

Indocyanine Green Fluorescent Cholangiography Versus Conventional White-Light Imaging for Identification of Biliary Anatomy During Laparoscopic Cholecystectomy: A Systematic Review and Meta-Analysis of Randomised Controlled Trials

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Abstract

Background: Bile duct injury during laparoscopic cholecystectomy is usually caused by misidentification of the biliary anatomy. Near-infrared fluorescent cholangiography with indocyanine green (ICG) shows the extrahepatic bile ducts without cannulation or radiation. This review pooled randomised trials published before 2023 that compared ICG cholangiography with conventional white-light laparoscopic cholecystectomy.

Methods: PubMed was searched for randomised controlled trials published up to 31 December 2022. Outcomes were visualisation of the extrahepatic biliary structures, time to the critical view of safety, conversion to open surgery, bile duct injury, bile leak, postoperative complications and operative time. Risk ratios (RR) were pooled with a DerSimonian-Laird random-effects model where at least two trials reported an outcome; other outcomes were summarised descriptively. Risk of bias was assessed with RoB 2 and certainty of evidence with GRADE.

Results: Of 27 records screened, three randomised trials with 799 randomised patients were included. In the largest trial (639 patients), ICG cholangiography improved the detection of all seven extrahepatic biliary structures before dissection; the cystic duct was seen before dissection in 66.6% of patients with ICG and 36.6% with white light. In a single-surgeon trial, the time to reach the critical view of safety was similar (mean difference -0.5 min, 95% CI -7.2 to 6.2). Conversion to open surgery occurred in 7 of 399 patients (1.8%) with ICG and 11 of 400 (2.8%) with white light (RR 0.71, 95% CI 0.27-1.82; I² = 0%). Bile duct injury occurred in no patient with ICG and two patients with white light, all in one trial. No adverse reactions to ICG were reported in the trials that described them.

Conclusion: ICG fluorescent cholangiography improves the visualisation of the extrahepatic biliary anatomy during laparoscopic cholecystectomy compared with white light alone. Randomised trials published before 2023 were too small to show an effect on conversion or bile duct injury, and the certainty of evidence for these outcomes is very low. ICG cholangiography is a reasonable adjunct, especially in difficult cases, but larger trials are needed.

Keywords: Indocyanine green; Fluorescent cholangiography; Laparoscopic cholecystectomy; Bile duct injury; Critical view of safety; Near-infrared imaging; Meta-analysis.

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Introduction

Laparoscopic cholecystectomy is one of the most common abdominal operations, and bile duct injury remains its most serious complication [1]. In a review of more than 500,000 patients, the reported rate of bile duct injury was 0.32% to 0.52% [2]. Injury is followed by poorer long-term survival: in a cohort of more than 1.5 million Medicare patients, bile duct injury was associated with a hazard ratio of 2.79 for death [3], and in a Swedish register, one-year mortality was 3.9% with injury compared with 1.1% without [4].

Most injuries are caused not by poor technical skill but by misidentification of the anatomy. In an analysis of 252 injuries, a visual perceptual illusion was the main cause in 97% of cases [5]. The critical view of safety was introduced to make identification of the cystic duct and artery more reliable before they are divided [1,6], and a multi-society guideline strongly recommends intraoperative biliary imaging when the anatomy is uncertain [7]. Conventional X-ray cholangiography, however, needs cannulation of

the cystic duct, radiation and time, and randomised evidence for its routine use is weak [8].

Near-infrared fluorescent cholangiography is a simpler alternative. ICG is given intravenously before surgery, is excreted into the bile and can be seen through the tissues with a near-infrared camera [9]. In early series, fluorescent cholangiography showed the cystic duct in all patients and the junction of the cystic and common hepatic ducts before dissection in 50 of 52 patients [10]. A comparison with X-ray cholangiography found that it was faster and more often obtainable [11], and a systematic review found cystic duct visualisation in 86.5% of patients before dissection [12]. Most of this evidence came from non-randomised studies. This systematic review and meta-analysis therefore compared ICG fluorescent cholangiography with conventional white-light imaging during laparoscopic cholecystectomy, using randomised controlled trials published before 2023.

Materials and Methods

Protocol and Reporting: The review was reported according to the PRISMA 2020 statement [13]. The protocol was not registered in advance. Ethics committee approval was not required because only published data were used.

