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Cohort Study

Initial experience of intraoperative fluorescent cholangiography during laparoscopic cholecystectomy: A retrospective study

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ABSTRACT

Background: Fluorescent cholangiography (FC) during laparoscopic cholecystectomy (LC) is a novel method to facilitate real-time visualization of extrahepatic biliary structures that avoiding risk of bile duct injury. Aims of this study are to investigate the feasibility and the safety of FC during LC.

Method: We evaluated the outcomes of FC during elective LC at our hospital from August 2017 to April 2018. Fifty-five patients who underwent FC during elective LC were enrolled in this study. Demographic and perioperative data were recorded and analyzed. The primary endpoints were visualization rate of FC during LC. The secondary endpoint was the optimal conditions and technical details for FC included to detect any potential adverse event.

Results: The visualization rate after FC of the cystic duct, common hepatic duct and common bile duct were increased significantly compared to before FC. The identification rate of the cystic duct and common bile duct were not associated with BMI and history of acute cholecystitis.

Conclusions: FC enabled real-time visualization of extrahepatic biliary structures during LC. FC appears to be a safe and efficient approach for elective LC.

1. Introduction

Laparoscopic cholecystectomy (LC) is one of the most commonly performed procedures in general surgery [1]. LC is the treatment of choice for benign gallbladder disease with the proven several advantages when compared to open cholecystectomy [2]. While, one of the most serious complication of LC is iatrogenic bile duct injury (BDI) that effected on increasing of hospital cost, quality of life and long term survival. [3], with an incidence of 0.3%–0.5% that needs operative repair [4]. The major cause of BDI are related to three factors; surgical technique, pathology at subhepatic area and variation of extrahepatic anatomy [5]. Previous studies showed that misinterpretation of bile duct anatomy is the major contribute to BDI (71%–97%) [6]. Since radiographic intraoperative cholangiogram (IOC) was first described in 1931 [7]. Using IOC for routine LC has been suggested by experts for reducing risk of BDI and early detection [8,9]. However, this procedures also present some limitations such as a longer operative time, radiation exposure to medical staffs and patients, additional medical devices and increase risk of BDI cause by tube insertion to the cystic duct. However improvement in LC technique and advance laparoscopic instrument, the incidence of BDI from LC remains stable over time.

Fluorescence image-guided surgery is one of the recent technique in minimal invasive procedure. Fluorescent cholangiography (FC) is a new method to facilitate intraoperative real-time visualization of the biliary anatomy, to identified the critical view of safety (CVS) [10]. This may facilitate dissection by providing a real-time visualization. The FC is less invasive and requires less operative time that offer real-time imaging [11].

The CVS was previously report about complete dissection at Calot's triangle by clearing of fatty and fibrous tissue for isolate only two structures. CVS identification has more likely to reduce risk of BDI [12]. Thus, in cases with severe inflammation, dense adhesion or biliary tract variation, alternative approaches such as bail-out procedure, conversion to open approach or IOC are useful methods for avoid BDI [13–15]. While the role of routine IOC during cholecystectomy remains controversial.

This study presents our initial experience and the results of 55 consecutive elective LC with intraoperative fluorescent cholangiography in a single center. The primary objective of this study was to access the detection rates of the extrahepatic biliary anatomy visualization with FC and the perioperative complications. The secondary aim was to analyze the optimal conditions and technical details for FC included to detect

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any potential adverse event. Our hypothesis was that this technique may be able to real-time identification of the extrahepatic biliary structures safely and would be helpful for the surgeon.

2. Materials and methods

2.1. Study design

The study was approved by the institutional review board of our institute (EC-61-07) and operated under the Declaration of Helsinki and register. Written informed consent was obtained from all of the patient before the procedure. This article is compliant with the STROCSS checklist and has been reported in line with the STROCSS criteria [16]. The research registry number is TCTR20210523001. https://www.thaiclinicaltrials.org/show/TCTR20210523001.

