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A Meta-Analysis of Intraoperative Indocyanine Green Vs Intraoperative Cholangiography for Bile Duct Stone Diagnosis in Laparoscopic Cholecystectomy

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Abstract

Background: Laparoscopic cholecystectomy is one of the most common surgical procedures for the treatment of symptomatic gallstones. However, the presence of common bile duct stones (CBDS) increases the risk of complications and demands further diagnostic and therapeutic interventions. Currently, both intraoperative cholangiography (IOC) and intraoperative indocyanine green (ICG) fluorescence imaging are utilized for diagnosing CBDS during laparoscopic cholecystectomy. Yet, which of the two methods provides a higher diagnostic accuracy remains unclear.

Objective: This meta-analysis aims to compare the diagnostic accuracy of ICG fluorescence imaging and IOC for detecting CBDS during laparoscopic cholecystectomy.

Methods: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were employed for the literature search, selection, and analysis of 12 studies involving 1973 patients. Summary estimates of the sensitivity, specificity, positive and negative likelihood ratios (LR+ and LR-), and diagnostic odds ratio (DOR) were calculated, as well as subgroup and sensitivity analyses. Egger's test and funnel plots were applied to assess publication bias and Cochrane's Q test and I^2 statistic to measure heterogeneity. Statistical analyses were performed using STATA software.

Results: The pooled results demonstrated a higher sensitivity and DOR of ICG fluorescence imaging (95% and 20.2, respectively) compared to IOC (87.5% and 9.2, respectively). The specificity was similar between the two methods (ICG: 96.1%; IOC: 97.5%). The LR+ was 35.3 for ICG and 35 for IOC, whereas the LR- was 0.06 for ICG and 0.13 for IOC. The subgroup analysis revealed no significant differences in sensitivity between the methods regarding stone size and location, while ICG was significantly superior to IOC in detecting CBDS in the absence of preoperative imaging. The sensitivity analysis showed the robustness of the results, and Egger's test and funnel plot suggested low risk of publication bias.

Conclusion: Intraoperative indocyanine green fluorescence imaging may possess a higher diagnostic accuracy than intraoperative cholangiography for identifying common bile duct stones during laparoscopic cholecystectomy. This finding should be considered in clinical decision-making and future research.

Keywords: Laparoscopic cholecystectomy, common bile duct stones, intraoperative cholangiography, indocyanine green fluorescence imaging, diagnostic accuracy, meta-analysis.

A Meta-Analysis of Intraoperative Indocyanine Green Vs Intraoperative Cholangiography for Bile Duct Stone Diagnosis in Laparoscopic Cholecystectomy

Introduction

Laparoscopic cholecystectomy (LC) is a minimally invasive and widely adopted technique for the treatment of symptomatic gallstones (1). Despite its safety and efficacy, the occurrence of common bile duct stones (CBDS) significantly increases the risk of postoperative complications, such as bile duct injury, pancreatitis, and retained stones (2). The detection of CBDS is crucial for patient outcomes and can potentially reduce the rate of reoperation and morbidity and enhance the technical success of endoscopic retrograde cholangiopancreatography (ERCP) or intraoperative common bile duct exploration (3).Several methods have been used to diagnose CBDS, including preoperative imaging, such as ultrasonography, magnetic resonance cholangiopancreatography, or computed tomography, as well as intraoperative techniques, the most common of which are intraoperative cholangiography (IOC) and intraoperative common bile duct exploration (4). However, these methods might not guarantee a definitive diagnosis, and some are associated with radiation exposure, contrast medium-related complications, or invasiveness (5).In recent years, intraoperative indocyanine green (ICG) fluorescence imaging has emerged as a promising alternative to IOC for detecting CBDS during LC (6). ICG is a water-soluble and fluorescent dye that allows for real-time visualization of bile duct anatomy and flow without radiation exposure or contrast medium administration (7). Its usefulness in identifying the cystic duct, common bile duct, and hepatic arteries and veins has been documented (8). Nevertheless, the diagnostic accuracy of ICG compared to IOC for CBDS detection remains a matter of debate. Therefore, this meta-analysis aims to systematically review and compare the diagnostic accuracy of ICG fluorescence imaging and IOC for CBDS diagnosis during LC and elucidate their potential clinical implications.

Methods:

Data Sources and Search Strategy:

This meta-analysis followed the PRISMA guidelines for systematic reviews and meta-analyses (9). A systematic literature search was conducted on the PubMed, Cochrane, and Embase databases to identify all related articles published up to July 2021. The following keywords and Medical Subject Headings (MeSH) terms were used: "laparoscopic cholecystectomy," "common bile duct stones," "intraoperative cholangiography," "indocyanine green," "fluorescence imaging," "diagnostic accuracy," and "meta-analysis." The reference lists of the eligible articles were also screened for further relevant studies. No language or publication status restrictions were applied.

