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DYNAMIC MANUSCRIPT

Near-infrared cholecysto-cholangiography with indocyanine green may secure cholecystectomy in difficult clinical situations: proof of the concept in a porcine model

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Abstract

Background Biliary injuries remain a major concern in laparoscopic cholecystectomy. New intraoperative guidance modalities, including near-infrared fluorescence cholangiography, are under evaluation. Initial results showed limitations in visualizing the biliary tree in specific clinical situations. The aim of this study was to examine the feasibility and potentiality of fluorescence cholecysto-cholangiography performed with a direct injection of indocyanine green (ICG) in the gallbladder and to compare it to systemic injection in such situations.

Materials and methods Seven pigs were included in this non-survival study. In two pigs, the gallbladder was punctured by a percutaneous needle, and 1 mL of ICG in different concentrations (0.001, 0.01, 0.1, and 1 mg/mL) was sequentially injected. Visibility and pattern of the fluorescent signal around Calot's triangle were examined and compared with those of two control pigs receiving 2.5 mg of intravenous ICG, 30 min prior to the operation. Different scenarios of cholecystitis were modeled using an injection of a mixture of blood and agarose gel around Calot's triangle area in the remaining three pigs, and the applicability of direct intragallbladder injection methods was evaluated.

Results The fluorescent signal was identified immediately after intragallbladder injection, and the cystic duct became visible by 0.1 and 1 mg/mL of ICG. The whole cystic duct and the infundibulum of the gallbladder were clearly enhanced by intragallbladder ICG injection, but not by systemic injection. In the cholecystitis models, the cystic duct could be identified only after partial dissection, and fluorescence visualization of the gallbladder infundibulum provided crucial information to find the correct starting point of dissection.

Conclusions Fluorescence cholecysto-cholangiography through direct intragallbladder ICG injection could rapidly provide an adequate visualization of gallbladder neck and cystic duct and might be a valid option to increase the safety of cholecystectomy in case of cholecystitis.

Keywords Fluorescence-guided surgery · Indocyanine green (ICG) · Laparoscopic cholecystectomy · Cholecystitis · Near-infrared cholangiography · Near-infrared cholecysto-cholangiography · Common bile duct injury

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Iatrogenic biliary injuries remain a major concern during laparoscopic cholecystectomy (LC), with an incidence ranging from 0.15 to 0.6 % [1]. Considering that LC is one of the most commonly performed surgical procedures, this incidence, although relatively low, represents a significant

healthcare burden. Misinterpretation of biliary anatomy, due to unrecognized anatomical variations or to an inflammatory status, represents the most frequent etiology of iatrogenic biliary tree lesions [2–4]. In the presence of acute cholecystitis, the rate of bile ducts injuries can be increased 20-fold [5].

A standardized operative approach, called the "critical view of safety" [6], has been designed to limit the risk of injuries. Additionally, intraoperative cholangiography (IOC) may be performed to localize the extrahepatic bile ducts and/or to evaluate the presence of an injury [7–9].

IOC has some limitations and constraints: The 2D image cannot be displayed in the operative field, the procedure is time-consuming and uses additional human resources, and radiation protection is inconvenient [10]. Fluorescence cholangiography using intravenous indocyanine green (ICG) injection and near-infrared optimized laparoscopes and cameras has been successfully evaluated in clinical trials as an efficient means to image the biliary tree during cholecystectomy [11–14]. ICG is a fluorophore, which is excreted in the bile and becomes fluorescent once it has been excited by means of a near-infrared laser. One of the most significant drawbacks of fluorescence cholangiography following systemic ICG injection is related to the high affinity of ICG to hepatocytes which yields a very intense background signal due to the accumulation of ICG in the liver. This accumulation can reduce optimal visualization of the cystic duct. Additionally, the cystic duct becomes visible at near-infrared only once it has been filled with bile mixed with ICG resulting from common bile duct (CBD) reflux, and its visualization is not constantly predictable.

A near-infrared cholecysto-cholangiography by direct ICG injection into the gallbladder could well improve the visualization of the cystic duct as well as the edges of the gallbladder and the junction between the cystic duct and the CBD. X-ray contrast-enhanced cholecysto-cholangiography is an alternative to IOC in difficult clinical cases [15]. However, this technique has the same limitations of IOC and can visualize the junction in only 80 % of cases.

The purpose of this acute experimental study was to evaluate the feasibility and usefulness of near-infrared cholecysto-cholangiography using direct intragallbladder ICG injection.

