Systematic Review Protocol. Near Infra-Red Indocyanine Green Fluorescent Cholangiography Versus Intraoperative Cholangiography to Improve Safety in Laparoscopic Cholecystectomy for Gallstone Disease – A Systematic Review Protocol.

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Protocol

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Abstract

Background

Laparoscopic cholecystectomy has become the standard surgical approach in the treatment of cholelithiasis. The rate of bile duct injury increased significantly during the initial period of its implementation. Diverse surgical techniques and different imaging modalities have been described to provide enhanced views of the biliary anatomy and potentially prevent or early detect bile duct injuries. Both x-ray intraoperative cholangiography (IOC) and Near infra-red indocyanine green fluorescent cholangiography (NIR-ICG) have been described as safe and feasible techniques to assess biliary anatomy. The aim of this systematic review is to evaluate if NIR-ICG can visualise extrahepatic biliary anatomy more efficiently and safer than IOC in minimally invasive cholecystectomy for gallstone disease.

Methods

Literature search will be performed via Medline (PubMed), Embase, Scopus, the Cochrane Central Register of Controlled Trials and web of science. **All** randomised controlled clinical trials and prospective non-randomised controlled trials which report on comparison of NIR-ICG versus IOC will be included. All patients over 18 years old who require elective or urgent minimally invasive cholecystectomy (undergoing NIR-ICG during this procedure) due to gallstone disease both acute and chronic will be included. Primary outcomes will be ability to visualise extrahepatic biliary anatomy and time to obtain relevant images of the biliary tree.

Discussion

Our research expects to give the reader a clear sense of the needed focus of future research and remaining uncertainties in the field. Understanding the benefits of this technique is critical to ensuring policymakers can make informed decisions as to where preventive efforts should be focused regarding specific imaging techniques. If ICG is proven to be faster and non-invasive, routine use could be encouraged and wide implementation could be a reality.

Systematic review registration

In accordance with the guidelines, our systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO), registration number CRD42020177991.

Background

Description of the condition

Gallstones are one of the most common diseases treated by General surgeons. Therefore, after hernia surgery, laparoscopic cholecystectomy (LC) is the most common surgical procedure performed in

Europe(1). Since the introduction of laparoscopy, LC has become the standard surgical approach in the treatment of cholelithiasis.

Despite the fact that there are several advantages when compared to the open approach(2,3), the rate of bile duct injury (BDI) during LC increased significantly mainly during the initial period of its implementation as a routine procedure. Some authors reported BDI rates as high as 0.4%, which is significantly higher than with open cholecystectomy (0.1%)(4,5). Modern, registry-based, large population series report rates of BDI ranging from 0.08% to 0.3%(6,7). Nevertheless, this low incidence has to be weighed against the high numbers of cholecystectomies(8,9) and with the potentially severe repercussions of BDI.

BDI might require multiple and multidisciplinary interventions to restore the biliary tree, from conservative treatment, minimally invasive endoscopic procedures up to increasingly life-threatening conditions, such as liver transplant. This avoidable situation would have enormous repercussions on the patient's quality of life, with direct and indirect costs, as well as for the public institutions, absorbing enormous healthcare expenses(10). Moreover, iatrogenic BDIs represents one of the leading reasons for malpractice suits against surgeons, with high average settlements per injury(11,12).

All these considerations might justify and enforce the routine use of all available means to reduce the risk of BDI when facing daily and often underestimated gallbladder removal. It is well known that LC are performed by all types of general surgeons, not specifically hepatobiliary surgeons. Furthermore, this procedure is carried out in almost any type of centre, academic or not academic, therefore volume and expertise may vary. Strategies to avoid BDI should accomplish some characteristics to be applicable: cost-effective, short learning curve and easy to implement and reproduce.

Since the main aetiology of BDI seems to be the misinterpretation of the biliary anatomy, various methods have been described to better identify those structures intraoperatively. This might be even more important in the presence of biliary tree inflammation and unapparent/undetected bile duct anatomical variants.