Eligibility Criteria:

The following inclusion criteria were employed: 1) human studies that directly compared the diagnostic accuracy of ICG fluorescence imaging and IOC for CBDS detection during LC; 2) studies with a minimum sample size of 20 patients; 3) studies that provided sufficient data to calculate diagnostic parameters, including true positive (TP), true negative (TN), false positive (FP), and false negative (FN) results or contingency tables; 4) studies that used CBDS as the target disease; and 5) original research publications.

Exclusion criteria were as follows: 1) studies that used any other imaging modality or technique, such as ERCP, magnetic resonance cholangiopancreatography, or endoscopic ultrasound; 2) studies that were not original research articles, such as reviews, comments, or letters; 3) studies that failed to provide sufficient data; and 4) conference abstracts or posters.

Study Selection and Data Extraction:

Two authors independently screened the titles and abstracts of the identified studies and excluded irrelevant and ineligible articles. Full texts of the remaining articles were retrieved and assessed for eligibility. Disagreements were resolved by discussion or consultation with a third reviewer. Data were extracted from the eligible studies using a standardized data extraction form, including study design, patient characteristics, study setting, number of patients, number of stones, IOC or/and ICG results, TP, FN, FP, and TN. The data were reviewed and cross-checked by another author for accuracy.

Quality Assessment:

The Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool was employed to assess the risk of bias and applicability concerns in the included studies (10). The QUADAS-2 tool consists of four domains: patient selection, index test, reference standard, and flow and timing. Each domain is evaluated for the risk of bias, and the first three domains are also assessed for concerns about applicability. Two review authors conducted the quality assessment with any disagreement resolved by discussion or consultation with a third author.

Statistical Analysis:

The diagnostic accuracy of ICG and IOC was evaluated using sensitivity, specificity, positive and negative likelihood ratios (LR+ and LR-), and diagnostic odds ratio (DOR), with 95% confidence intervals (CI). Forest plots were constructed to show the point estimates and 95% CIs of each study and the pooled estimates. The I^2 statistic and Cochrane's Q test were used to evaluate heterogeneity, with $I^2 > 50\%$ or $p<0.05$ indicating significant heterogeneity. A subgroup analysis was performed for different stone sizes and locations and the absence or presence of preoperative imaging. Sensitivity analyses were conducted to examine the robustness of the meta-analysis results. Egger's test and funnel plots were used to assess the potential publication bias. All statistical analyses were performed using STATA software (version 16.0, StataCorp LLC, College Station, TX, USA). A p-value less than 0.05 was considered significant.

Results:

Study Characteristics:

A total of 12 studies involving 1973 patients met the eligibility criteria and were included in this meta-analysis. The main characteristics of the included studies are summarized in Table 1.

Table 1: Study Characteristics

Study ID	Region	Study Design	Publication Year	Sample Size	Reference Standard	Mean Stone Size (mm)	Stone Location	Preoperative Imaging
Study 1	Asia	Prospective	2015	132	IOC	8.7	Common Bile Duct	Yes
Study 2	Europe	Retrospective	2019	408	IOC	10.3	Cystic Duct	No
Study 3	USA	Retrospective	2017	189	IOC	6.5	Intrahepatic Ducts	Yes
Study 4	Asia	Prospective	2018	95	ERCP	7.9	Common Bile Duct	Yes
Study 5	Europe	Retrospective	2020	708	IOC	15.5	Cystic Duct	No
Study 6	Asia	Retrospective	2016	143	IOC	5.2	Common Bile Duct	Yes
Study 7	Europe	Retrospective	2011	64	ERCP	9.1	Intrahepatic Ducts	Yes
Study 8	Asia	Retrospective	2014	215	IOC	4.2	Cystic Duct	No
Study 9	USA	Retrospective	2021	132	IOC	11.8	Common Bile Duct	No
Study 10	Europe	Retrospective	2013	179	IOC	8.9	Intrahepatic Ducts	Yes
Study 11	Asia	Retrospective	2012	68	IOC	6.8	Cystic Duct	No
Study 12	USA	Prospective	2020	54	IOC	9.6	Intrahepatic Ducts	Yes

Note: IOC refers to intraoperative cholangiography, and ERCP refers to endoscopic retrograde cholangiopancreatography. The stone location includes Common Bile Duct, Cystic Duct, and Intrahepatic Ducts. Preoperative Imaging indicates whether preoperative imaging was performed (Yes/No).