Materials and methods

Animals

A total of seven swine (*Sus scrofa domesticus*, ssp. Large white; mean weight 27.01 ± 6.01 kg) among which four males were used in this non-survival study. All animals used in the experimental laboratory were managed according to ARRIVE guidelines [16], French laws for animal use and care, and the directives of the European Community Council (2010/63/EU). In accordance with the ethical principle of reduction, animals were included in the present experimental study at the end of a different experimental protocol, which received full approval from the local ethical committee on animal experimentation (Protocol No. 38.2014.01.064) and from the French Ministry of Higher Education and Research (Reference No. 04297.01).

Two pigs were used to test the proper ICG dosage for intragallbladder injection.

Two additional pigs were used for systemic IV ICG injection as a control group.

In three additional pigs, various clinical scenarios were modeled.

Pigs were fasted for 24 h before surgery with free access to water. Premedication with intramuscular injection of ketamine (20 mg/Kg) and azaperone (2 mg/Kg) (Stressnil, Janssen-Cilag, Belgium) was administered 10 min before surgery. Induction was achieved using intravenous propofol (3 mg/Kg) combined with rocuronium (0.8 mg/Kg). Anesthesia was maintained with 2 % isoflurane. At the end of the procedure, animals were humanely killed with an intravenous injection of a lethal dose of potassium chloride.

Procedures

Evaluation of the appropriate dosage of intragallbladder ICG to visualize the extrahepatic biliary tract (n = 2)

A three-port laparoscopic approach was used, and the gallbladder was punctured percutaneously with an 18-G needle. Bile juice was extracted, and the gallbladder was emptied. Four escalating concentrations of ICG (INFRACYNINE® 25 mg/10 mL, SERB Laboratories, Paris) in 5 % dextrose (0.001, 0.01, 0.1, and 1.0 mg/mL) were injected into the gallbladder through the needle with a volume of 1 mL every 15 min (Fig. 1). The D-Light P, a near-infrared optimized laparoscope (Karl Storz, Tuttlingen, Germany), was used to detect the ICG fluorescence signal arising from the gallbladder, the cystic duct, and the bile duct before and during cholecystectomy (Fig. 2).

Comparison with fluorescent cholangiography by systemic injection of ICG (n = 2)

A single dose of 2.5 mg of ICG was injected intravenously as previously reported [17].

Thirty minutes after injection, the gallbladder, the cystic duct, and the CBD were observed using the D-Light P (Fig. 3).

