The Added Value of Intraoperative Near-Infrared Fluorescence Imaging in Elective Laparoscopic Cholecystectomy

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Abstract

Bile duct injury is a major complication of laparoscopic cholecystectomy (LC). Intraoperative cholangiogram is useful, but faster techniques are available to assist the surgeon, like near-infrared fluorescent cholangiography (NIFC) with indocyanine green (ICG). The aim of our study is to evaluate the usefulness of NIFC during LC. This is a retrospective study conducted on prospectively recorded data of the General Surgery department of Trieste Academic Hospital, Italy. All patients underwent elective LC from January 2016 to January 2020. Patients were randomly divided in 2 groups: in one group, only white light imaging was used (n = 98 patients), in the NIFC group (n = 63) ICG was used. NIFC has been chosen more frequently by residents than consultants (P = .002). Operative time and length of stay resulted shorter in ICG group (P = .002 and .006), and this group showed also fewer intraoperative complications (P = .007). NIFC does not require any learning curve and makes surgery faster and safer.

Keywords

laparoscopic cholecystectomy, indocyanine green, bile duct injury, near-infrared fluorescent cholangiography, cholangiography

Introduction

Laparoscopic cholecystectomy (LC) is one of the most commonly performed surgical procedures worldwide (750,000 cases/year only in the United States).[1] Bile duct injury (BDI) is a rare complication of this procedure, accounting for the .4–7% of the total LCs.[2] Nevertheless, its consequences are extremely serious, impacting both on quality of life and overall survival of the patients.[3] In 70–80% of cases the BDI is caused by an intraoperatory misinterpretation of biliary anatomy and many studies show that, whatever the training level, from 34% to 49% of all surgeons will experience a BDI during their careers.[4,5]

At present, intraoperative cholangiography (IOC) is the only recommended method to reduce the risk of BDI. However, IOC is not routinely used since it is time-consuming (10–23 minutes meanly added to each procedure),[6] it requires expertise and a learning curve, it is not so easy to obtain especially in an emergency setting since a radiology technician is needed in many hospital facilities, it exposes the patient to radiation, and it is not free from costs and inherent risks.[1]

Near-infrared fluorescence cholangiography (NIFC) is a new technique that uses indocyanine green (ICG) to provide an intraoperative mapping of the extrahepatic biliary system. ICG is a fluorescent dye that after intravenous injection remains in the vascular compartment only to be successively excreted in the bile. When excited with a near-infrared laser, ICG emits visible light that allows the surgeon to visualize biliary anatomy.[1]

Methods

Study Design

This is a retrospective single center study conducted on prospectively collected data from the General Surgery department of Trieste academic hospital database. We considered all the patients undergoing elective LC from October 2016—when we started to use near-infrared

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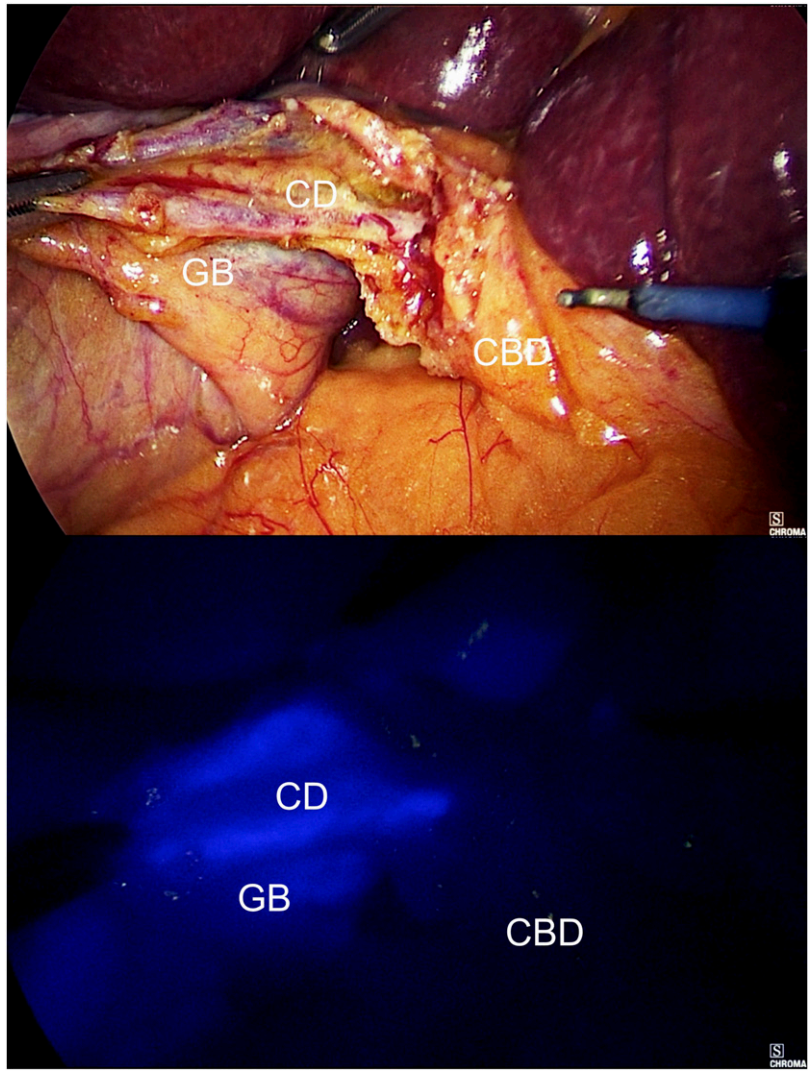