Eligibility Criteria: Studies were included if they met all of the following criteria. (1) Design: randomised controlled trial. (2) Population: adults undergoing elective or emergency laparoscopic cholecystectomy for benign gallbladder disease. (3) Intervention: near-infrared fluorescent cholangiography with ICG given intravenously at any dose and time. (4) Comparator: conventional laparoscopic cholecystectomy under white light without fluorescent imaging. (5) Outcomes: at least one of visualisation of extrahepatic biliary structures, time to the critical view of safety, conversion to open surgery, bile duct injury, bile leak, postoperative complications or operative time. (6) Publication: full report in a PubMed-indexed journal with a publication date up to 31 December 2022. Non-randomised and retrospective studies, trials of open or robotic cholecystectomy, trials comparing ICG with X-ray cholangiography or comparing ICG doses or timings, protocols, reviews and conference abstracts were excluded.

Information sources and search: PubMed was searched on 20 October 2026 for publications from 1 January 2010 to 31 December 2022. The search combined indocyanine green, ICG, near-infrared and fluorescent or fluorescence cholangiography

with cholecystectomy, and with the term random or the randomised controlled trial publication type. Reference lists of included trials and of systematic reviews [12,14,15] were searched by hand.

Study Selection and Data Extraction: Titles and abstracts were screened, and full texts of potentially eligible reports were assessed against the criteria.[15].

Risk of Bias Assessment: Risk of bias was assessed with the revised Cochrane tool for randomised trials (RoB 2) [16]. Each domain and the overall risk were judged as low, some concerns or high.

Statistical Analysis: Dichotomous outcomes were expressed as risk ratios (RR) and continuous outcomes as mean differences (MD), each with a 95% confidence interval (CI). Outcomes reported by at least two trials were pooled with the inverse-variance method and a DerSimonian-Laird random-effects model [17]; 0.5 was added to each cell of trials with no events in one arm [18]. Heterogeneity was assessed with the I² statistic [19]. Because only three trials were available, the Hartung-Knapp-Sidik-Jonkman method was used as a sensitivity analysis [20]. Bile duct injury was too rare for reliable pooling, and outcomes with zero events in both arms do not contribute to a risk ratio, so these were reported descriptively [21].

Outcomes reported by only one trial, or reported as medians, were summarised without pooling. Certainty of evidence was rated with GRADE [22]. Analyses were performed in Review Manager (RevMan) version 5.4 (The Cochrane Collaboration, 2020), and the Hartung-Knapp-Sidik-Jonkman analysis was run in R version 4.2 with the meta package.

Results

Study Selection: The search returned 27 records. After screening of titles and abstracts, 18 were excluded, including two reports with a journal issue date in 2023, and nine full-text reports were assessed (Figure 1). Six were excluded: one retrospective study in which the use of ICG was chosen by the surgeon [23], one randomised trial that compared ICG with X-ray cholangiography [24], one study of open cholecystectomy [25], one trial that compared timings of ICG without a white-light control [26], and two trial protocols, one of which belonged to the X-ray cholangiography trial [27]. Three randomised trials were included [28-30].