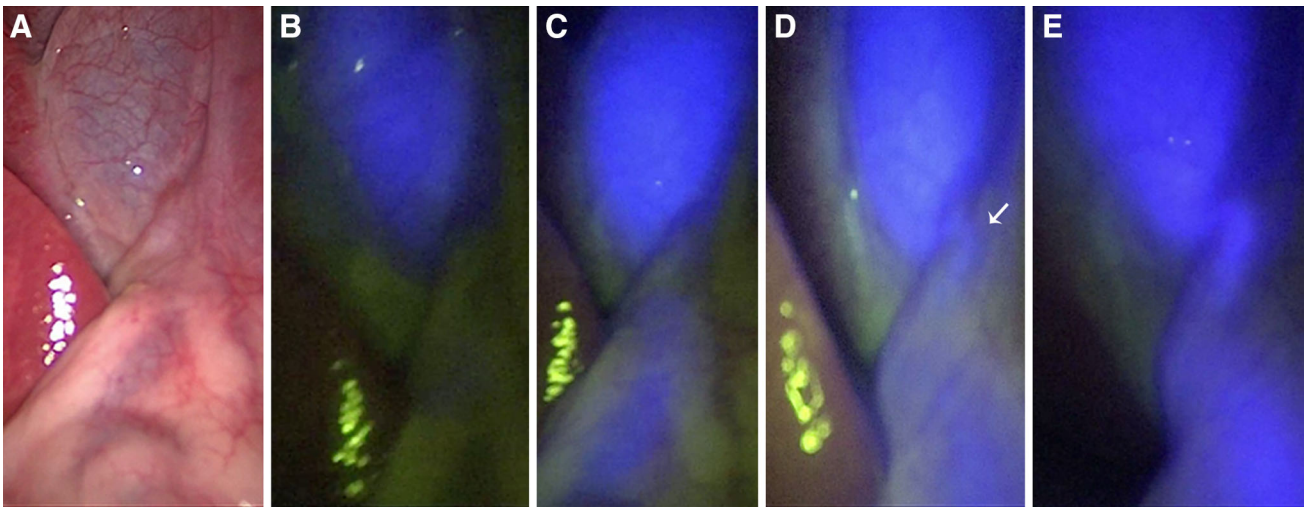

Fig. 1 Feasibility of near-infrared cholecysto-cholangiography and evaluation of ICG dosage. **A** white-light visualization of the gallbladder and CBD; **B** visualization of the gallbladder's margins after injection of 0.001 mg/mL of ICG 1cc; **C** enhancement of gallbladder and CBD following 0.01 mg/mL of ICG 1cc injection; **D** initial visualization of the cystic duct (*arrow*) after 0.1 mg/mL of ICG 1cc injection; **E** brighter enhancement of the cystic duct, the gallbladder, and of the CBD following 1.0 mg/mL of ICG 1cc injection

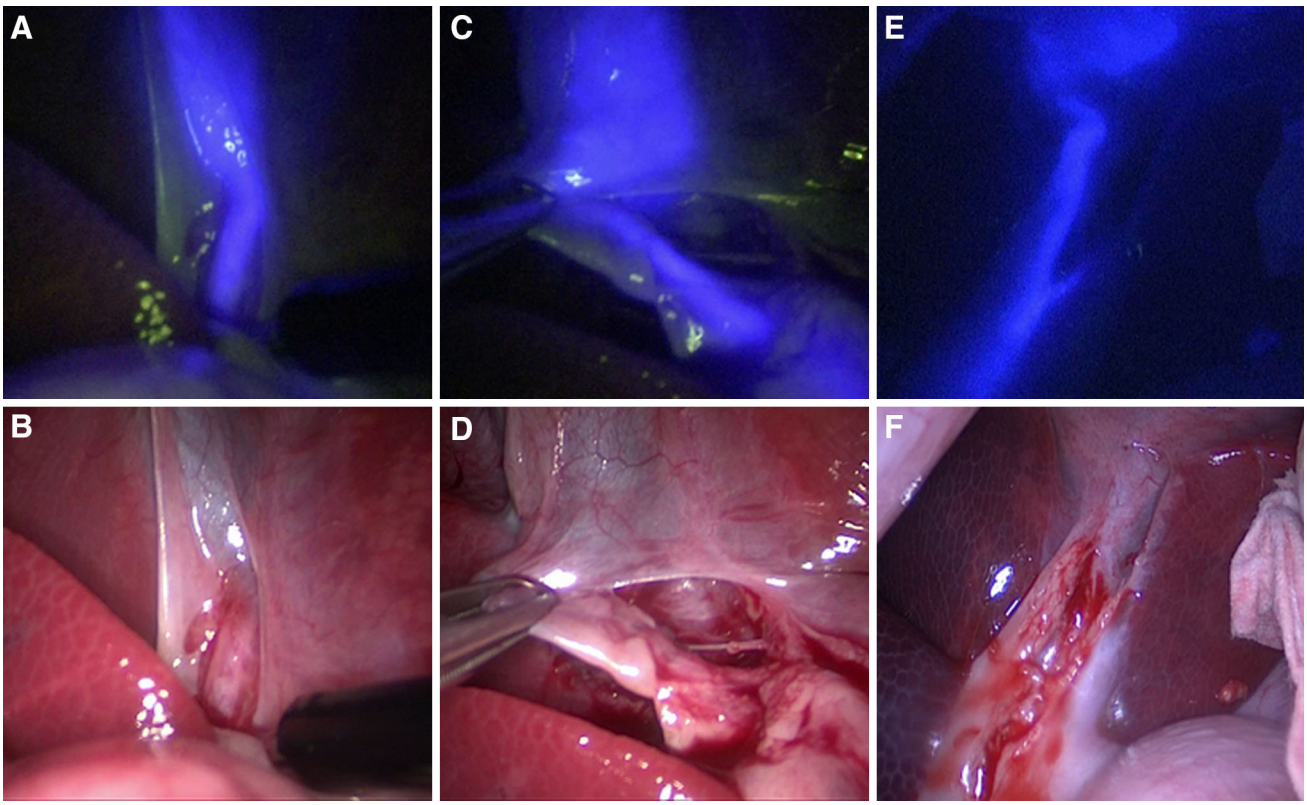

Fig. 2 Calot's triangle exposure following near-infrared cholecysto-cholangiography as compared to white-light view during dissection. **A**, **B** Clearer determination of the gallbladder-cystic duct junction by near-infrared cholecysto-cholangiography when compared to WL visualization; **C**, **D** Calot's triangle exposure; **E**, **F** the cystic duct/CBD junction can be more easily identified by fluorescence imaging when compared to a white-light view

