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Use of indocyanine green fluorescence during hepatobiliary surgery

Maharjan DK[1], **Thapa PB**[2]

[1]Dhiresh Kumar Maharjan, Assistant Professor; [2]Prabin Bikram Thapa, Professor, Department of Surgery, Kathmandu Medical College Teaching Hospital, Sinamangal, Kathmandu, Nepal.

Abstract

Background: Indocyanine green fluorescence image has been used in hepatobiliary surgery, which was mainly started by Japanese surgeons to visualize hepatobiliary structures probably because it is regarded as a reagent for estimation of hepatic function.

Objectives: The objective of this study is to see the feasibility of use of indocyanine green in our setting during hepatobiliary surgery and its potential applications in the surgical treatment of benign and malignant liver pathology along with its selective use during difficult cholecystectomy to visualize extrahepatic biliary radical.

Methodology: This is a prospective cross sectional observational study performed including all consecutive patients who were posted for liver resection, both benign or malignant and selectively used in biliary surgery when biliary anatomy was uncertain.

Results: A total of thirty-nine patients had usage of indocyanine green, with a mean age of 51.6 ± 11.6 years (range, 31-75 years). In all our patients we were able to visualize the biliary system and liver parenchymal lesion.In the selective use of indocyanine green during difficult biliary anatomy during laparoscopic cholecystectomy 15/400 (3.75%), we were able to delineate biliary tree and hence five patients (1.2%) had to be converted to open cholecystectomy further preventing injury to the bile duct.

Conclusion: Indocyanine green fluorescence imaging can be used safely and easily to identify liver tumors, hepatic segments, and extrahepatic bile ducts in real time during open and minimally invasive surgery. This allows surgeons to map the anatomical variations, status of resection margin and prevent surgical complications.

Key words: Indocyanine Green (ICG); Liver tumor; Laparoscopic cholecystectomy.

INTRODUCTION

Since the year 2000,there has been wide use of Indocyanine green fluorescence image (ICG-FI) in hepatobiliary surgery, mainly started by Japanese surgeons to visualize hepatobiliary structures probably because it is regarded as a reagent for estimation of hepatic function [1-3]. In 2009, the first report of fluorescence cholangiography during laparoscopic cholecystectomy described using ICG excreted into bile following preoperative intravenous injection as the source of fluorescence[4]. Its use in malignancy has also gained wide popularity as it accumulates in cancerous tissues of hepatocellular carcinoma (HCC) and around benign adenomas [5,6].

Hence, the aim of this study is to see the feasibility of the use of Indocyanine green (ICG) during hepatobiliary surgery and its potential applications in the surgical treatment of benign and malignant liver pathology along with its selective use during difficult cholecystectomy to visualize extrahepatic biliary radical.

METHODOLOGY

This is a prospective cross sectional observational study performed including all consecutive patients who were posted for liver resection, both benign or malignant

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Address for correspondence

Dr. Dhiresh Kumar Maharjan
Assistant Professor, Department of Surgery
Kathmandu Medical College Teaching Hospital
Sinamangal, Kathmandu, Nepal
E-mail: maharjandhiresh@gmail.com

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and selectively used in biliary surgery when biliary anatomy was uncertain. This study was performed at the Department of Surgery, Kathmandu Medical College Teaching Hospital, from 1st June 2019 to 1st June 2020 performed by a single surgical team. All study protocols were approved by the Institutional ReviewCommittee of the institute and informed consent for data collection was obtained from each patient.

The data were prospectively collected and entered into a database for analysis.

INCLUSION CRITERIA:

- Benign liver disease including hydatid cyst, hemangioma measuring more than 10 cm.
- Malignant liver disease including Hepatocellular carcinoma, liver metastasis including colorectal metastasis.
- Selective biliary disease when biliary anatomy was uncertain during laparoscopic cholecystectomy.

Exclusion criteria: Patient with a history of allergic reaction to iodide components.

HOW DOES IT WORK?

Indocyanine green (ICG) is a water-soluble dye that emits wavelengths in serum at 778 and 830 nm, respectively[7]. ICG binds to plasma proteins and is then rapidly taken up by hepatocytes, thus quickly disappearing from the bloodstream (half-life ~3-4 minutes) and then secreted into the bile without metabolization[8,9].This hepatocytic uptake can be visualized by near-infrared fluorescence imaging camera which allows detection of hepatocellular (tumor fluorescence) and non-hepatocellular tumors (peri-tumoral fluorescence) along with metastatic tumors [10-16]. In addition, it helps to delineate extra hepatic biliary radicals during difficult cholecystectomy helping to prevent bile duct injury.