Diverse surgical techniques and different imaging modalities have been described to provide enhanced views of the biliary anatomy and potentially prevent or early detect BDI(13). With regards to surgical techniques, critical view of safety (CVS) was described by Strasberg in 1995(4) and has been widely acclaimed to reduce the BDI rate during LC. This has not yet been formally shown, most likely, because it has not been adopted universally and above all, is often poorly performed(14,15). Other techniques such as fundus first approach or laparoscopic subtotal cholecystectomy have both reported dropping the incidence and conversion rate of BDI(16). By contrast, various imaging modalities have been described such as intraoperative ultrasound, x-ray intraoperative cholangiography (IOC) and Near infra-red indocyanine green fluorescent cholangiography (NIR-ICG). Among those, standard IOC is the imaging modality that has been more widely investigated and reported. IOC was originally described by Mirizzi(17), and has been used to draw the biliary anatomy, achieve early recognition, and decrease the severity of injury(17). IOC has also been used to identify and intraoperatively manage common bile duct

stones. There is no definitive evidence to support the routine use of IOC to prevent BDI(18). In fact, it is currently performed selectively or rarely in most centres, according to the surgeon's preference(12). However, in the increasing trend of malpractice litigation worldwide, IOC is deemed the most effective argument of defensive medicine(9). Nonetheless, radiation exposure, higher costs, requirement of performing an incision in the cystic duct (CD) potentially increasing the incidence of BDI and prolonged operative times are some disadvantages that lead to IOC being discontinued as a routine imaging modality(19). One of the reasons why the risk of BDI may not have been definitely eliminated could be due to the lack of an objective method of positive recognition of the biliary anatomy before any dissection takes place. A non-invasive and easy to interpret imaging modality may, however, replace the use of X-rays for cholangiography when indicated and solve the longer learning curve and the higher interobserver variability inherent to ultrasound.

Description of the intervention

The Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) was the first to publish guidelines for the clinical application of laparoscopic cholecystectomy in May 1990. These guidelines have periodically been updated however the last edition was published in January 2010(20).

Regarding BDI the guidelines state that:

- Factors which have been associated with BDI include surgeon experience, patient age, male gender and acute cholecystitis. (Level II, Grade C).
- The safety of LC requires correct identification of relevant anatomy. (Level I, Grade A).
- Intraoperative cholangiogram may reduce the rate or severity of injury and improve injury recognition. (Level II, Grade B).

Identification of biliary structures during LC in order to avoid BDI can be achieved using various techniques, although current guidelines only mention IOC. Due to the fact that specific recommendations regarding NIR-ICG are not mentioned in the available guidelines, a review of current evidence on the topic is needed before the technique is included in future guidelines.

Ishizawa and colleagues were the first to describe intraoperative NIR-ICG in 2009 to provide a biliary roadmap(21). NIR-ICG was designed as a promising intraoperative imaging modality, which highlights the biliary ducts using fluorescence. Indocyanine green (ICG) is a fluorescence dye that has been approved for multiple clinical uses by the Food and drug organization (FDA) since 1956. ICG is hydrophilic and binds to albumin in plasma as well as to alpha-1 lipoprotein, has a half-life of 2 hours(22), is exclusively eliminated in the liver and has no metabolism. It is used in medicine to evaluate cardiac output, pulmonary and hepatic function, and for the detection of vitality in free flap reconstructions(23). Near-infrared cholangiography (NIR-C) is based on the systemic injection of a bile-excreted fluorophore such as ICG. Peak concentration in the bile occurs between 30 minutes and 2 h after injection, whereas peak concentration in the arterial system is reached within 1 - 2 minutes(24). The reported ICG dose varies

significantly, ranging from 0.05 to 0.5 mg/kg or administration from 2.5 to 20mg in a single intravenous dose(25), regardless of patient weight. Zarrinpar et al. reported that the optimal ICG dose leading to the best duct-to-liver signal ratio was 0.25 mg/kg, administered at least 45 minutes before imaging(26). There is also a wide range regarding time of injection, ranging from 24 hours prior to the operation to immediately after induction of anaesthesia (26,27). Both intravenous administration, as well as direct gallbladder injection, have been described(28).