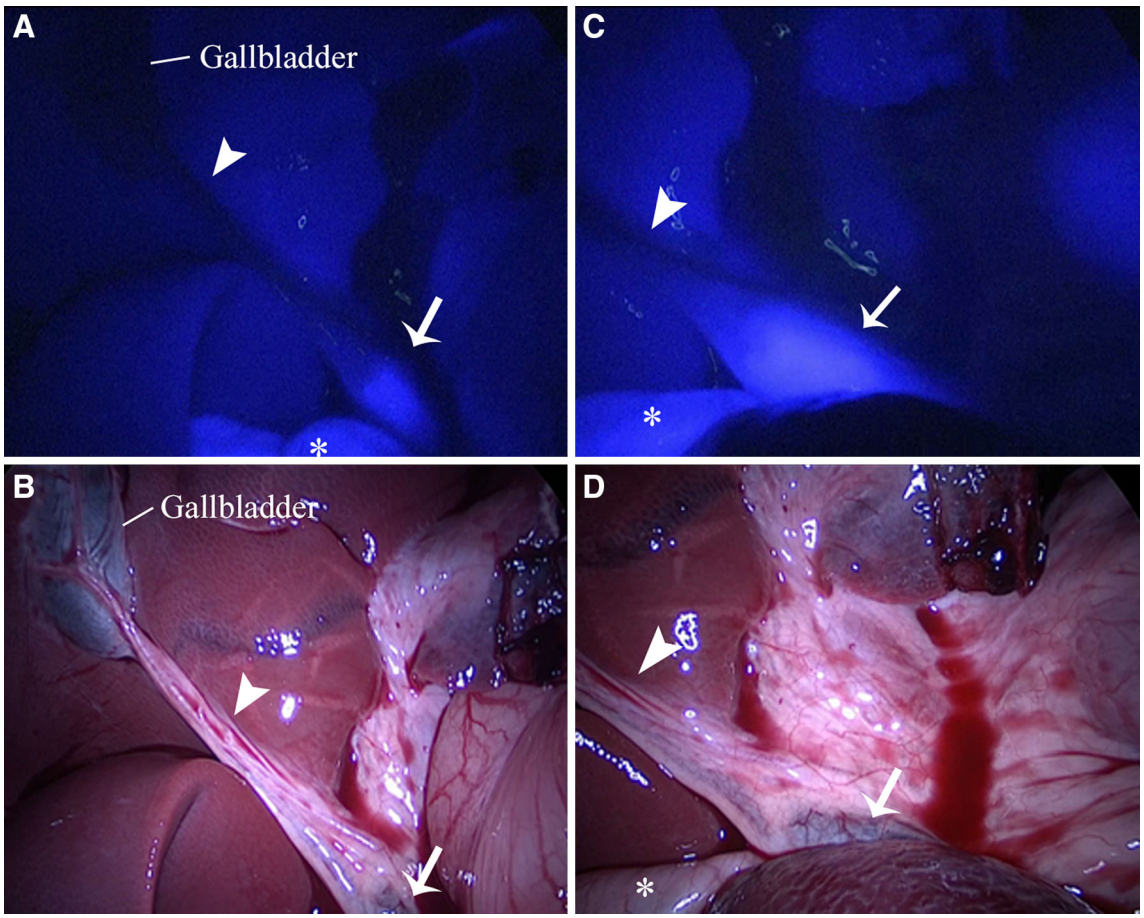

Fig. 3 Near-infrared cholangiography by systemic injection of ICG. **A** and **C** fluorescence imaging after systemic injection of ICG allows visualization of the CBD (*arrow*), but the cystic duct (*arrow head*) and the gallbladder are not enhanced. The liver parenchyma has a diffuse enhanced signal. The signal from the duodenum (*) is also enhanced. **B** and **D** same views at white light

Porcine models of clinically relevant scenarios to evaluate the benefits of near-infrared cholecysto-cholangiography (n = 3)

1. Acute cholecystitis model: 20cc of blood were withdrawn from the venous access and mixed with 10cc of agar gel. Through a mini-laparotomy access, the blood–agar mixture was injected into the gallbladder subserosa around Calot's triangle until it generated significant swelling which extended to the lower part of the gallbladder, the cystic duct, and the right margin of the CBD.