Procedure: Use of Indocyanine green (Aurogreen®, Aurolab, Madurai, Tamil Nadu) depended upon pathology and was given after a test dose as anaphylactic reactions have been documented before[17, 18].

DOSAGES

- Benign disease of liver (for example: Hydatid cyst): Intravenous (IV) injection of ICG at a dose of 0.25 - 0.5 mg/kg was administered half an hour before surgery.
- Malignant disease of liver: IV injection of ICG at a dose of 0.25 - 0.5 mg/kg was administered twenty-four hours before surgery.
- Biliary disease for difficult biliary anatomy: IV injection of ICG at a dose of 0.25 - 0.5 mg/kg was administered during surgery.

Equipment: Laparoscopic and open surgery imaging was performed using the D-LIGHT P System (Karl Storz® GmbH & Co. KG, Tuttlingen, Germany) by the high-end full high definition camera system (IMAGE 1 SPIES™, KARL STORZ) connected to a laparoscope with 30° field of direction and 10 mm diameter equipped with a specific filter for optimal detection of the near-infrared fluorescence imaging (NIR- FI) and white light with switching controlled by the surgeon by means of a pedal. This imaging system comprises two wavelength-isolated light sources: a white light source and a near-infrared light source that produce light of 805-nm wavelength, and this imaging system detects infrared light of 835nm and provides real time qualitative fluorescent imaging.

STATISTICAL ANALYSES

For quantitative data, the results were expressed as the mean ± SD. For categorical data, the results were expressed as the number and percentage of cases. Values are expressed as the mean and range, or percentages, when appropriate. All statistical analyses were performed using the Statistical Package for the Social Sciences version 16.0 statistical software (SPSS Inc Chicago, IL) [19].

RESULTS

During the period from 1st June 2019 till 1st June 2020, a total of thirty-nine patients had usage of ICG including 18 male and 21 female, with a mean age of 51.6 ± 11.6 years (range, 31-75 years). A preoperative ultrasonic documentation of normal liver morphology in 19, fatty liver in 12, cirrhosis due to viral hepatitis in 4 and obstructive jaundice in 4 patients were noted.

BENIGN LIVER DISEASES

Laparoscopic de-roofing for hydatid cyst was performed in eight patients.With use of ICG, two patients showed bilio-cystic communication which was visible as dye communicating into the cyst cavity and was sutured with 5.0 polydioxanone absorbable suture.

ICG can be used to assess the vascular pattern of the hemangioma subjected for surgery. Hemangioma is characterized by a faster and brighter enhancement compared to normal liver parenchyma and a more rapid 'wash out'. This pattern of fluorescence allows the identification of the correct surgical plane between the mass and normal parenchyma. Two patients had hemangioma in segment II/III (Laparoscopic lateral

sectionectomy performed) while the third was at segment 6 open (enucleation performed).

MALIGNANT LIVER DISEASES

Four patients with hepatocellular carcinoma (HCC) underwent surgery among which three patients had anatomical resection of the liver (open right hemi-hepatectomywas performed in two patients and open left hemihepatectomy in one patient, respectively) [Figure1 (a,b) and 2 (a, b)] while one patient with isolated segment 8 HCC underwent non- anatomical resection.

One patient with liver metastasis in segment V extending to segment VIII (following post Whipples operation for pancreatic head adenocarcinoma 3 years back) and three other patients had parenchymal sparing metastatectomy for colorectal liver metastasis (CRLM), among which two patients had synchronous surgery for rectal cancer along with metastatectomy afterneoadjuvant therapy during the same setting and one had metastatectomy post right hemicolectomy for ascending colon adenocarcinoma after 2 years of primary surgery.

All tumor lesions were visualisable when ICG was injected 24hours prior to surgery and per operative intra-biliary injection of ICG via cystic duct along with intravenous. This helped in the detection of segmental fluorescence, clarification of the biliary anatomy and demarcation line after pedicle clamping.

BILIARY DISEASE

During the study period, a total of 400 patients underwent laparoscopic cholecystectomy. ICG was used in 15 patients (3.75%) with difficult biliary anatomy with failure to achieve critical view of safety. Among them, five patients (1.2%) had to be converted to open cholecystectomy due to difficult anatomy because of frozen Calot's triangle while ten patients could proceed with laparoscopic cholecystectomy as it helped to delineate biliary anatomy. No incidence of bile duct injury was noticed during this period (Figure 3).

ICG was used in four patients with advanced gallbladder cancer with liver bed involvement for anatomical segment IVb/V resection. We have been performing a Glissonian approach for anatomical liver resection and after separating the right posterior pedicle. Right anterior intra-portal injection of ICG at 0.25mg/kg, diluted in 50ml of normal saline was performed and liver resection proceeded.