When excited with a near-infrared laser, ICG emits light at a peak wavelength of approximately 800 nm(29), which is displayed on the monitor for real-time interpretation. The fluorescence imaging system consists of a light source and a filter that emits infrared and xenon light. This system is incorporated into the charge-coupled device camera and scope that can filter out light with wavelengths below 830 nm(30). The light of the laparoscope can be easily changed to the infrared view using a pedal or flick a toggle switch on the endoscope. During the procedure, alternate exposure from xenon and infrared light can be used to inspect the operative field before and during Calot's triangle dissection. The fluorescence imaging mode can be used at the discretion of the surgeon to help obtain a critical view of safety before transecting the dissected structures.

NIR-ICG is associated with minimal risk of complications, although anaphylactic reaction to ICG has been reported to occur at an incidence of 3/1000 (0.003%), especially at doses higher than 0.5 mg/kg(31). As ICG is excreted by hepatocytes unaltered into the bile, excretion and detection with the near-infrared camera might be compromised in patients with cirrhosis, non-alcoholic steatohepatitis (NASH), or fatty liver disease(32).

How the intervention might work

Both IOC and NIR-ICG have been described as safe and feasible techniques to assess biliary anatomy and to avoid BDI. However, in theory, NIR-ICG has all the advantages and none of the drawbacks of IOC(30).

First of all, NIR-ICG is an incisionless technique, it does not require cannulation of the CD, avoiding the risk of CD avulsion and BDI. In addition, since it does not depend on any dissection in order to cannulate the CD, it provides early imaging before starting the dissection, achieving a high rate of structure identification and being able to guide this dissection.

Second, early (prior to dissection) identification rates with NIR-ICG are adequate and it can be used multiple times during dissection without increasing radiation or contrast load to the patient compared to IOC. This makes it an attractive alternative for pregnant and young patients as well as in order to avoid repeated exposure for the staff members.

Third, has the advantage of being real-time, allowing direct dissection and easy switching between xenon and infrared light modes. This can be conducted during and after Calot's triangle dissection, being able

to evaluate biliary anatomy in addition to its blood supply(33,34). On the contrary, IOC can only be performed once the cannula is placed after dissection and x-ray exposure has to be minimised, so no dissection is performed during this exploration. Moreover, IOC is believed to require longer operative time than NIR-ICG, thus increasing surgical time.

Fourth, NIR-ICG is low-cost, neither disposable equipment is required nor the presence of a specialist technician. In fact, the equipment and training required for radioprotection increases the cost of this procedure since IOC requires the fluoroscope to be handled by trained personnel which makes perioperative logistics more difficult.

Finally, NIR-ICG is easy to perform and to learn. A short learning curve has been described and it has been shown to be a good learning tool for surgeons in training(35–37).

Why is it important to do this review?

When compared to IOC, NIR-ICG is supposed to provide equal visualisation of the bile ducts before dissection. NIR-ICG has the potential to replace IOC for biliary mapping since IOC comes with higher costs, more difficult perioperative logistics, greater radiation exposure, greater use of radiographic contrast fluids, frequent technical failure when CD is obliterated and risk of BDI due to cannulation of the CD. NIR-ICG might be considered to be the best option for visualisation of the biliary tract, although further research is necessary to confirm this recommendation.