ICG was injected into the gallbladder, and cholecystectomy was performed with frequent changes of visualization modes between white-light and near-infrared imaging (Fig. 4 and Video Clip 1 in ESM).

1. Acute cholecystitis with cystic-duct-impacted stone model:

In addition to the injection of the blood and agarose gel mixture as previously described, 5cc of liquid agar gel were injected into the gallbladder, close to the cystic duct inlet. We added 3cc of 10 % calcium chloride, as previously described [18] to solidify the gel and generate an obstruction of the cystic duct. Fluorescent cholecysto-cholangiography was performed with intragallbladder ICG injection, followed by a cholecystectomy (Fig. 5).

2. Severe acute cholecystitis model and clipping of the CBD

The blood and liquid agar gel mixture was injected around the CBD until it covered the lower part of the gallbladder and the entire visible area of the CBD with significant swelling. This injection simulates the scenario of distorted biliary anatomy, with a sort of pseudo-infundibulum caused by the gel, which can lead to a wrong localization of Calot's Triangle. Cholecystectomy was started from the pseudo-infundibulum produced by the

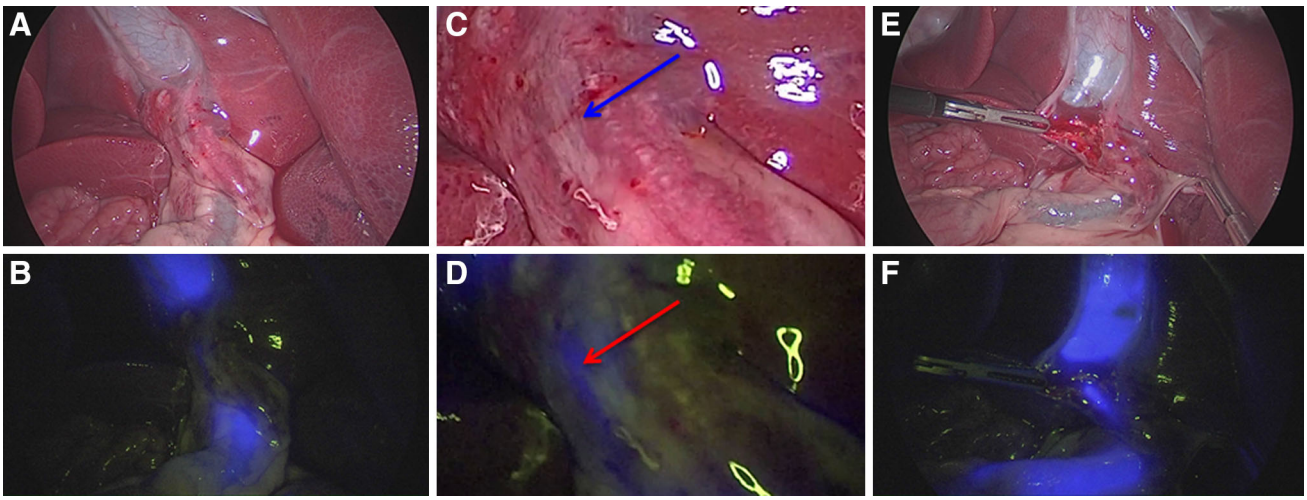

Fig. 4 Simulated model of acute cholecystitis. **A** a non-survival acute cholecystitis model was produced by injecting a mixture of blood clot and opaque agar gel into Calot's triangle. **B** after injection of 1cc 0.1 mg/mL of ICG, the border of the gallbladder and the CBD could be identified. **C** and **D** closer view of **A** and **B**. The *blue arrow* indicates a tubular structure which was wrongly interpreted as the cystic duct at WL imaging, due to swollen tissues. On near-infrared, the proper location of the cystic duct could be identified (*red arrow*). **E** and **F** dissection performed according to the critical view of safety under WL could not clearly identify the cystic duct, in this cholecystitis simulation. By switching to a near-infrared mode, the cystic duct could be easily identified (Color figure online)