Table 1: Indications for use of Indocyanine green (ICG) in hepatobiliary surgery (n=39)

			Total
Benign liver disease	Hydatid cyst: 8	Hemangioma:3	11
Malignant liver disease	HCC:4	Colorectal metastasis:3 Post Whipples liver metastasis:1	8
Biliary surgery	Intra-hepatic cholangiocarcinoma:1 Advanced gallbladder cancer:4	Difficult biliary anatomy:15	20

Table 2: Surgery done after use of ICG (n=39)

	Surgery done	Total
Benign liver disease		
Hydatid cyst	Laparoscopic de-roofing	8
Hemangioma	Open enucleation Laparoscopic left lateral sectionectomy	1 2
Malignant liver disease		
Hepatocellular cancer(HCC)	Open non anatomical 8th segmental HCC resection Open right hemihepatectomy Open left hemihepatectomy (4b,2,3)	1 2 1
Colorectal metastasis	Open parenchymal sparing metastatectomy	3
Post Whipples liver metastasis	Open central bisegmentectomy	1
Biliary Diseases		
Intrahepatic cholangiocarcinoma	Open left extended hepatectomy	1
Advanced gall bladder carcinoma	Open anatomical bisegmentectomy IVb/V	4
Difficult biliary anatomy during laparoscopic cholecystectomy	Laparoscopic cholecystectomy	15

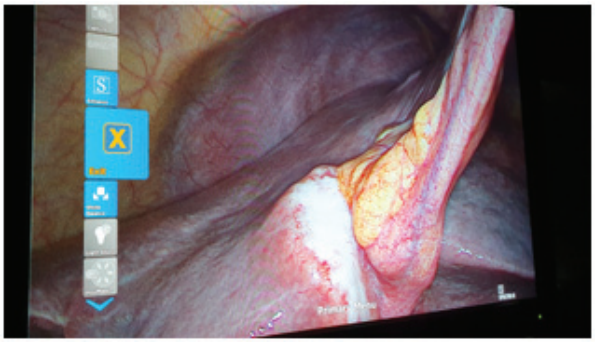

Figure 1a: Diagnostic laproscopic view of IVb lesion in white light

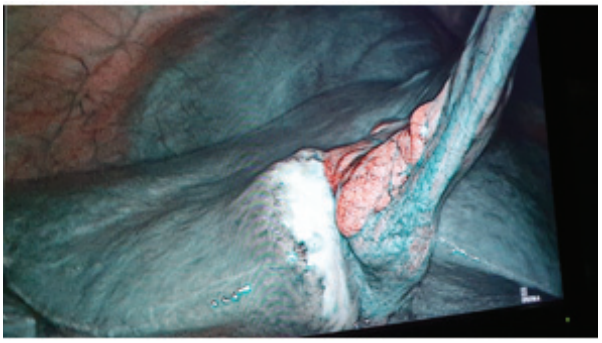

Figure 1b: Same lesion in near-infrared fluorescence imaging (NIR-FI) after intravenous ICG 24 hours prior to surgery

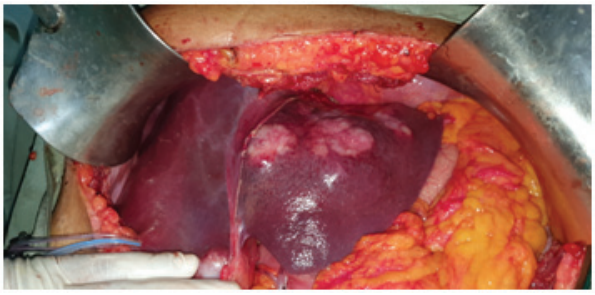

Figure 2a: Open view os segment 2,3 and 4b lesion and line of demarcation after pedicle clamping

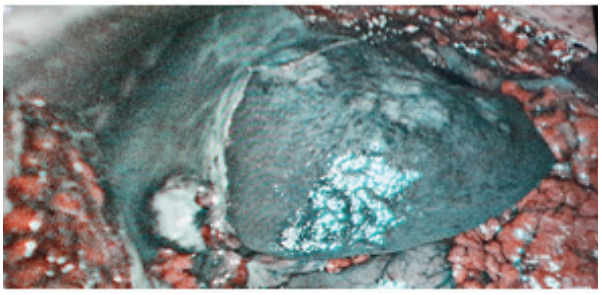

Figure 2b: Same lesion in near-infrared fluorescence imaging 9nir-FI) after intravenous ICG 24 hours prior to surgery

