholangiography with intraoperative fluorescent cholangiography in a randomised setting.

For the present study, we have chosen a non-inferiority design, firstly, as we expect our fluorescent group to have at least the same success rate for delineation of the bile duct anatomy and to be faster and easier to perform than our reference treatment. We assume an 80% visualisation success rate for our reference treatment and the intervention success rate is set to 90% based on previous literature reporting success rates ranging from 71-100% [15-20] with the majority of studies demonstrating an above 90% success rate. The non-inferiority margin is set to 10% (delta), which is relatively low, but reflects our emphasis on the superiority of fluorescent cholangiography in terms of time expenditure and ease of use.

Aim

The primary objective is to compare intraoperative fluorescent cholangiography with conventional X-ray cholangiography for identification of the junction between the cystic duct, the common hepatic duct and the common bile duct during laparoscopic cholecystectomy for complicated gallstone disease.

Time expenditure and surgeon's satisfaction are also registered.

METHODS

Study design

Randomised controlled trial including 120 patients

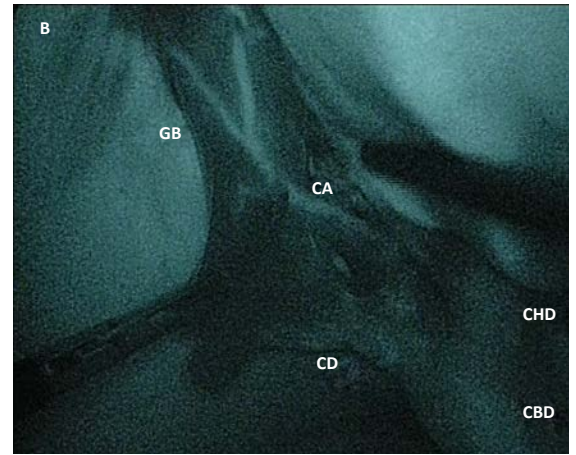
PROTOCOL ARTICLE

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FIGURE 1

Laparoscopic cholecystectomy with intraoperative fluorescent cholangiography and arteriography. The field is firstly inspected in normal white light mode (A) and then the image is changed to fluorescent mode (B). In the fluorescent mode, the common hepatic duct, common bile duct and cystic duct are easily identified. Approximately 10-20 seconds after reinjection of intravenous indocyanine green, the cystic artery is visualised.



CA = cystic artery; CBD = common bile duct; CD = cystic duct; CHD = common hepatic duct; GB = gallbladder.

undergoing elective laparoscopic cholecystectomy for complicated gallstone disease from a single university hospital centre with unrestricted referral of patients.

Complicated gallstone disease is defined as patients with gallbladder stones and a medical history of at least one of the following:

- Cholecystitis or
- Gallstone pancreatitis or
- Cholangitis or
- Common bile duct stone verified by either ultrasonography, magnetic resonance imaging, computed tomography, endoscopic retrograde cholangiopancreatography or blood samples (bilirubin > 4 g/dl (68 µM)).

Inclusion criteria:

- Patient scheduled for planned laparoscopic cholecystectomy by two of the study authors
- Complicated gallstone disease
- Patient age ≥ 18 years.

Exclusion criteria:

- Open cholecystectomy
- Emergency laparoscopic cholecystectomy
- Allergy towards iodine, lohexol or indocyanine green
- Liver or renal insufficiency
- Thyrotoxicosis
- Pregnancy or lactation
- Legally incompetent for any reason
- Withdrawal of inclusion consent at any time.

Patients are examined preoperatively and screened for renal or liver disease during a visit in either our out-pa-

tient clinic or surgical emergency department. In addition, patients are screened for common bile duct stones by ultrasound, liver enzymes and magnetic resonance cholangiopancreatography/endoscopic ultrasound according to SAGES guidelines, if relevant [6]. Patients with preoperative common bile duct stones will undergo preoperative endoscopic retrograde cholangiopancreatography to remove the stones prior to surgery.

Patients are enrolled to the study after receiving oral and written information and are assigned a sealed randomisation envelope. Written consent is obtained by the study surgeon prior to surgery.