2.2. Data collections and participants

This was a retrospective observational study that enrolled all patients who underwent elective LC with intraoperative FC from August 2017 to April 2018 at our hospital. Electronic medical records were reviewed. Patients' demographic data included age, gender, BMI, American Society of Anesthesiologist (ASA) classification and indication of surgery were recorded. Peri-operative data included operative time (skin incision to skin closure), estimated blood loss, conversion to open approach and peri-operative complication were collected. Inclusion criteria were symptomatic gallstone or benign gallbladder disease (as documented by abdominal ultrasonography or abdominal compute tomography or magnetic resonance imaging), age $\geq$ 15 years, tolerate to laparoscopic surgery and complete medical records. Exclusion criteria were emergency case, oncologic surgery, pregnancy, single incision cholecystectomy and patients underwent a concomitant procedure during LC were excluded. Complication of LC were defined as BDI, allergy to ICG and surgical site infection.

2.3. Operative details

All patients were intravenously injected with 2.5 mg of ICG (Daiichi Sankyo, Tokyo, Japan) approximately 30 min before beginning of the procedure by the anesthesiologist. After anesthesia, a infra-umbilical incision was made to entered the intraperitoneal cavity then a 10 mm trocar was placed and the pneumoperitoneum was maintained at 14 mmHg. The second port and the third port was placed at subxiphoid area and right upper quadrant of abdominal wall, respectively. The laparoscopic imaging system used was PINPOINT endoscopic fluorescence imaging system (Novadaq, Mississauga, ON, Canada). The extra-hepatic biliary structure were observed and recorded before dissection to identified the CVS. Then, the near-infrared fluorescence was applied to identified the extra-hepatic biliary anatomy. The cystic duct (CD) and cystic artery were identified, ligated and divided. After divided the CD, cystic artery, and the gallbladder were removed from the gallbladder fossa by electrocautery hook.

2.4. Statistical analysis

Data were collected from electronic medical record and analyzed to determine patients' demographic data, operative finding, peri-operative data, post-operative clinical course and complication. Descriptive statistics were utilized on patients' demographic data. Continuous data were presented as means $\pm$ standard deviation. Categorical data were expressed as numbers and percentages. A subgroup analysis was performed to determine independent factor of visualization rate of the extra-hepatic structure. Any *p*-values less than 0.05 were considered statistically significant. All statistical analyses were performed with STATA (Stata Corp, College Station, TX USA).

3. Results

3.1. Patients characteristics

Fifty-five patients underwent elective laparoscopic cholecystectomy with intraoperative fluorescent cholangiography at our hospital were included in this study. Patients' demographic data and the indications for surgery are showed in Table 1. The average age of the patients was 49.8 ($\pm$12.4) years and 17 patients were male. The mean BMI was 24.2 ($\pm$2.9) kg/m^2. The median American Society of Anesthesiologists was class II. The indication for LC are listed in Table 1.

3.2. Procedure details

The mean operative time was 61.7 ($\pm$27.6) minutes. The mean estimate blood loss was 10.9 ($\pm$8.3) ml. There were no peri-operatively and post-operatively adverse event. Procedure details are listed in Table 1.

3.3. Peri-operative details

Before to dissection, the visualization rates of cystic duct (CD), common hepatic duct (CHD) and the common bile duct (CBD) were 65.4%, 21.8% and 69.9%, respectively. The identification rate of cystic CD, the CHD and the CBD after fluorescent intraoperative cholangiography were 96.3%, 70.9% and 94.5% respectively (Table 2). The visualization rates of the CD, CHD and CBD after FC were increased significantly compared to before FC. The use of FC provided clear image for the surgeon (Fig. 1).

The FC detection rate of the CD and CBD were not associated with BMI and history of cholecystitis that presented in Table 3 and Table 4 respectively. In patient with BMI $<$25, the FC detection rate of the CHD was significantly increase when compared with the detection rate without FC. There were no peri-operatively and post-operatively adverse event such as post-operative bleeding, bile duct and vascular injury, surgical site infection and drug allergy.