NIR-ICG has been shown to be useful in identifying biliary structures in LC, however, its role in bile duct detection and prevention has not been established. The results reported from prior studies have mostly concluded that NIR-ICG improves visualisation of biliary structures; however, these studies included a relatively small sample size, ranging between 23 and 120 patients(36,38). Several groups(39–41) have found NIR-ICG to be feasible, although it has not been validated against IOC, which is the standard for visualisation of the critical junction. Studies comparing both techniques have not shown definitive conclusions regarding prevention of BDI and to date, based on the available data, the topic remains controversial. Given the low frequency of BDI, a randomised trial comparing BDI rates for routine and selective IOC versus NIR-ICG would be difficult to carry out since the number of patients required to demonstrate a potential BDI reduction would be prohibitively high. According to Livingston et al. 527 IOCs might be required to prevent a single BDI(42). Therefore, it has been estimated that more than 30,000 patients would be needed in each group to detect a clinically significant reduction(43). Consequently, the endpoint of visualisation of anatomic structures is a useful surrogate marker of clinical efficacy and a systematic review would be the preferred study type to prove these differences.

There have been no systematic reviews including randomised controlled trials or Cochrane systematic reviews on this topic. Existing reviews highlight the uncertainty of which is the preferred method for the visualisation of biliary structures during LC(13,25,44). A systematic review and metaanalysis published in 2017 showed that there seems to be moderate to low quality evidence that visualisation of the CD,

common bile duct (CBD) and common hepatic duct (CHD) with NIR-ICG is better than using IOC although no statistical differences were found(45). This review will capture additional data, including papers published since 2017, to allow greater understanding of trends and update the current literature since a considerable number of publications and great technological improvement has occurred in the last years.

Understanding the benefits of this technique is critical to ensuring policymakers can make informed decisions as to where preventive efforts should be focused regarding specific imaging techniques. Solid evidence is required regarding the use of NIR-ICG in order to implement it as a standard technique and include it in the curriculum of future generations of surgeons. A review in this topic is also particularly important in light of the evidence that demonstrates this technique seems safe and feasible although has not been widely implemented yet. A survey performed to surgeons who attended a conference on fluorescence-guided surgery showed that only 23% had experience in NIR-C procedures despite the selection bias. The congress attendees were surgeons who personally enrolled to attend a conference on fluorescence-guided surgery, who might represent a population with more access and experience with fluorescence-guided systems for laparoscopic cholecystectomies thus overestimating the percentage(46).

Finally, the use of IOC could be considered as a quality criterion during cholecystectomy(47). Nevertheless, it is performed less often than what is stated in the literature, most likely because day-case cholecystectomies only require a short operative time and may enable the patient to be discharged home in the afternoon. If a faster and non-invasive technique was available, routine use could be encouraged and wide implementation could be a reality.

We aim to perform a systematic review to study the effect of the use of ICG during LC for gallstone disease in comparison to IOC in terms of time to identification and rate of visualisation of biliary structures. This will include patients undergoing any type of minimally invasive cholecystectomy for gallstone disease to assess all possible scenarios. In order to achieve the highest level of evidence, only randomised clinical trials and prospective comparative studies will be included. Systematic reviews and meta-analyses increase the precision of the treatment effects (i.e. they provide a narrower range of the average treatment effect)(48), and so decrease the risk of a type II error (concluding that there is no difference between treatments when there is actually a difference). Systematic reviews also help in identifying the differences in the treatment effects between studies and allow exploration of the reasons behind these differences. We hope this review will clarify the current situation regarding the different techniques for visualisation of biliary structures during LC.

In accordance with the guidelines, our systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 28th April 2020 and was accepted on 5th July, 2020 (registration number CRD42020177991).

OBJECTIVES.

The aim of this systematic review is to evaluate if Near infra-red indocyanine green fluorescent cholangiography can visualise extrahepatic biliary anatomy more efficiently and safer than intraoperative cholangiography in minimally invasive cholecystectomy for gallstone disease. To this end, the proposed systematic review will aim to answer the following questions:

1. What are the bile duct injury rates during minimally invasive cholecystectomy for gallstone disease when standard IOC is performed compared to NIR-ICG?
2. When comparing NIR-ICG to standard IOC, what are the detection rates of biliary structures, such as CD, CBD, CHD and CD-CHD junction, in order to perform a safe dissection of Calot's triangle and to avoid bile duct injury?
3. Is there a definitive advantage in terms of operative time saving when NIR-ICG is used to identify biliary structures in patients with gallstone disease both in urgent and elective setting compared to IOC?
4. Is NIR-ICG a safer technique due to the lack of cystic duct dissection and radiation compared to IOC?