Figure 1. Common bile duct (CBD), cystic duct (CD) and gallbladder (GB) vision in white light imaging versus near-infrared fluorescence cholangiography.

(NIR) technology at our Institute—to January 2020. We randomly selected a group of 63 patients undergoing LC with the intraoperative use of NIFC (IGC group) and a group of 98 patients undergoing LC with only white light imaging (WLI group).

Preoperative variables were collected, including sex, age, BMI, American Society of Anesthesiologists (ASA) score, Charlson Comorbidity Index (CCI), previous abdominal surgery, previous biliary pancreatitis, and previous ERCP. Intraoperatory variables included the first operator (consultant vs resident), surgery duration, intraoperative complications, and use of drainage. We finally considered postoperative variables, like postoperative early and late complications (within the fifth postoperative day and after), length of in-hospital stay, Clavien–Dindo classification, readmission, and postoperative ERCP.

Patient data were collected at enrollment, during surgery, during hospital stay, and postoperatively.

Laparoscopic Equipment

Near-infrared fluorescence cholangiography was performed using a laparoscopic SPIES system (KARL STORZ GmbH&Co. KG, Tuttlingen, Germany) and a full high-definition camera system (IMAGE 1 SPIESTM, KARL STORZ). A xenon light source was employed (D-LIGHT P SCB, KARL STORZ), providing both WLI and NIR excitation light (>780 nm). The surgeon controlled the switch from WLI to NIR by means of a foot switch.

Table 1. Preoperative variables.

	ICG group (63)	WLI group (98)	*P*
Female	30 (48%)	48 (49%)	P = .99
Male	33 (52%)	50 (51%)	
Mean age (years) ± SD	61.4 ± 15.6	62.5 ± 15.2	*P* = .67
BMI median (min–max)	24.1 (18.2–34.8)	23.8 (19.2–32.6)	*P* = .56
ASA score	8 (13%)	10 (10%)	*P* = .25
1	33 (52%)	64 (65%)	
2	22 (35%)	24 (25%)	
3			
CCI median (min–max)	3 (0–8)	3 (0–9)	*P* = .89
Preoperative ERCP	10 (16%)	24 (25%)	*P* = .19
Preoperative biliary pancreatitis	16 (25%)	18 (18%)	*P* = .29
Previous abdominal surgery	27 (43%)	45 (46%)	*P* = .70

The fluorescence cholangiogram showed the biliary tree in blue or green color.

Indocyanine Green Fluorescent Dye

Indocyanine green is a fluorophore that responds to NIR irradiation, absorbing light from 790 to 805 nm and re-emitting it with an excitation wavelength of 835 nm. Administered intravenously, ICG binds to plasma proteins and becomes confined to the intravascular space. It is then exclusively metabolized by the liver and excreted via the biliary system 15 to 20 minutes after administration. These properties, combined with the absence of any native biological fluorescence within these wavelengths, render ICG an ideal agent for acquiring high-quality biliary tract images.