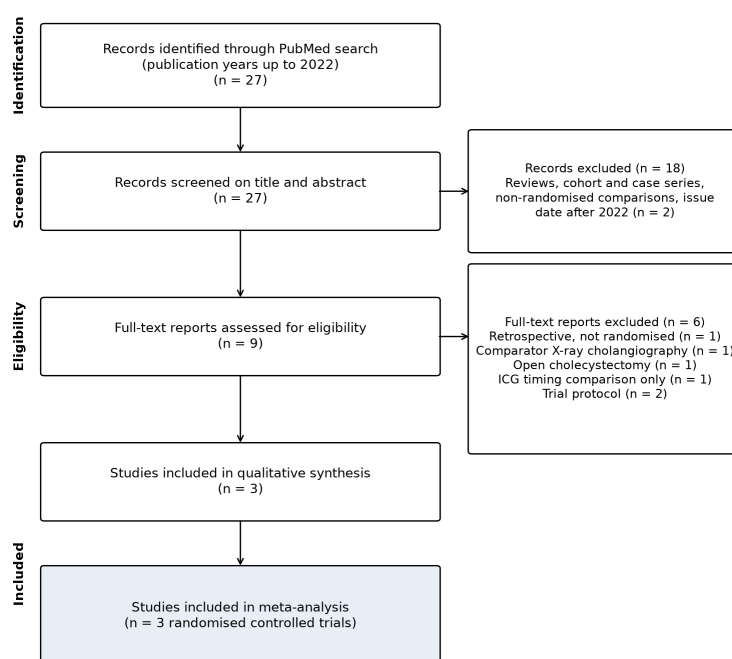


Figure 1: PRISMA 2020 flow diagram of study selection

Characteristics of included trials: The trials were published from 2019 to 2022 and randomised 799 patients: 399 to ICG cholangiography and 400 to white light (Table 1). The largest was a multicentre trial from the United States, Argentina, Germany, Italy and Japan that randomised 639 patients undergoing elective cholecystectomy [28]. A single-surgeon trial from Malaysia randomised 68

patients and analysed 63 after excluding converted cases [29].

A trial from Hong Kong randomised 92 patients with acute cholecystitis undergoing emergency surgery [30]. ICG was given intravenously before surgery in all trials.

Table 1: Characteristics of the included trials

Trial	Country and centres	Setting	Patients randomised (ICG/white light)	ICG protocol	Main outcome
Dip 2019 [28]	United States, Argentina, Germany, Italy, Japan; multicentre	Elective laparoscopic cholecystectomy	321/318	0.05 mg/kg intravenously, at least 45 min before surgery	Detection of 7 extrahepatic biliary structures before and after dissection
Koong 2021 [29]	Malaysia; single centre, single surgeon	Laparoscopic cholecystectomy	32/36 (30/33 analysed)	2.5 mg intravenously before induction of anaesthesia	Time to the critical view of safety
She 2022 [30]	Hong Kong; single centre	Emergency laparoscopic cholecystectomy for acute cholecystitis	46/46	Intravenous; median 67 min before surgery	Conversion and biliary injury

ICG: indocyanine green.

Risk of bias: All three trials had some concerns about risk of bias (Table 2). Surgeons could not be blinded to the use of fluorescence, and visualisation of structures and time to the critical view of safety were judged by the operating surgeon, which raises

concern for these outcomes. The large trial was single-blind and registered [28].

The Malaysian trial excluded converted patients from its main analysis [29]. Conversion and bile

duct injury are objective outcomes and are less exposed to bias.

Table 2: Risk of bias in the included trials (RoB 2)

Trial	Random isation	Deviations from intended interventions	Missing outcome data	Outcome measurement	Selection of reported result	Overall
Dip 2019	Some concerns	Low	Low	Some concerns (surgeon-assessed visualisation)	Low (registered)	Some concerns
Koong 2021	Some concerns	Low	Some concerns (converted patients excluded)	Some concerns (unblinded timing)	Low (registered)	Some concerns
She 2022	Some concerns	Low	Low	Low (objective outcomes)	Some concerns	Some concerns

Judgements are based on the published trial reports.

Visualisation of biliary anatomy and time to the critical view of safety: Only the large trial reported the detection of biliary structures. Before dissection, all seven extrahepatic biliary structures were seen significantly more often with ICG, with detection rates ranging from 9.1% versus 2.9% for the right hepatic duct to 66.6% versus 36.6% for the cystic duct, and odds ratios from 2.3 to 3.6 [28]. After dissection, the advantage remained for all structures except the cystic duct and the junction of the cystic duct with the gallbladder. A higher body mass index reduced detection in both groups. In the Malaysian trial, the mean time to reach the critical view of safety was 22.3 ± 12.9 min with ICG and 22.8 ± 14.3 min with white light (MD -0.5 min,

95% CI -7.2 to 6.2), and the time was shorter with ICG at every level of difficulty, although not significantly [29].

Conversion to open surgery: All three trials reported conversion. Conversion occurred in 7 of 399 patients (1.8%) with ICG and 11 of 400 (2.8%) with white light (Figure 2). The pooled RR was 0.71 (95% CI 0.27-1.82; $p = 0.47$; $I^2 = 0\%$). With the Hartung-Knapp-Sidik-Jonkman method, the interval was 0.15 to 3.42. In the two trials of elective surgery the RR was 0.49 (95% CI 0.13-1.90), and in the trial of acute cholecystitis the conversion rate was 8.7% in both groups [30].