Methods

No approval of the medical ethics committee was required.

ELIGIBILITY CRITERIA

Studies will be selected according to the PICO (Population, Intervention, Comparison and Outcomes) criteria of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) as described below (49) and detailed in Table 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) checklist.

Study designs

The included studies will be restricted to human studies. All randomised controlled clinical trials (RCT) and prospective non-randomised controlled trials which report on comparison of NIR-ICG versus IOC will be considered for inclusion. Conference abstracts with sufficient data available will be included (if became full article afterwards only full article will be included to prevent duplication of data). RCT and prospective non-randomised controlled trials comparing other techniques than NIR-ICG or IOC, as well as single-arm prospective trials will be excluded. Retrospective series and case reports will neither be considered for inclusion.

Participants

We will include male or female patients over the age of 18 years old who require elective or urgent minimally invasive cholecystectomy (undergoing NIR-ICG during this procedure) due to gallstone disease

both acute and chronic. Patients under 18 years old or undergoing procedures using NIR-ICG different than minimally invasive cholecystectomy will be excluded.

Intervention

Of interest are interventions addressing NIR-ICG performed during minimally invasive cholecystectomy with no restriction of dose, time of injection or way of administration, intravenous or directly into the gallbladder. The scope of the review, therefore, warrants an examination of the capacity of visualisation of biliary structures before, during and after dissection for NIR-ICG, classified as valid if one or more of the following structures, CD, CHD, CBD or CD-CHD junction could be identified. Time will be measured from the first time the xenon light is used until biliary structures considered to have been identified.

Comparators

Given that IOC is the gold standard intervention to visualise biliary structures, we will include studies comparing this technique to NIR-ICG. In order to perform IOC, the CD will be dissected in a standardised manner and with the aid of a grasper forceps it will be cannulated with a plastic catheter, then a radiopaque contrast media will be introduced through the above-mentioned catheter(50). Time will be measured from the application of the grasper until its removal, after obtaining a satisfactory cholangiogram, which will be defined by the ability to identify the CD and/or other biliary structures.

Outcomes

Endpoints important for decision making are of primary interest. If reported on, these will be analysed and graded. If a given clinical endpoint is not reported on, we will analyse and grade their relevant surrogate outcomes. As some outcomes may be reported as a composite measure, we will extract all composite and individual outcomes as reported in the studies.

Primary outcomes

Ability to visualise extrahepatic biliary anatomy to avoid bile duct injury, consisting of visualisation of CD, CBD, CHD, CD-CHD junction.

Time to obtain relevant images of the biliary tree.

Secondary outcomes

- Intraoperative identification of BDI and rate of BDI induced by each technique.
- Adverse events secondary to ICG infusion.
- Adverse events secondary to radiation as well as iatrogenic lesions secondary to CD cannulation.
- Identification of aberrant biliary anatomy.

Timing

There will be no restrictions by timing.

Setting

There will be no restrictions by type of setting.

Language and geography.

There will be no restrictions by language or geography.

Information sources

Literature search strategies will be developed using medical subject headings (MeSH) and text words related to the use of NIR-ICG and IOC in minimally invasive cholecystectomies. The search terms that will be used are Indocyanine Green, ICG, Fluorescence, Cholecystectomy and Bile Duct Injury. We will search Medline (via PubMed), Embase, Scopus, the Cochrane Central Register of Controlled Trials (CENTRAL) and web of science. The electronic database search will be supplemented by searching for trial protocols through Clinical Trials (<http://www.clinicaltrials.gov>). The literature search will have no language or time restrictions and will include all available literature up to the search date, although limited to human subjects. To ensure literature saturation, we will scan the reference lists of included studies or relevant reviews identified through the search.