Indocyanine Green Use

We administered 0.2 mg/kg of ICG intravenously the night before surgery to the first patient of the operatory session, or 0.1 mg/kg of ICG at 7 o'clock of the morning of the procedure to the second and third patient of the operatory session. We used a higher dosage when 12 hours elapsed between administration and start of surgery, a lower dosage when 3–6 hours elapsed. We administered ICG to every patient admitted for elective LC, but the choice of intraoperative use of NIFC was left to the first operator of the procedure. NIFC enhances the common biliary tract, the cystic duct, and also accessory biliary ducts, so it may be used during every step of the procedure.

Surgical Technique

We perform LC in the French-position. We always put an epigastric 5-mm trocar for better exposition. We always start LC in the retrograde way, opening the peritoneum and trying to achieve the critical view of safety exposing the Calot triangle until all the structures (i.e., cystic duct, cystic artery, and lower liver margin) are clearly distinguishable. NIFC allows the surgeon to visualize the extrahepatic biliary tree before Calot triangle dissection, facilitating its isolation (Figure 1). Once isolated, we tie the cystic duct and artery by means of metal clips or hem-o-loks. At the end of the dissection, we irrigate the cholecystectomy bed to identify any bleeding or biliary leak. We do not usually put a drain at the end of the procedure even if the gallbladder has been injured during the dissection. The gallbladder is extracted in a specimen retrieval bag.

In our hospital, we do not routinely use IOC.

Statistical Analysis

Quantitative data are reported as mean ± standard deviation (SD) or as mean (minimum-maximum) depending on whether the data are distributed normally or not, respectively (checked with the Shapiro–Wilk test). Qualitative variables are expressed as absolute frequencies and percentages. Differences in categorical data were compared using chi-squared test or Fisher's exact test when appropriated; differences in continuous variables were compared using Student's t-test or nonparametric Mann–Whitney test. All statistical analyses were performed using R software, version 3.5.0-2018 (http://www.r-project.org). A *P* value of less than .05 was considered to indicate a statistically significant difference.

Results

A total of 161 patients were enrolled in the study. The NIFC group consisted of 63 patients and the WLI group of 98 patients, with a mean age of 61.4 ± 15.6 years in the NIFC group and 62.5 ± 15.2 years in the WLI group, respectively (*P* = .67). All preoperative data (i.e., sex, BMI, ASA score, CCI, history of preoperative ERCP, preoperative biliary

Table 2. Intraoperative variables.

	ICG group (63)	WLI group (98)	*P*
First surgeon		41 (41%)	**P = .02**
Resident	42 (66%)	57 (59%)	
Consultant	21 (34%)		
Operatory time (minutes) Median (min–max)	61 (25–160)	85 (20–285)	**P = .002**
Intraoperative complications	0 (0%)	10 (10%)	P = .02
Drain placement	12 (19%)	26 (27%)	P = .34

Table 3. Postoperative variables.

	ICG group (63)	WLI group (98)	*P*
Postoperative early complications	5 (8%)	10 (10%)	P = .63
Length of in-hospital stay (days) Median (min–max)	1 (1–12)	2 (0–35)	**P = .006**
Late complications	3 (5%)	5 (5%)	P = .92
Dindo–Clavien score	42 (67%)	71 (72%)	P = .69
0	15 (24%)	18 (18%)	
1	6 (9%)	9 (9%)	
≥2			
Readmission	1 (2%)	3 (3%)	P = 1.00
Postoperative ERCP	1 (2%)	2 (2%)	P = 1.00

pancreatitis, and previous abdominal surgery) resulted homogeneous between the 2 groups (Table 1).

As for the intraoperative data, NIFC has been used more frequently by residents than consultants and the difference is statistically significant ($P = .02$). Despite the fact that 66% of LCs were performed by residents—versus 41% of the WLI LCs—the operative time resulted significantly shorter in the NIFC group (61 (25–160) minutes versus 85 (20–285) minutes, respectively; $P = .002$). To rule out the possibility of a bias related to surgeons' personal skills, we individually analyzed all the surgeons that performed at least one cholecystectomy in both NIFC and WLI groups. We found out that 8 consultants and 12 residents performed at least one surgery in both groups. We calculated the mean operative time of each surgeon per each group, and we found it to be shorter in NIFC group for 6/8 consultants (75%) and 7/12 residents (58%). The total mean gain in time in NIFC group was 13 minutes per surgeon.