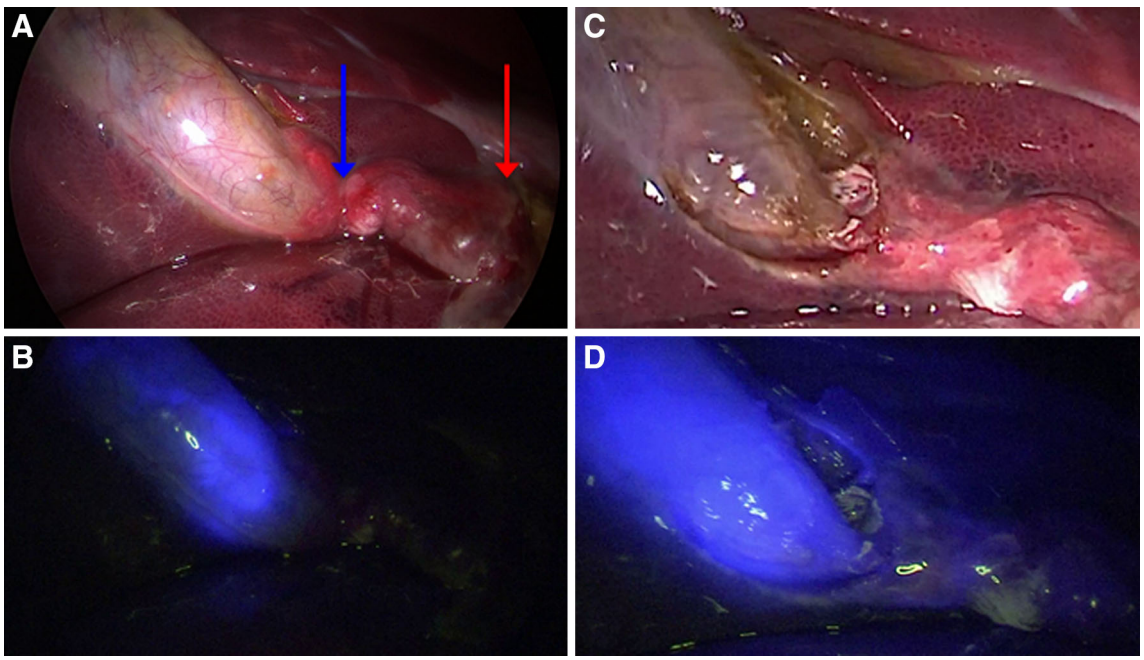

Fig. 5 Acute cholecystitis with cystic-duct-impacted stone model. **A** and **B** white-light and near-infrared view of the acute cholecystitis with cystic-duct-impacted stone model. The model tries to simulate the situation with inflammatory status and edema around the cystic duct/CBD junction (*red arrow*). The *blue arrow* represents the real infundibulum. However, the swollen cystic duct could be misinterpreted as the prolongation of the gallbladder's infundibulum. **B** near-infrared light after injection of ICG shows the border of the gallbladder and helps to identify the infundibulum and start dissection under fluorescence guidance safely. **C** white-light image after the beginning of the dissection. **D** although the "impacted stone" prevents fluorescence-guided visualization of the cystic duct, dissection can be safely performed following the enhanced infundibulum of the gallbladder (Color figure online)

injection of gel, under only white light, to simulate a condition in which the surgeon has wrongly interpreted the CBD as the cystic duct. ICG was then injected into the gallbladder, and near-infrared-guided cholecystectomy was performed (Video clip 2 in ESM).

Results

ICG dosage for extrahepatic biliary tract enhancement following intragallbladder injection

The lowest concentration (0.001 mg/mL) allowed to visualize the gallbladder only (Fig. 1B). The gallbladder and the CBD were visualized starting from a concentration of 0.01 mg/mL of ICG (Fig. 1C). The cystic duct was weakly enhanced with 0.1 mg/mL of ICG and clearly identified with 1.0 mg/mL of ICG, before any dissection of connective tissues around the biliary structures. All signals could be identified immediately, within a few seconds after intragallbladder injection. The 1.0 mg/mL concentration was selected for subsequent experiments in acute cholecystitis simulations.

During dissection, near-infrared cholecysto-cholangiography could provide an improved visualization when compared to white-light observation of both the cystic duct and the CBD, as well as the junction between the cystic duct and the CBD. Direct injection provides a very bright fluorescence signal of the biliary tree with a high signal-to-background ratio given the lack of enhancement of the liver parenchyma (Fig. 2).

Following systemic ICG injection, the CBD could be visualized approximately 30 min later. However, the cystic duct and the gallbladder were not enhanced, and the liver had a relatively high background signal (Fig. 3).

Simulation of acute cholecystitis scenarios and near-infrared cholecysto-cholangiography

The different cholecystitis models were successful and realistic.