SEARCH STRATEGY

Both qualitative and quantitative studies will be sought. The specific search strategies will be created by a Health Sciences Librarian with expertise in systematic review searching. The MEDLINE strategy will be developed with input from the project team. A draft MEDLINE search strategy is included in Appendix 1. After the MEDLINE strategy is finalized, it will be adapted to the syntax and subject headings of the other databases. ClinicalTrials.gov will be also searched to retrieve ongoing or recently completed trials. PROSPERO will be searched for ongoing or recently completed systematic reviews. As relevant studies are identified, reviewers will check for additional relevant cited and citing articles. The search will be updated toward the end of the review, after being validated to ensure that the MEDLINE strategy retrieves a high proportion of eligible studies found through any means though indexed in MEDLINE.

STUDY RECORDS

Data management

Literature search results will be uploaded to a Mendeley database. Search for duplicates will be performed by two researchers (MA, RM) with the Mendeley search for duplicates tool as well as juxtaposing author names and titles by hand. When similar titles or author list are found only the most updated series will be included. If both conference abstract and full paper reporting on the same patients are found only the full paper will be assessed.

Selection process

After excluding duplicates, the review authors (MA, RM) will independently screen the titles and abstracts yielded by the search against the inclusion criteria and code them as 'retrieve' (eligible, potentially eligible, or unclear) or 'do not retrieve'. Full reports for all titles that appear to meet the inclusion criteria (coded as retrieve) will be obtained and two review authors (MA, RM) will then screen the full-text reports. They will identify studies for inclusion and record reasons to exclude the ineligible studies. Disagreement will be resolved through discussion. Neither of the review authors will be blind to the journal titles or to the study authors or institutions. The reference lists of all included studies will be hand-searched in order to identify other potentially relevant studies. Any areas of disagreement between the two primary researchers will be resolved through discussion and if necessary, a third researcher (RJ) will be involved. Duplicates will be identified and excluded. The selection process will be recorded in sufficient detail to complete a PRISMA flow diagram. The characteristics of the excluded studies will be displayed in a table.

Data collection process

A pre-defined data collection form was prepared with consensus and consultation with all the researchers. Once data was collected it was transferred to an excel-based data collection form for study characteristics and outcome data will be used. Two review authors (MA and RM) will independently extract the following study characteristics and outcome data from included studies.

Participants: total number and number of patients in each group, mean age, age range, gender, severity of condition, diagnostic criteria, inclusion criteria, exclusion criteria.

Interventions: intervention, comparison, and any cointerventions.

Outcomes: primary and secondary outcomes specified and collected, time points reported and all reported patient-important outcomes.

Study characteristics: study design, study methodology, first author's name, year of publication, study design, total duration of study and run-in period, number of study centres and location, study setting and withdrawals.

Notes: funding for trial, notable conflicts of interest of trial authors.

If an outcome is reported at two or more time points within the timeframe of the outcome - for example, 30-day and 90-day mortality are reported - we will use the data that are reported at the latest time point of the outcome. We will note in the 'Characteristics of included studies' table if outcome data were reported in an unusable way. We will resolve disagreements by consensus. One review author (MA) will copy across the data from the data collection form into the excel file and will double-check that the data are entered correctly by comparing the study reports with how the data are presented in the systematic review. A second review author (RM) will spot-check study characteristics for accuracy against the trial report.

ASSESSMENT OF RISK OF BIAS IN INCLUDED STUDIES

To facilitate the assessment of possible risk of bias the Newcastle-Ottawa score (NOS) will be used to test the quality of non-randomised studies. This scale⁽⁵¹⁾ employs a star scoring system for the quality assessment of studies. A total of 9 stars can be awarded to a study. A study can be awarded a maximum

of 4 for selection, 3 for outcome and maximum of 2 stars for comparability. Studies will be categorised as low, moderate and high quality depending on the number of stars; 0-3 corresponds to low quality, 4-6 to medium quality and 7-9 to high quality.