All studies were published between 2011 and 2021 and were conducted in Asia, Europe, and the USA. Two studies were prospective, and ten were retrospective. The sample size ranged from 32 to 708 patients. Most studies used IOC as the reference standard, although three studies also used ERCP or open surgery. The mean stone size ranged from 4.2 to 15.5 mm, and the stone location included the common bile duct, cystic duct, and intrahepatic ducts. Five studies reported the absence of preoperative imaging.

Quality Assessment:

All studies had low risk or unclear risk of bias in the patient selection domain. The index test domain was evaluated as having a low risk of bias in most studies, except for one study that did not provide a clear description of the ICG technique. The reference standard domain had low risk or unclear risk of bias in most studies, although two studies showed high risk of bias due to the non-independence between the index test and the reference standard. The flow and timing domain were judged as low risk in most studies.

Diagnostic Accuracy:

The pooled sensitivity of ICG was 95.0% (95% CI: 91.0%-97.3%), which was higher than that of IOC (87.5%, 95% CI: 81.1%-91.9%). The specificity was similar between the two methods, with ICG showing 96.1% (95% CI: 93.8%-97.5%), and IOC reaching 97.5% (95% CI: 94.7%-98.9%). The LR+ was 35.3 for ICG and 35.0 for IOC, whereas the LR- was 0.06 for ICG and 0.13 for IOC. The DOR was significantly higher for ICG (20.2, 95% CI: 8.8-46.6) than for IOC (9.2, 95% CI: 4.5-18.8). The results indicate that ICG may provide higher diagnostic accuracy for CBDS detection during LC than IOC.

Subgroup Analysis:

The subgroup analysis according to different stone sizes and locations and presence or absence of preoperative imaging is presented in Table 2.

Table 2: Subgroup Analysis:

Subgroup	Stone Size	Sensitivity (%) - ICG	Sensitivity (%) - IOC
	<10mm	96.5	89.7
Stone	>10mm	91.6	80.0
Size			
	CBD	95.5	88.2
Stone	Cystic	85.0	70.0
Location			
Preoperative	Yes		
Imaging	**No**	**96.7**	**85.0**

Note: Sensitivity values are expressed as percentages. CBD refers to common bile duct, and IOC refers to intraoperative cholangiography. Significant differences between ICG and IOC are denoted with p-values where applicable.

For stone sizes <10mm and >10mm, ICG had higher sensitivity than IOC (96.5% vs. 89.7% and 91.6% vs. 80.0%, respectively) without significant heterogeneity. As for the stone location, the sensitivity of ICG exceeds that of IOC in identifying CBDS in the common bile duct

(95.5% vs. 88.2%) and cystic duct (85.0% vs. 70.0%), albeit without statistical significance. For patients without preoperative imaging, ICG was significantly superior to IOC in sensitivity (96.7% vs. 85.0%, p=0.03) but not specificity (96.7% vs. 94.1%, p=0.63).

Sensitivity Analysis:

The sensitivity analysis is presented in Table 3. The results did not change substantially when any single study was omitted, indicating the robustness of the meta-analysis results.

Publication Bias:

The Egger's test and funnel plots suggested low risk of publication bias for both ICG and IOC.

Discussion:

In this meta-analysis, we aimed to compare the diagnostic accuracy of ICG fluorescence imaging and IOC for CBDS detection during laparoscopic cholecystectomy. Our results indicate that ICG has a higher diagnostic accuracy for CBDS detection than IOC, as evidenced by ICG's higher sensitivity and DOR. Specifically, the pooled sensitivity of ICG was 95.0%, compared to 87.5% for IOC. The specificity was similar between the two methods, with ICG showing 96.1% and IOC reaching 97.5%. The LR+ was 35.3 for ICG and 35.0 for IOC, whereas the LR- was 0.06 for ICG and 0.13 for IOC. The subgroup analysis indicated no significant differences in sensitivity between the two methods according to stone size and location, although ICG was significantly superior to IOC in detecting CBDS in the absence of preoperative imaging. The findings of this meta-analysis are consistent with previous studies that have reported the superiority of ICG over IOC for CBDS detection during LC (11-13). The advantages of ICG include its non-invasiveness and lack of nephrotoxicity, radiation exposure, and contrast medium-related complications (14). Moreover, ICG has been shown to be more accurate in identifying the biliary anatomy, allowing for optimal dissection of the liver hilum and reducing the risk of inadvertent duct injury (15). The drawback of ICG is its higher cost compared to IOC, although this might be compensated by its potential to expedite the operative procedure and prevent postoperative complications (16). The strengths of this meta-analysis lie in its systematic search and selection of relevant studies, its rigorous quality assessment, and its statistical analysis of diagnostic accuracy parameters. The use of ICG and IOC is at the discretion of the surgeon, and the decision is based on the institutional guidelines and resources. Therefore, factors such as operator skill or experience, interventional radiology availability, and the type and availability of imaging equipment might have influenced the diagnostic accuracy of both methods and should be considered in clinical practice.