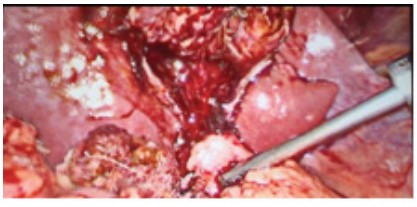

Figure 3a

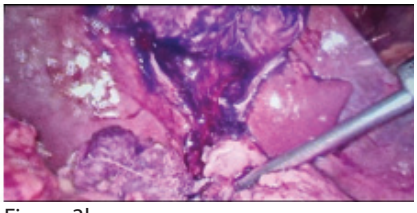

Figure 3b

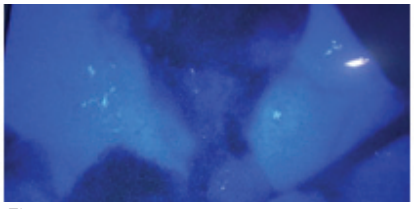

Figure 3c

Figure 3: Use of ICG and the near-infrared fluorescence imaging (NIR- FI) and white light with switching controlled by the surgeon by means of a pedal showing frozen Calot's triangle (Figure 3a), narrow band blue color vision (Figure 3b) and intraoperative view of biliary system after the use of ICG (Figure 3c).

DISCUSSION

Indocyanine green (ICG) has been used for near infra-red (NIR) photography image since 1955 [20]. Since then its clinical use has been diversified in many clinical scenarios from ophthalmology[21], neurosurgery[22], colorectal surgery[23] and hepatobiliary surgery[24-27].

In our study, we have found its benefit in the benign disease of liver like hydatid cyst where we were able to delineate cysto-biliary communication in two patients. Studies done by Kimura et al have shown that ICG helps to identify biliary leakage after surgery [28]. Use of ICG in hemangioma has been limited, though literature has suggested early uptake and early wash out being characteristic for it [29].

Similarly, its importance in benign biliary diseases cannot be undermined, as we were able to delineate biliary anatomy during difficult cholecystectomy for acute calculous cholecystitis, though it has been used only in selected cases. Meta-analysis by *Vlek SL et al.* in 2017 has shown that ICG is better to delineate biliary anatomy and more likely to visualize cystic duct than intraoperative cholangiography (IOC) (RR 1.16; 95% CI 1.00–1.35)[30]. Similarly,a study done by *Ambe PC et al.* has shown that conversion rate could be reduced significantly with

the use of ICG during laparoscopic cholecystectomy and may help in protection of bile duct[31]. Likewise, we did not have any bile duct injury, however five patients had to be opened due to frozen Calot's despite visualization of cystic duct and CBD during laparoscopic cholecystectomy with ICG.

The use of ICG in malignant liver pathology like HCC and colorectal metastasis has been of more importance either to delineate segmental anatomy or for parenchymal sparing hepatectomies. However, Aoki *et al.* first described its use to outline liver segments after intraoperative selective portal vein injection in 2008[32]. Similarly, Gotoh *et al.* in 2009 used it for first time to localize and navigate resection margins for HCC lesions[33].

Delineation of liver segments can help surgeons to perform anatomical segmental resections, which has been the main basis for oncological safety and preservation of future liver reserve (FLR) volume[34]. In our study, we were able to delineate tumour lesions when injected 24 hours prior to surgery. Intraoperative intravenous ICG helped to delineate anatomical demarcation segment while intrabiliary injection of ICG through cystic duct helped us to check for biliary leakage from the resection margin. It allowed accurate visualization of liver segment, as first reported by Ishizawa *et al.* in 2012 about their initial experience on the use of laparoscopic fluorescence imaging guidance in staining of hepatic segments during resection[35]. Similarly, Uchiyama *et al.* first used ICG fluorescence in localizing colorectal-cancer liver metastases and were able to document microscopically positive tumor cells even in radiologically invisible tumor after neoadjuvant chemotherapy but still showed a positive fluorescent signal[36]. Moreover, ICG helped to detect bile duct leakages during hepatectomies that were missed by other routine tests[37].

CONCLUSION

ICG-fluorescence imaging can be used safely and easily to identify liver tumors, hepatic segments, and extrahepatic bile ducts, in real time during open and minimally invasive surgery and helps to perform anatomical resection of liver and shows us anatomical map during difficult laparoscopic cholecystectomy when critical view is not achievable.. This study being descriptive and having a small sample number does have some limitations. Hence, further clinical studies to assess the sensitivity and specificity of ICG during hepatobiliary surgery is recommended.

Conflict of interest: None
Source(s) of support: None

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