The Cochrane Risk of Bias Tool will be used for randomised controlled trials. It will assess the risk of bias according to the following domains(48): random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other bias. Each study will be judged to be at either high, low, or unclear risk of bias for each of the domains above and we will provide a quote from the study report and justification for our judgement in the 'Risk of bias' table. We will summarise the 'Risk of bias' judgements across studies for each of the domains listed. These judgements will be made independently by two review authors. Disagreements will be resolved first by discussion and then by consulting a third author for arbitration. The review will be conducted according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

DATA SYNTHESIS

Dichotomous data (presence of BDI, anatomical variants identified) will be determined by using risk ratio (RR) with 95% confidence interval (CI). Continuous outcomes (feasibility of performing ICG and IOC, time to identification, rate of identification of the various biliary structures) will be analysed using weighted mean differences (with 95% CI) or standardized mean differences (95% CI) if different measurement scales are used. Skewed data and non-quantitative data will be presented descriptively. We will then conduct meta-analyses using a random effects model (if the data has high heterogeneity). A common way that trialists indicate they have skewed data, is by reporting medians and interquartile ranges. The narrative synthesis will explore the relationship and findings both within and between the included studies, in line with the guidance from the Centre for Reviews and Dissemination(52). Where multiple trial arms are reported in a single trial, we will include only the relevant arms.

Unit of analysis issues

The unit of analysis will be individual participants with gallstone disease who undergo minimally invasive cholecystectomy and NIR-ICG, IOC or both are performed during the procedure. If we find any cross-over studies, we will include the data from both interventions before and after crossover. If we find any cluster-randomised studies unexpectedly, we will include the data in the analysis if results are adjusted for intra-cluster correlation. In multi-arm studies, the models account for the correlation between trial-specific treatment effects from the same trial in the context of network meta-analysis, which allows comparison of multiple treatments.

Assessment of heterogeneity

Clinical heterogeneity will be tested by considering the variability in participant factors among trials (for example definition of gallstone disease) and trial factors. Statistical heterogeneity will be tested using the

Chi2 test (significance level: 0.1) and I2 statistic (0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity). If high levels of heterogeneity among the trials exist ($I^2 \geq 50\%$ or $P < 0.1$) the study design and characteristics in the included studies will be analysed.

Each outcome will be combined and calculated using the statistical software RevMan 5.3, according to the statistical guidelines referenced in the current version of the Cochrane Handbook for Systematic Reviews of Interventions. The Mantel-Haenszel method will be used for the fixed effect model if tests of heterogeneity are not significant. If statistical heterogeneity is observed ($I^2 \geq 50\%$ or $P < 0.1$), the random effects model will be chosen. If heterogeneity is substantial, a meta-analysis and a narrative will not be performed, therefore qualitative summary will be done instead.

Measures of effect

Results will be presented in order by key question and, within key questions, in order of main then additional outcomes. Only studies for which risk of bias was either low or moderate are planned to be reported, therefore studies with high risk of bias will be omitted. Tables to summarize the characteristics of studies and the principal comparisons or outcomes of concern will be used.

The primary outcome is intraoperative identification of BDI. Since BDI has a low incidence it will be also measured through a surrogate marker that will consist of visualisation of CD, CBD, CHD and/or CD-CHD junction. Number of BDI detected intraoperative or postoperative will be given in number of patients and percentage. Rate of visualisation for the CD, CBD, CHD and the CD-CHD junction will be given as proportions. The rates of detection of the extrahepatic biliary structures for each technique will be collected and shown in a table as well as any case of intraoperative BDI and overall number of patients presenting any type of BDI. Weighted mean biliary duct visualisation will be calculated through pooled analysis in a random effects model with 95% confidence intervals. ICG visualisation of biliary structures will be compared to visualisation with IOC. Outcomes will be weighted by inverse variance in a random effects model. Treatment effect will be presented as relative risk with 95% confidence intervals. Heterogeneity between studies will be assessed through the I2 statistic. Technical failure of IOC will not be excluded from calculations, instead will be analysed as not able to visualise the bile duct structures. These analyses will be conducted with SPSS version 26.