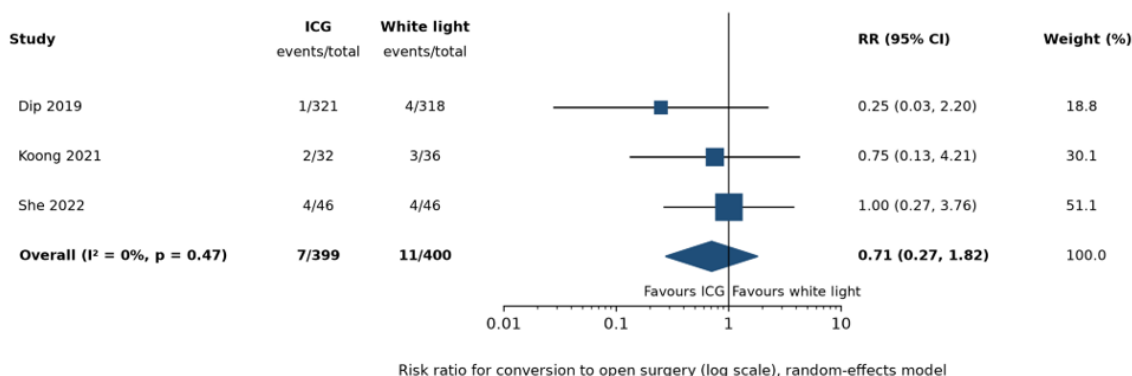


Figure 2: Forest plot of the effect of indocyanine green (ICG) fluorescent cholangiography compared with white light on conversion to open surgery (random-effects model, intention to treat). Squares show trial risk ratios, with size proportional to weight; horizontal lines show 95% confidence intervals; the diamond shows the pooled estimate

Bile duct injury, bile leak and other complications: Bile duct injury occurred in two patients, both in the white-light group of the large trial (0 of 321 vs 2 of 318) [28]. No major complication occurred in either group of the Malaysian trial [29]. In the acute cholecystitis trial, bile leak occurred in one patient in each group (2.2%), and the overall complication rate was

10.9% with ICG and 15.2% with white light (RR 0.71, 95% CI 0.24-2.09) [30].

In the same trial, the median operative time was 149.5 min with ICG and 140.5 min with white light ($p = 0.086$), and the median hospital stay was 4.0 and 3.5 days [30]. No adverse reaction to ICG was reported in the trials that described safety (Table 3).

Table 3: Summary of outcomes in the included trials

Outcome	Dip 2019	Koong 2021	She 2022	Pooled or summary result
Cystic duct seen before dissection, ICG vs white light	66.6% vs 36.6%	Not reported	Not reported	Single trial; all 7 structures better seen with ICG (odds ratios 2.3-3.6)
Time to critical view of safety, min	Not reported	22.3 ± 12.9 vs 22.8 ± 14.3	Not reported	MD -0.5 (-7.2 to 6.2); single trial
Conversion to open surgery	1/321 vs 4/318*	2/32 vs 3/36	4/46 vs 4/46	RR 0.71 (0.27-1.82); I ² = 0%
Bile duct injury	0/321 vs 2/318	0/30 vs 0/33	Not reported	0/351 vs 2/351; not pooled
Bile leak	Not reported	No major complication	1/46 vs 1/46	Not pooled
Overall complications	Not reported	No major complication	10.9% vs 15.2%	Single trial; RR 0.71 (0.24-2.09)
Operative time, min	Not reported	Not reported	Median 149.5 vs 140.5	Not pooled (medians)
Adverse reaction to ICG	None*	None*	Not reported in abstract	None in the trials that reported it

Values are ICG vs white light. MD: mean difference; RR: risk ratio. *Conversion counts for Dip 2019 and adverse-reaction data for Dip 2019 and Koong 2021 were taken from a published systematic review [15].

Certainty of evidence: Certainty of evidence was rated low for visualisation of biliary structures, because it came from a single trial with an unblinded outcome assessment. It was rated very

low for conversion and bile duct injury because of very serious imprecision and some concerns about risk of bias (Table 4).