Biometric data and previous medical history are recorded. All patients are operated by one of two specialist upper-gastrointestinal surgeons from our study group using a standardised surgical technique, which is in accordance with Danish and international guidelines (the Critical View of Safety Technique) [6].

Non-eligible patients will be registered in a log-book for later drop-out analysis.

Equipment and contrast for performing both an X-ray and a fluorescent cholangiography are present at the operating room prior to the opening of the randomisation envelope. The scrub nurses are all familiar with the equipment and techniques and are responsible for time registration during surgery.

Intraoperative cholangiography

The cholangiography is performed after dissection of the cystic duct in a standardised manner, by cannulation of the cystic duct with a catheter using either a Kumar or Olsen grasper. Leakage is controlled by injecting saline prior to injection of lohexol (GE Healthcare, Denmark). A mobile X-ray C-arm system is used, and the monochrome X-ray image is shown on a separate screen.

After satisfactory identification of the extra-hepatic biliary ducts, the intraoperative cholangiography is discontinued and the gallbladder is removed in a standardised manner. Time consumption is measured by a study nurse and includes the period from application of the Kumar/Olsen grasper until it is removed again after obtaining a satisfactory cholangiogram.

Intraoperative fluorescent cholangiography

Immediately following induction of anaesthesia, 2.5-7.5 mg of indocyanine green (0.05 mg/kg) (Pulsion Medical Systems, Germany) is injected intravenously. Indocyanine green rapidly binds to plasma proteins and is exclusively and entirely excreted by the hepatic parenchymal cells into the bile, starting within a few minutes after injection.

An Olympus Laparoscopic Imaging System for Indocyanine Green Fluorescence Observation with easy switchable white light-/fluorescent mode is used.

The operative field is routinely inspected in the fluorescence imaging mode before dissection of Calot's triangle. During dissection, the fluorescence imaging mode is used when needed until critical view of safety is obtained. Before division of any tubular structure, the fluorescence imaging mode is routinely used again, and fluorescent angiography is performed by re-injecting the same dose of indocyanine green as initially used. After division of the cystic duct and artery, the fluorescence imaging mode is applied again to check for bile leakage. Time consumption is registered by a study nurse as the total time in fluorescent mode.

Outcomes

Primary outcome:

- Visualisation of the junction between the cystic duct, the common hepatic duct and the common bile duct by either intraoperative fluorescent cholangiography or conventional X-ray cholangiography.

Secondary outcomes:

- Time consumption by intraoperative fluorescent cholangiography/conventional X-ray cholangiography
- Surgeon's technical score (perioperative).

Success is defined as: visualisation of the junction between the cystic duct, the common hepatic duct and the common bile duct. The separate inlet of all three structures must be visualised. Visualisation of the entire common hepatic duct (intrahepatic part) and the entire common bile duct (retro-duodenal part) is not necessary.

The operating surgeon completes a structured questionnaire focusing on anatomical identification of the bile ducts immediately after each operation.

The surgeon's satisfaction score is given on a subjective visual analogue scale ranging from 1 to 5 (1 = very easy, 5 = very difficult).

Peroperative complications are registered immediately after surgery by the surgeon and after 30 days (Regional Medical Journal System (OPUS)).

Blinding and randomisation

Patients are randomised to either intraoperative fluorescent cholangiography or conventional X-ray cholangiography using a 1:1 allocation ratio. Randomisation is central and block-randomisation (block size 4) is performed by using www.randomization.com. A non-transparent envelope is made for each patient, which contains the code for either fluorescent- or X-ray cholangiography. The envelopes and randomisation list are produced by one of the study authors and kept in a locked cabinet until immediately prior to surgery. The envelope is opened after the patient is anaesthetised, but immediately prior to the beginning of surgery. The patient is blinded to the result of the randomisation until after the surgery. The data analyst is blinded to the randomisation code.