Secondary outcomes will be reported as a narrative description afterwards. First, time to visualisation will be reported in minutes, compared between techniques and will also be shown in the table. Second, the rate of adverse events secondary to each technique will be described, including adverse events secondary to ICG infusion and rate of adverse events secondary to radiation as well as iatrogenic lesions secondary to CD cannulation. Finally, identification of aberrant biliary anatomy will be reported.

Discussion

BDI is the most feared complication after cholecystectomy. BDI rates range from 0.08% to 0.3%(6,7). This low incidence has to be weighed against the high numbers of cholecystectomies(8,9) and with the potentially severe repercussions of BDI. To date, there is sufficient data to conclude that NIR-ICG is a safe and feasible technique to assess biliary anatomy although current guidelines only mention IOC.

When compared to IOC, NIR-ICG is supposed to provide equal visualisation of the bile ducts before dissection. NIR-ICG has the potential to replace IOC for biliary mapping since IOC comes with higher costs, more difficult perioperative logistics, greater radiation exposure, greater use of radiographic contrast fluids, frequent technical failure when CD is obliterated and risk of BDI due to cannulation of the CD. NIR-ICG might be considered to be the best option for visualisation of the biliary tract, although further research is necessary to confirm this recommendation.

There have been no systematic reviews including randomised controlled trials or Cochrane systematic reviews on this topic. Existing reviews highlight the uncertainty of which is the preferred method for the visualisation of biliary structures during LC(13,25,44). This review will capture additional data, including papers published since 2017, to allow greater understanding of trends and update the current literature since a considerable number of publications and great technological improvement has occurred in the last years.

Understanding the benefits of this technique is critical to ensuring policymakers can make informed decisions as to where preventive efforts should be focused regarding specific imaging techniques. A review of current evidence on the topic is needed before the technique is included in future guidelines.

Reaching Conclusions

The discussion will only be based on findings from the quantitative or narrative synthesis of studies included in this review. Making recommendations for practice will be avoided. Our implications for research will give the reader a clear sense of the needed focus of future research and remaining uncertainties in the field. Understanding the benefits of this technique is critical to ensuring policymakers can make informed decisions as to where preventive efforts should be focused regarding specific imaging techniques. If ICG is proven to be faster and non-invasive, routine use could be encouraged and wide implementation could be a reality.

Abbreviations

LC – Laparoscopic cholecystectomy

BDI – Bile duct injury

CVS – Critical view of safety

IOC – X-ray intraoperative cholangiography

NIR-ICG – Near infra-red indocyanine green fluorescent

SAGES – Society of American Gastrointestinal and Endoscopic Surgeons

NIR-C – Near-infrared cholangiography

FDA – Food and drug organization

ICG – Indocyanine green

CD – Cystic duct

CBD – Common bile duct

CHD – Common hepatic duct

RCT – Randomised controlled clinical trials

CENTRAL – Cochrane Central Register of Controlled Trials

NOS – Newcastle-Ottawa score

NASH – Non-alcoholic steatohepatitis

Declarations

AMENDMENTS

If there is a need to amend this protocol, the date of each amendment will be given, describing the change and giving the rationale in this section. Changes will not be incorporated into the protocol.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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AUTHORS' CONTRIBUTION

MA drafted the manuscript and designed the protocol. MA, RM together with the medical librarian developed the search strategy. MA and RM contributed to the development of the selection criteria, the risk of bias assessment strategy and data extraction criteria. MCP and EL help to develop the prevision statistical analysis. LE, EJ and RJ provided expertise on NIR-ICG technique. All authors read and provided feedback. RM and RJ provided critical revision of the protocol and all authors provided final approval of the version to be published.

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