In the first case, the peri-ductal injection of agarose gel provided considerable swelling, which made the identification of the cystic duct difficult (Fig. 4A, B). The swelling, in fact, generated a thickening of the structures, which led to a misinterpretation of the cystic duct anatomy when using the white-light view. On near-infrared imaging, the cystic duct was correctly localized in a deeper and slightly aside position as compared to what had been interpreted when using the white-light view (Fig. 4C, D). After a superficial dissection starting from the infundibulum of the gallbladder, the cystic duct was clearly identified, although it was surrounded by the gel. When using the white light, it was difficult to discriminate the duct from the swollen tissue (Fig. 4E, F).

The impacted stone model resulted in the blockage of the cystic duct and simulated inflammation around the cystic duct, offering a realistic scenario in which it was difficult to distinguish the junction of the infundibulum from the cystic duct at white-light observation (Fig. 5A, B). Intragallbladder ICG injection did not result in the enhancement of either the cystic duct or the CBD because of the blockage. However, the border of the gallbladder's infundibulum was clearly demarcated from swollen tissues by ICG fluorescence, and this helped to guide the initial dissection line (Fig. 5C, D).

In the third simulated scenario, the entire extrahepatic portion of the bile duct and the infundibulum of the gallbladder became severely swollen. While trying to identify Calot's triangle following tubular structures when using white light, we completed the procedure by clipping the CBD. Near-infrared cholecysto-cholangiography allowed to identify the mistake highlighting the gallbladder's infundibulum and the cystic duct (Video clip 2 in ESM).

Discussion

Imaging is one of the mainstays of the emerging model of "Precision Medicine and Surgery" [19]. Image-guided surgery aims to improve the efficacy and safety of procedures providing operators with an enhanced appreciation of patient-specific anatomy [20, 21].

Fluorescence image-guided surgery (FIGS) is a form of image-guided surgery, which offers an enhanced visualization of anatomical structures or organs' functions based on the administration of substances (fluorophores) which become fluorescent after being excited by specific light wavelengths. Open or endoscopic cameras equipped with ad hoc filters can capture the fluorescent signal generated by fluorophores, which can be visualized in real time in the operative field. FIGS has many advantages over standard image-guided surgery. As it does not interfere with the surgical workflow, it does not require any bulky equipment, and it is relatively cheap and does not use ionizing radiations. The use of FIGS as a potential means to prevent biliary injuries during cholecystectomy has been proposed by Ishizawa et al. [12, 22] and is still actively studied in many centers using different near-infrared technologies [14, 23–25].

After systemic injection, ICG is secreted by the liver into the bile and enhances the extrahepatic biliary tract and partially the distal portion of the cystic duct by bile reflux, helping to clarify the anatomy of Calot's triangle. However, systemic injection is limited by the occurrence

of a bright liver enhancement, which considerably reduces the signal-to-background ratio and the ability to identify crucial landmarks. Additionally, the refilling of the gallbladder and of the cystic duct with fluorescent bile by reflux is unpredictable, and consequently the junction could not always be perfectly visualized using intraoperative fluorescence, within the standard cholecystectomy timing. Dip et al. [23] described the "reflux maneuver" to identify the cystic duct junction, consisting in some squeezing of the bile duct below the cystic duct junction. This maneuver forces fluorescent bile to enter the cystic duct, allowing to visualize the junction by following the reflux of the fluorescent signal. However, the reflux maneuver will not help to visualize the gallbladder's infundibulum or to design the gallbladder profile in order to decide where to start the dissection. The visualization of such landmarks is particularly critical in case of severe cholecystitis, which also represents the best indication for any additional imaging modality to secure the extrahepatic biliary tract.

Ozkan et al. [26] have recently reported enhanced visualization of the biliary tracts following isosulfan blue injection directly into the gallbladder (cholecysto-cholangiography) of 10 cadavers. However, isosulfan blue, as other dyes in the visible light spectrum, has a limited tissue depth penetration, which might influence the success of cholangiography, particularly in case of inflammation [15].

Additional limitations include the occurrence of adverse reactions (1.5 % of cases) and the fact that it may stain the surgical field durably in case of extravasation, since it is not easy to wash out.

When compared to dyes in the visible spectrum, ICG shows a deeper tissue penetration and is more easily eliminated in case of contamination of the surgical field's white-light view.