4. Discussion

FC during LC has provided real-time visualization of the extra-hepatic biliary structure before dissection for CVS identification. Our aims were performed to purpose the potentiality and safety of FC to visualize the extrahepatic biliary structures during LC. In our study, the routine use of FC in LC was incorporated smoothly into the procedure and no difficulty in the operative room. Ours results revealed that the visualization rate of FC is better than the visualization rate without FC significantly. There was no bile duct injury, no serious adverse event from ICG allergy and no conversion to open fashions. From a surgeon's perspective in this study, FC was helpful to identify the CVS that may decrease rate of iatrogenic bile duct and vascular injury. Although, the

Table 1
Characteristic of patients.

Demographic (N = 55)	
Mean age (SD)	49.8 ($\pm$12.4)
Male (%)	17 ($\pm$30.9)
Mean BMI (kg/m^2)	24.9 ($\pm$2.9)
Median ASA	ASA class II
Indication of Surgery	
Biliary colic	41
History of acute cholecystitis	10
Previous ERCP due to choledocholithiasis	4
Procedure details	
Operative time (minutes)	61.7 ($\pm$20.6)
Estimated blood loss (ml.)	10.8 ($\pm$8.3)
Conversion to open surgery	0
Adverse event	0

Table 2
The visualization rates of the CD, CHD and CBD before FC compared to after FC.

Biliary structure	Identification rate without FC (%)	Identification rate with FC (%)	*P*-value
Cystic duct	46 (65.4%)	53 (96.3%)	0.001
Common hepatic duct	12 (21.8%)	39 (70.9%)	0.000
Common bile duct	38 (69.9%)	52 (94.5%)	0.002

FC during LC has provided the better view of the extra-hepatic biliary structure but we found the CD and the CBD were able to identified before FC application in most patients and there are some cases which needed further dissection before FC application. Thus, the comparative study should be done to detect potential different between LC with FC and LC without FC.

In this study, the detection rate of extrahepatic biliary structure before and after utilization of FC ranged from 65.4% to 96.3% for CD, 21.8%–58.1% for CHD and 69.9%–94.5% to CBD. Our result was similar detection rates of previous study that FC improved the identification of the biliary tract [17]. Our study showed FC allowed better visualization of CD, CHD and CBD that may help surgeons work more safely and better visualization of the biliary tree before dissection to CVS identification. Moreover, the rate of CHD visualization was relatively low when compared with the CBD and CD visualization rate. According to the principle of dissection for CVS identification, the CHD may not need to identified. To identify CVS, we should keep the dissection level away from the hilar plate because of avoidance to injury the CHD. In our experience, the fatty tissue that cover the CHD usually thicker when comparison to the fatty tissue that cover the CBD, that may cause the CHD visualization was decreased when compared to the CBD. Previous study reported the limitation of dense fatty tissue or adhesion accumulation at the subhepatic area in determination of the biliary structure by FC [18–20]. From our observation, in case of non-visualized CD after FC, an initial dissection of Calot's triangle before apply FC were able to identify the CD more accurately and clearly (Fig. 2). This method makes the surgeon safer divided the CD. However, the recently study conducted a randomized controlled study of patients who underwent FC compared with conventional cholangiography using fluoroscopy, the authors concluded that FC was non-inferior to conventional cholangiography to visualized the critical junction between the CD, CHD and CBD [21]. But the FC was no need to performed bile duct puncture that avoiding the risk of bile duct injury, no need for fluoroscopy machine that avoiding radiation to surgical staffs and patients.