The intraoperative placement of a drain was not significantly different, while the amount of intraoperative complications was higher in the WLI group ($P = .02$). We experienced only minor intraoperative complications, and only in the WLI group: 4 bleedings (we defined "intraoperative bleeding" every bleeding needing intraoperative use of absorbable hemostats or patient needing blood transfusion or re-operation for hemostasis), and 3 lesions of accessory biliary duct (managed with postoperative conservative treatment). All the intraoperative data are shown in Table 2.

As far as the postoperative course was concerned, there were no statistically significant differences in terms of postoperative early and late complications (in order of frequency intra-abdominal collections, pneumonia, bleedings, biliary fistulas, and pancreatitis), Dindo–Clavien score, need for postoperative ERCP (2 residual choledocolithiasis in the WLI group and 1 biliary fistula in the NIFC group, likely due to a clip misplacement on the cystic duct), and readmission. We found a statistically significant difference in the length of in-hospital-stay: a median of 1 (1–12) days for the NIFC group versus 2 (1–35) for the WLI group ($P = .006$). Even the truncated mean removing the 5% of the outliers confirmed the difference (2.13 days vs 3.22, $P = .01$). All the intraoperative data are shown in Table 3.

We finally compared the results of the subgroup of ICG LCs performed by residents with the results of the subgroup of WLI LCs performed by consultants. The operatory time showed a statistically significant difference in favor of the residents (a median of 61.5 minutes vs 95 minutes, $P < .001$), and similar results were found for the length of in-hospital stay (a median of 1 day vs 3, $P < .001$), and intraoperative complications (0% vs 12%, $P = .02$). All the data are shown in Table 4.

Table 4. Comparison between intra and postoperative variables of LCs performed by residents in the ICG group vs consultants in the WLI group.

	ICG group—residents (42)	WLI group—consultants (57)	*P*
Operatory time (minutes) Median (min–max)	61.5 (25–118)	95 (20–285)	**P < .001**
Intraoperative complications	0 (0%)	7 (12%)	P = .02
Drain placement	8 (19%)	20 (35%)	*P* = .13
Postoperative early complications	2 (5%)	4 (7%)	*P* = .97
Length of in-hospital stay (days) Median (min–max)	1 (1–10)	3 (0–23)	**P < .001**
Late complications	1 (2%)	3 (5%)	*P* = .64
Dindo–Clavien score	33 (78%)	40 (70%)	*P* = .58
0	7 (17%)	11 (19%)	
1	2 (5%)	6 (11%)	
>=2			
Readmission	0 (0%)	2 (3%)	*P* = .61
Postoperative ERCP	0 (0%)	2 (3%)	*P* = .61

Discussion

Considering the relative rarity of BDI, NIFC's potential in BDI reduction is not easy to prove: considering for example an incidence of 4/1000 BDI, the number of subjects required to verify a 50% relative reduction in BDI would approach about 25,000 patients.[7]

In any case, up to 97% of BDI have been attributed to an inadequate visualization or interpretation of biliary anatomy.[8,9] Anatomical anomalies of the biliary tree are extremely common, starting from a short cystic duct that reduces the space available within the operative field. Although the most common risk factor for BDI is an aberrant right hepatic duct (2% of population).[10] Acute or chronic inflammation and the consequent scarring of the tissues significantly obscures the landmarks of Calot triangle and plays a role in causing intraoperative bleeding that may lead by itself to BDI.[11] Excessive dissection may also lead to biliary injuries in unexperienced hands, either by diathermy lesions or ischemic stricture formation.[12]

Surgical inexperience as well as overconfidence may increase the risk of BDI. In fact, following the correct plane, as well as the correct use of different clipping devices and of a rational number of clips have been shown to prevent injuries.[10] At the same time, two-port and single-port LCs—techniques developed to improve recovery and reduce postoperative pain—are associated to increased risk of biliary injuries (.7% of BDI for single-port LC).[13]

IOC is a useful tool to avoid misinterpretation of extrahepatic biliary anatomy. However, its routine use is associated with increased length of operative time, costs, and risk of complications. It is clear that eliminating the need to cannulate the biliary tree, a major source of BDI is already removed. Nevertheless, surgeons not performing regularly IOC may also have difficulty in interpreting the intraoperatory findings.[14] NIFC's capacity to enhance and facilitate process and interpretation could further reduce the risk.[7,]

The present study managed to confirm NIFC's use is related to a statistically significant reduction in intraoperative complications ($P = .02$), operative time ($P = .002$), and length of in-hospital stay ($P = .006$). We believe that NIFC reduces intraoperative complications even if not directly related to BDI, and this significantly shortens the length of in-hospital stay as well as the costs related to both the hospitalization and the additional procedures that may be required to manage the complications. We also suppose that NIFC may add a supplemental self-assurance leading the surgeon to limit the use of the drainage and reduce the length of in-hospital stay of the patient.