Our hypothesis was that injecting ICG directly into the gallbladder, using a near-infrared cholecysto-cholangiography, would have provided several advantages over systemic injection, especially in case of inflammation. In this experimental study, we could confirm our hypothesis and appreciate the potential of this technique. First, intragallbladder injection allows for the simultaneous visualization of all extrahepatic biliary structures, including the CBD, the cystic duct, and the shape of the gallbladder. Secondly, the dose of fluorophores can be more controllable, which allows to perform repeated injections and to eventually adjust optimal concentration case by case. In the preliminary calibration study, using the D-Light P (Karl Storz Endoskope, Tuttlingen; Germany) near-infrared optimized laparoscope, we have found that the gallbladder and the CBD were visualized from 0.01 mg/mL, while the cystic duct was only slightly enhanced. Clear delineations of the cystic duct were obtained at 0.1 mg/mL of ICG. Individual factors, such as the degree of inflammation or the thickness of the adipose tissue, might influence the required dose of fluorophores to obtain clear images, and dose adjustments using systemic administration imply a simultaneous increase in liver background brightness. Using direct injection, the dose can be tailored case by case and injections can be repeated whenever required, without influencing the background signal from the liver. However, structures remained highlighted for approximately 1 h, which represents a reasonable duration for a cholecystectomy.

A third advantage lies in the fact that intragallbladder injection allows for a very fast, almost real-time, visualization of the biliary tree. Typically, using systemic injection, 2.5 mg of ICG are administered 30–45 min before surgery, since some time is required for ICG to be extracted from the blood by hepatocytes and secreted at the biliary pole to reach the biliary duct [22]. However, recent studies have outlined that ICG administration should be performed as early as possible prior to the intervention in order to reduce background fluorescence from the liver [27]. Verbeek et al. [28] reported optimized dosing and timing of intravenous ICG injection to perform near-infrared cholangiography, and compared the visualization of ICG fluorescence 30 min and 24 h after injection. The conclusion was that injecting ICG 24 h before surgery provides an optimal view of the biliary tree with almost no liver fluorescence background. However, such a long timing before the surgical procedure might be difficult to justify from economical and logistical standpoints. A good compromise would probably be to inject the dye 6–10 h before surgery. However, this would probably exclude emergency cases and would require that ICG fluorescence cholangiography be considered as a standard of care technique in order to be accepted, which is not the case yet. Additionally, it should be stressed that the injection of ICG to obtain fluorescence imaging is still considered an off-label indication. ICG is a very safe drug. However, it is FDA-cleared only for liver and cardiac function assessment and in ophthalmology for chorion angiography. Some cases of anaphylactic reactions following ICG administration have been reported, and for safety reasons, it is easier and more prudent to inject ICG when the patient is already intubated and ventilated.

Another point is that the evidence on NIRS cholangiography is still too limited to be proposed as a routine technique. NIRS cholecysto-cholangiography allows for intraoperative decision-making, according to the operative status to determine which is the best candidate for enhanced fluorescence imaging. In selected cases, intragallbladder ICG injection could be performed in addition to timely systemic injections, to further enhance contrast.

Additionally, intragallbladder ICG injection does not require the cannulation of the cystic duct, as per IOC, which is time-consuming.

This near-infrared cholecysto-cholangiography could intraoperatively complement the percutaneous drainage of a tense gallbladder, which is usually performed to facilitate the grasping of the gallbladder's fundus. In case of initial non-surgical management, with a transhepatic drain left in the gallbladder, the drain itself could be used during a delayed cholecystectomy as the route of ICG injection before starting the dissection [29–32].

An ancillary aim of this experimental trial was to generate large animal models simulating clinical scenarios, such as severe cholecystitis or impacted stones in which the fluorescent signal might be limited. We injected a biocompatible gel, which was previously used to simulate solid tumors [18]. Although such models might not be perfectly representative of real-life situations, the gel created a significant "edema" of the area surrounding biliary structures with a quite realistic effect, which allowed to appreciate the clinical usefulness of near-infrared cholecysto-cholangiography. For example, we could demonstrate the ability of near-infrared fluorescent cholecysto-cholangiography to identify the border of the gallbladder's infundibulum, which is a safe starting point of dissection, in a simulated situation where it was not clearly visible when using white light.

Although limited by the small sample size, the results of this proof of the concept allowed us to design a prospective clinical trial on near-infrared cholecysto-cholangiography in cholecystitis (NEAR-I-CHECK), which will be initiated at the IHU-Strasbourg Institute for Image-Guided Surgery.

Conclusions

Near-infrared fluorescence cholecysto-cholangiography using a direct intragallbladder injection of fluorophores provided real-time guidance to identify biliary structures. As compared to systemic injection of fluorophores, this method provides a faster and better contrasted enhancement of Calot's triangle and of the gallbladder itself. The next step is to apply this method to the clinical setting.

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Compliance with ethical standards

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