The most important step of LC is the dissection of the hepato-cystic triangle to identify the CVS. This step is the most difficult and time-consuming step as well, particularly in patient with history of imacute cholecystitis, acute cholangitis, acute pancreatitis, Mirrizi syndrome, obesity and abnormal of biliary anatomy. Previous study reported that the quality of bile duct visualization from FC is diminished in patients who BMI >25 kg/m^2 [22]. In our study, the visualization rate after FC was relatively decrease but no statistically significant when compared between BMI < 25 kg/m^2 and BMI > 25 kg/m^2. However, then visualization rate of biliary structure after FC was not difference in patients with history of cholecystitis. The large scale and comparative study may be show the difference in subgroup analysis.

ICG is the only agent that approved by the Food and Drug Administration for human used with 0.003% in risk of anaphylaxis[[23]]. The proper dose and timing of administration of ICG remain controversy. In previous studies, the reported timing of administration to applying of ICG varied from 30 to 60 min but the adequate image of the extrahepatic biliary structures were visualized in all studies [24]. Thus, this may be another reason for not well visualization of biliary structures. A less likely reason of unclear biliary structures from FC is an undiagnosed liver disease; such as steatosis, early cirrhosis or chronic viral infection, which would affected hepatic uptake and clearance of ICG. In our study, we did not work up patients with underlying liver disease in both pre-operative and post-operative period. Thus, future studies should focus on the optimal dose and the interval timing of ICG administration and extrahepatic biliary visualization.

According ASGE guideline, a laparoscopic IOC is most commonly performed in patients with intermediate risk of CBD stone [25]. One of the advantage of the conventional IOC over the FC is more accurately and better visualization to the CBD stone. Thus, the exact role of FC is

Table 3
The FC visualization rates of the extrahepatic biliary structures in relation to BMI.

Biliary structure	BMI <25 kg/m^2 (n = 37)	BMI ≥ 25 kg/m^2 (n = 18)	*P*-value
Cystic duct	36 (97.3%)	17 (94.4%)	0.552
Common hepatic duct	25 (67.5%)	32 (38.8%)	0.042
Common bile duct	34 (91.8%)	18 (100%)	0.543

Table 4
The FC visualization rates of the extrahepatic biliary structures in relation to history of acute cholecystitis.

Biliary structure	History of acute cholecystitis (n = 10)	No history of acute cholecystitis (n = 45)	*P*-value
Cystic duct	10 (100%)	43 (95.5%)	0.667
Common hepatic duct	4 (40%)	28 (62.2%)	0.290
Common bile duct	10 (100%)	42 (93.3%)	0.541

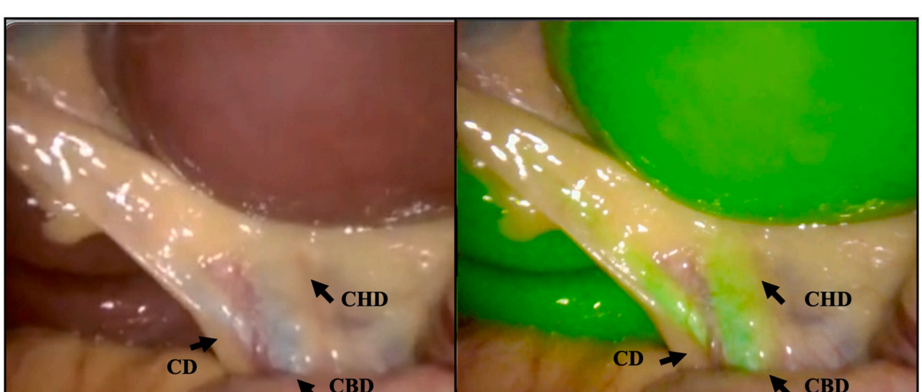

Fig. 1. Identification of extrahepatic biliary structures with. (a) white light mode without FC (b) fluorescent cholangiography.