We believe that our results may be of immediate clinical interest, given the numerous advantages that this technique has, especially if compared to IOC. In fact NIFC allows the surgeon to visualize the extrahepatic biliary tree before Calot triangle dissection, facilitating its isolation and not needing incisions of the cystic duct.[7] It is not time-consuming, and it rather seems to significantly shorten operative time, especially if we consider that the majority of LC were performed by residents in the NIFC group (the difference being statistically significant when compared to the WLI group, $P = .002$, even when directly comparing NIFC LCs performed by residents vs WLI LCs performed by consultants, $P < .001$). This reinforces also the concept that NIFC does not require any learning curve, since it is easy to learn and easy to supervise.[15,16] As for the safety of the procedure, ICG has been proved to cause allergic reactions in only .7–1–9% of patients and it is considered safe for use during pregnancy, given its minimal transfer to the

fetus.[17] Compared to IOC, NIFC does not require radiation, expensive equipment, dedicated personnel, and specific expertise.[18] It can be used for longer periods of time, for example, when Calot dissection is particularly difficult, given that its peak visualization lasts at least 2 hours, and since it is usually administered intravenously, it can be re-administered if necessary.[19] In addition, it has been shown to facilitate biliary anatomy detection even in obese patients, in patients who previously underwent abdominal surgery, and in severe operative field inflammation.[7] Last, the only cost to bear is the phial (80–250$) that may however be used for up to 2–3 patients.[20] This technique is not meant to intraoperatively identify bile duct stones.

In our experience, NIFC has been found useful also to identify and preserve accessory bile ducts that may be responsible of low output biliary fistulas (interviewed surgeons reported twice the identification of Luschka accessory duct thanks to NIFC). This postoperative complication in most cases may be managed conservatively, but even when it does not require supplemental procedures—that is, ERCP—it prolongs in-hospital stay and relative costs.

Up to the present, we have used NIFC only in elective LCs, but we are strongly convinced that this technique may be extremely useful also in an emergency setting, when severe inflammatory conditions may impair normal biliary anatomy and increase the risk of misinterpretation and consequently of intra- and postoperative complications.

Conclusion

We believe that NIFC is an easy tool that may replace IOC for biliary anatomy visualization in everyday clinical practice. When compared to WLI, it is more frequently chosen by residents and nevertheless it shows to reduce the rate of minor intraoperative complications, the duration of surgery, and the length of in-hospital stay. It can be considered a useful tool especially for trainees and young surgeons and when the surgeon faces up with difficult anatomy or severe inflammatory conditions.

Author Contributions

Cristiana Iacuzzo contributed to design of the study, creation and collection of the database, and writing of the manuscript Livia Bressan contributed to design of the study, collection of the database and supervising, Marina Troian contributed to design of the study and supervising, Paola Germani contributed to design of the study and supervising, Fabiola Giudici contributed to statistical analysis of the data, Marina Bortul contributed to supervising.

Declaration of Conflicting Interests

On behalf of all authors, I declare that this work is original, it has not been published elsewhere, and it is not currently under consideration for publication elsewhere. All authors satisfied the minimum criteria for authorship defined by the International Committee of Medical Journal Editors Recommendation for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. All the authors have contributed to the creation of the manuscript—specifically Iacuzzo and Bressan have been involved in all the stages (design, database collection, statistical analysis, writing, and editing), Troian and Germani contributed to the writing and editing, Giudici took care of statistical analysis, and Bortul contributed to design, editing, and supervision. All authors have read and approved the final version of this paper. All authors declare that there are no financial ties or conflicts of interest to be disclosed. All procedures performed in the study were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent by the institutional research committee was not required. However, informed consent was obtained from all patients included in the study.

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