Table 4: Summary of findings and certainty of evidence (GRADE)

Outcome	Trials (patients)	Effect (95% CI)	Absolute effect per 1000 patients	Certainty and reasons
Visualisation of cystic duct before dissection	1 (639)	66.6% vs 36.6%	About 300 more patients with the duct seen	Low; single trial, unblinded assessment
Conversion to open surgery	3 (799)	RR 0.71 (0.27-1.82)	8 fewer (20 fewer to 23 more) [†]	Very low; risk of bias and very serious imprecision
Bile duct injury	2 (702)	Not estimable (0 vs 2 events)	Not estimated	Very low; very serious imprecision

[†]Control-group risk 28 per 1000 (pooled white-light groups).

Discussion

This review of three randomised trials found that ICG fluorescent cholangiography made the extrahepatic bile ducts visible more often and earlier during laparoscopic cholecystectomy than white light alone. The cystic duct was seen before dissection in two thirds of patients with ICG and in about one third with white light [28]. Conversion was less frequent with ICG and no bile duct injury occurred in the ICG groups, but the trials were far too small to show a difference in these rare outcomes.

The improvement in visualisation agrees with earlier non-randomised evidence. The first clinical series showed the cystic duct in every patient [10], and a systematic review of 19 studies reported cystic duct visualisation in 86.5% before dissection [12]. The lower rates in the randomised trial may reflect differences in ICG dose and timing and

imaging systems, and the inclusion of patients with a high body mass index, in whom detection was reduced [28]. Visualisation is a surrogate outcome. It matters because most bile duct injuries are caused by a perceptual error in which the common bile duct is mistaken for the cystic duct [5], and better identification of the anatomy before dissection directly addresses this error.

Effects on clinical outcomes are less certain. Bile duct injury occurs in about 0.3% to 0.5% of cholecystectomies [2], so a trial would need tens of thousands of patients to show a reduction. A meta-analysis of mainly non-randomised studies reported weighted bile duct injury rates of 6 per 10,000 with ICG and 25 per 10,000 without, and conversion rates of 16 and 271 per 10,000 [14].

A systematic review published in 2022 also reported lower conversion and injury rates with ICG across all study types [15]. The randomised

trials included here point in the same direction for conversion, but the confidence interval was wide. In acute cholecystitis, where dense inflammation may block the fluorescent signal, ICG made no difference to conversion [30].

ICG cholangiography has practical advantages over X-ray cholangiography. It does not need cannulation of the cystic duct or radiation, it can be repeated during the operation, and it was faster and more often successful than X-ray cholangiography in a direct comparison [11]. ICG has a long safety record [9], and no adverse reactions were reported in the included trials that described them. The main barrier is the cost of the near-infrared imaging system, which may limit its use in low-resource settings. Time to the critical view of safety was not shortened in the only trial that measured it [29], so ICG should be seen as an aid to identification rather than a way to speed up the operation. It does not replace the critical view of safety [6,7].

Strengths and limitations

This review included only randomised trials, followed the intention-to-treat principle for conversion and rated the certainty of evidence for each outcome. It also has important limitations. Only PubMed was searched, and only reports published before 2023 were included, so later trials were not considered.

Only three trials were available, and they reported different outcomes, so only conversion could be pooled. The visualisation outcome came from a single trial and was assessed by surgeons who knew the allocation. Some outcome data were taken from a published review because the trial abstracts did not report them [15]. The trials differed in setting (elective or emergency surgery), ICG dose and timing, and imaging system. Bile duct injury was too rare to analyse formally.

Conclusion

In randomised trials published before 2023, ICG fluorescent cholangiography improved the identification of the extrahepatic biliary anatomy during laparoscopic cholecystectomy compared with white light alone. Its effects on conversion and bile duct injury were uncertain because these events were rare and the trials were small. ICG cholangiography is safe and simple and can be used as an adjunct to the critical view of safety, particularly in difficult cases and in surgical training. Large multicentre trials or registries are needed to show whether it reduces bile duct injury.

Declarations

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Conflict of interest: The author declares no conflict of interest.

Ethical approval: Not required, as the review used only published data.

Author contribution: Dr. Mayur Pradip Gangwal conceived the review, performed the search, extracted and analysed the data, wrote the manuscript and approved the final version.

Data availability: All data used in this review are available in the published reports of the included trials and in the cited systematic review.

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