Statistics

Sample size was estimated using simulations for a non-inferiority design. Thus, 10,000 datasets were simulated assuming a success rate for identifying the cystic duct, the common hepatic duct and the common bile duct of 80% for the conventional intraoperative cholangiography and 90% for the intraoperative fluorescent cholangiography. This was done for a range of sample sizes. We then analysed each dataset to test whether intraoperative fluorescent cholangiography was no more than 10% inferior to conventional intraoperative cholangiography in a one-sided test applying a 5% level of significance. In conclusion, 60 patients in each group would yield a power of 90%.

Data will be analysed according to intention-to-treat principles.

Our primary endpoint is composed of the visualisation of the junction of three different structures – the cystic duct, the common hepatic duct and the common bile duct. This implies an increased risk of incorrectly rejecting the null hypothesis (type 1 error) if visualisation of all three structures is considered as one. To counteract this risk, we use the Bonferroni correction and thus test each hypothesis (structure) at $\alpha/m = 0.05/3 = 0.0166$. Non-parametric statistics are used. For continuous variables, we use the Mann-Whitney test to compare the surgical groups. To compare dichotomous variables, a chi-squared test or Fisher's test is used when appropriate. Data are accompanied by 95% confidence intervals when appropriate. $p < 0.05$ is considered significant.

An outcome analysis will be made of all non-eligible laparoscopic cholecystectomy patients operated at the Surgical Section of the Gastrounit at Hvidovre Hospital during the inclusion period.

Economy

The study is not funded. Enrolled patients will receive no fee for their involvement. The investigator group will have no economic gain from the study.

Trial registration: The study was registered with clinicaltrials.gov (no. NCT02344654), with the National Committee on Health Research Ethics (Reg. no. H-15000817) and with the Danish Data Protection Agency (Reg. no. AHH-2015-005).

DISCUSSION

The most well-known technique for intraoperative visualisation of the extrahepatic bile duct system is X-ray cholangiography. Its routine use has been discussed since before the introduction of laparoscopic cholecystectomies, and the discussion is ongoing. The technique has the advantage of visualising the biliary ducts as well as the gall stones in the ducts intraoperatively. The disadvantage is the need to dissect and cannulate the cystic duct before the first cholangiogram is obtained. Furthermore, there is a risk of injuring the bile ducts during the procedure, which can potentially result in severe complications.

A novel technique, intraoperative fluorescent cholangiography, has been proposed as a replacement for intraoperative visualisation of the extrahepatic bile duct system. This new technique has proven feasible, faster and more inexpensive than conventional X-ray cholangiography. Unfortunately, there are indications that it lacks the ability to visualise gall stones in the bile ducts, but this needs to be tested in a future study. Another limitation of the technique is the limited tissue penetration of fluorescent light. This may hamper precise identification of the anatomic structures in case of overlying tissue.

It is clear that an accurate identification of the anatomical structures is mandatory to safely perform cholecystectomy. Patients with complicated gall stone disease have an increased risk of inflammation and fibrosis in the region of the extrahepatic bile ducts. This implies a larger risk of anatomical misinterpretation. In these patients it seems even more relevant to accurately visualise the bile ducts. However, biliary duct lesions are rare (0.2-0.5%), and a randomised clinical trial with bile duct lesion as an endpoint would demand several thousand patients in each group for sufficient power, and is therefore difficult to perform. We have chosen a comparative design with visualisation of the crucial anatomical structures (the junction between the cystic duct, the common

hepatic duct and the common bile duct) as the best alternative to indicate which method will best support the safety of laparoscopic cholecystectomy.

Dip et al previously compared fluorescent cholangiography with X-ray cholangiography, but in a cross-over design with 45 patients, and found fluorescent cholangiography to be safe, feasible, fast and cost-effective [16]. Based on this study and our own feasibility study [18], we choose a randomised controlled non-inferiority design in order to eliminate selection bias and confounding between methods. The reference method (X-ray cholangiography) is a well-known and widely used examination, and this merits a non-inferiority design. Accordingly, a non-inferiority design (10% margin) will require randomisation of 120 patients (60 in each arm).

CONCLUSION

The present study will provide further evidence for optimised cholangiography techniques during laparoscopic cholecystectomy.

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