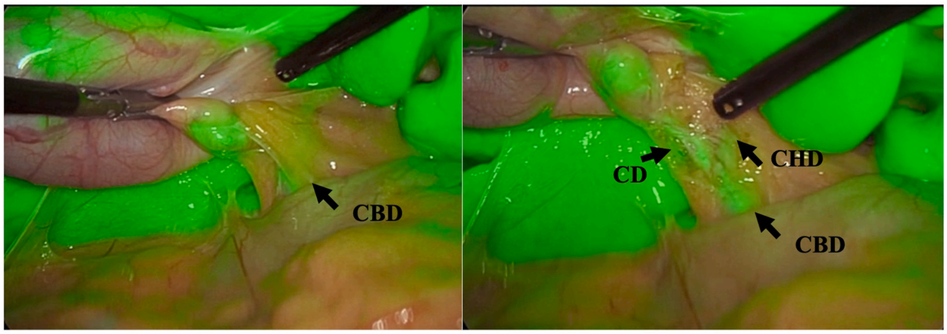

Fig. 2. Identification of extrahepatic biliary structures with (a) FC before dissection at Calot triangle (b) FC after initial dissection at Calot triangle.

still debatable. There is no supported evidence about efficacy of FC to detect the CBD stone. Increasing of CBD size maybe observed in FC that make suspicious of CBD obstruction. Conventional IOC would still beneficial in these cases. From our study, we did not identified the cystic duct stone by FC even the presence of the cystic duct stone. Nowadays, there are few reports about the effective utility of FC for biliary stone detection during LC [26]. Thus, FC is not sensitive enough for detection of biliary stone. Conventional IOC is still prefer for biliary stone detection in case of high suspicious for biliary stone.

However, the cost of startup for the fluorescence-guided surgery is still more expensive when compare to the white-light system. But additional operative cost was increase about 1650 baht ($52) per one patient from 1 vial of ICG (25 mg/10 ml) for FC. In real-practice, the need of ICG is only 2.5 mg for one patient. We believe this technique and technology are more cost effective and more time efficient in long term using. However, even if the ICG cost is negligible but the total cost of the fluorescence-guided surgery system and its maintenance remain a question.

There are some limitations in this study. First, the study is a retrospective study that may be unexpected confounding factors that may affect patients in our results. Second, patients in this study were rather small that may not have sufficient power to detect rare serious complication. However, this is consistent with several previous retrospective studies that analyzed fewer than 50 patients [18,19,27,28]. Third, we only include patients in elective setting with normal liver function that may not have sufficient to determine the ability of FC in biliary stone detection. Further large scale, multicenter and randomized controlled studies are needed to evaluate the efficacy and cost-efficiency of FC in the safety of LC. Forth, a future study should focus on the proper timing and optimal dose of ICG administration and the factor that impact to the visualization of FC. Moreover, further study should be evaluate the effectiveness on the setting of acute cholecystitis and benefit in reduced rates of BDI. And lastly, cost analysis is need to investigation for support the clinical benefit of FC. Furthermore, the use of FC could decrease the operative time, especially in step of dissection at hepato-cystic junction that potentially result in a cost benefit.

5. Conclusions

Fluorescent cholangiography is a simple, safe, non-invasive and effective method to provide real-time identification of the biliary structure during LC and may help to improve the efficacy of dissection. This method may become standard practice for LC in order to prevent BDI. The sensitivity of FC for biliary stone detection is not good enough.

Ethical Approval

The consent form and information sheet using in the process of obtaining a consent were approved by IRB at Suranaree University of Technology. (EC-61-07).

Author contribution

Nattawut Keeratibharat: study design, collected data, contributed to conceptualization, data analysis, wrote, and editing the manuscript.

Consent

The patients have been informed prior to the conduction of this manuscript and informed consent has been also obtained. The copy of the written consents is available for review by the editor-in-chief of the journal on request.

Registration of research studies

Name of the registry: Thai Clinical Trial Registry
Unique Identifying number or registration ID: TCTR20210523001
https://www.thaiclinicaltrials.org/show/TCTR20210523001.

Guarantor

Nattawut Keeratibharat.

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The author declared that there is no conflict of interest regarding the publication of this study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2021.102569.

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