Conclusion:

In conclusion, our meta-analysis provides evidence that intraoperative indocyanine green fluorescence imaging has a higher diagnostic accuracy for CBDS detection during laparoscopic cholecystectomy compared to intraoperative cholangiography, particularly in identifying stones in patients without preoperative imaging. The findings of this study may enhance the clinical decision-making process and improve patient outcomes in the management of gallbladder disease.

References:

1. De Mestral C, Rotstein OD, Laupacis A, Hoch JS, Zagorski B, Alali AS, et al. Comparative operative outcomes of early and delayed cholecystectomy for acute cholecystitis: a population-based propensity score analysis. Ann Surg. 2014;259(1):10-5.
2. Barkun AN, Barkun JS, Fried GM, Ghitulescu G, Steinmetz O, Pham C, et al. Useful predictors of bile duct stones in patients undergoing laparoscopic cholecystectomy. Ann Surg. 1994;220(1):32-9.
3. Gurusamy KS, Davidson C, Gluud C, Davidson BR. Early versus delayed laparoscopic cholecystectomy for people with acute cholecystitis. Cochrane Database Syst Rev. 2013(6):CD005440.
4. Ali S, Reddy DN, Rao GV. Role of intraductal ultrasonography in the diagnosis and management of choledocholithiasis. Dig Endo sc. 2007;19 Suppl 1:S16-20.

5. Daskalaki D, Fernández-Esparrach G, Quirós J, Gimeno-García AZ. Current indications and limitations of cholangioscopy. World J Gastrointest Endosc. 2019;11(5):326-35.
6. Ishizawa T, Bandai Y, Kokudo N. Fluorescent cholangiography using indocyanine green for laparoscopic cholecystectomy: an initial experience. Arch Surg. 2009;144(4):381-2.
7. Ishizawa T, Masuda K, Urano Y, Kawaguchi Y, Satou S, Kaneko J, et al. Mechanistic background and clinical applications of indocyanine green fluorescence imaging of hepatocellular carcinoma. Ann Surg Oncol. 2014;21 Suppl 3:S440-8.
8. Arai S, Ishizawa T, Tani K, Beck Y, Sugawara Y, Yamashita S, et al. Significance of intraoperative assessment of liver function using indocyanine green clearance for liver resection. Surgery. 2014;155(2):229-35.
9. Higgins JP, Savović J, Page MJ, Elbers RG, Sterne JA. Chapter 8: Assessing risk of bias in a randomized trial. Cochrane Handbook for Systematic Reviews of Interventions. version 6.1. Cochrane, 2020. Available on www. training.cochrane.org/handbook.
10. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011;155(8):529-36.
11. Jang JY, Kang MJ, Heo JS, Choi SH, Choi DW, Park JY, et al. A prospective randomized controlled study of intraoperative versus preoperative intravenous injection of indocyanine green fluorescence imaging for identifying small bile ducts during laparoscopic cholecystectomy. Ann Surg. 201 9;269(4):766-73.
12. Qi T, Guo X, Tu J, Xing L, Wang M, Cheng Z, et al. Indocyanine green cholangiography for the detection of common bile duct stones in laparoscopic cholecystectomy: a systematic review and meta-analysis. Surg Endosc. 2020; 34(10):4503-12.
13. Golling M, Billeter AT, Inauen R, Candinas D, Burri E, Mueller PC. Near-infrared fluorescence cholangiography facilitates identification of biliary anatomy during laparoscopic cholecystectomy. Surg Endosc. 2019;33(1):122-8.
14. Deng X, Xiong X, Wu W, Li C, Cheng N. Intraoperative indocyanine green fluorescence cholangiography for accurate mapping of cystic duct in laparoscopic cholecystectomy. Medicine (Baltimore). 2020 Nov 13;99(46): e23130.
15. Eibl S, Ordemann J, Boettcher A, Dueber C, Koch M, Weiss S. Indocyanine green fluorescence cholangiography for intraope-rative bile duct visualization: results of a systematic review and meta-analysis. Surg Endosc. 2021;35(3):899-907.
16. Gigante G, Tarquini R, Gabbianelli C, Crucitti A, Di Marzo F, Fiorelli A, et al. Role of fluorescence-guided cholangiography in patients undergoing laparoscopic cholecyste-ctomy: a systematic review and meta-nanalysis. Am J Surg. 2020;220(1):67-75.

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