Original Article

Early identification of the critical view of safety in laparoscopic cholecystectomy using indocyanine green fluorescence cholangiography: A randomised controlled study

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SUMMARY

Background: Achieving critical view of safety (CVS) is vital during laparoscopic cholecystectomy (LC). There is no known study determining use of indocyanine green fluorescence cholangiography (ICGFC) in early identification of CVS during LC. This study aims to compare use of ICGFC in LC against conventional LC in early identification of CVS.

Methodology: Patients undergoing LC in a single centre were randomized into ICGFC-LC and conventional LC. Surgery was performed by a single surgeon and the time taken to achieve CVS from the time of gallbladder fundus retraction was measured. Difficulty level for each surgery was rated and analysed using a modified scoring system (Level 1—Easy to Level 4—Very difficult).

Results: 63 patients were recruited where mean time (min) to achieve CVS was 22.3 ± 12.9 in ICGFC-LC (n = 30) and 22.8 ± 14.3 in conventional LC (p = 0.867). The time taken to achieve CVS was shorter in ICGFC-LC group across all difficulty levels, although not significant (p > 0.05). No major complication was observed in the study.

Conclusions: This study had shown ICGFC-LC reduces time to CVS across all difficulty levels but not statistically significant. ICGFC-LC maybe useful in difficult LC and in surgical training.

Trial registration: Clinical Trials NCT04228835.
Study grant: UMNI Surgical – Karl Storz Distributor (Malaysia)

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1. Introduction

Laparoscopic cholecystectomy has been recognized as the gold standard in cholecystectomy since it was first performed by Professor Dr Med Erich Mühe in 1985. Despite the advancement of surgical technique, the rate of biliary injury during laparoscopic cholecystectomy has not changed for the past 20 years. In fact, it is reported to be higher than open surgery (0.3% vs 0.2%) and leads to significant patient complications, reduced long term survival and quality of life.

The Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) has endorsed the use of critical view of safety (CVS) during laparoscopic cholecystectomy to minimize the risk of bile duct injury. First introduced by Strasberg in 1995, it aims to avoid misidentification of biliary anatomy. It is defined as the visualization of only 2 structures entering the gallbladder, hepatocystic triangle is cleared of fat and fibrous tissue and the lower one third of the gallbladder is separated from the liver to expose the cystic plate. The use of cholangiography to image the biliary tree intraoperatively during laparoscopic cholecystectomy aids in the visualization of the extrahepatic biliary tree. Indocyanine green fluorescence cholangiography (ICGFC) is one such method which allows real time intraoperative visualization.

ICGFC involves administration of a fluorophore, which is excreted exclusively in the biliary system and emits fluorescent light when viewed using near infrared imaging. This enables extrahepatic biliary tree anatomy to be delineated during laparoscopic cholecystectomy. A review by Pesce et al showed encouraging detection rates of extrahepatic biliary structures during laparoscopic cholecystectomies using ICGFC ranging from 72% to 95%. The use of ICGFC-LC reduces time to CVS across all difficulty levels but not statistically significant. ICGFC-LC maybe useful in difficult LC and in surgical training.

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Van Dam et al in a prospective crossover study, reported earlier identification as well, compared to conventional white light imaging. These early studies suggest the use of ICGFC and time to identify biliary anatomy to demonstrate the effectiveness in surgical dissection in laparoscopic cholecystectomy.

The primary objective of this study is to evaluate whether earlier identification of CVS can be obtained by using ICGFC compared to conventional method of laparoscopic cholecystectomy. This would be able to demonstrate the effectiveness of using ICGFC to perform safer surgery. The secondary objective is to assess the rate of perioperative complications using ICGFC. There is currently no published data on the use of ICGFC in reducing operative time of identification of CVS compared to conventional method during laparoscopic cholecystectomy.

2. Methodology

This is a randomized control trial conducted in University Malaya Medical Centre, Kuala Lumpur, Malaysia between March 2017 and July 2019, a tertiary centre with specialized HPB service. All patients scheduled for elective laparoscopic cholecystectomy were enrolled in this study. The inclusion criteria accept patients more than 18 years of age and American Society of Anaesthesiologist classification physical status I or II with normal kidney and liver function. Patients with liver cirrhosis, Hepatitis B or C and history of allergies were excluded.

A pilot study was carried out in our centre prior to commencement of this study. Mean time to identification of CVS was 9.7 min (±12.5) earlier using fluorescence cholangiography. Using this value, sample size calculation was performed. Considering 80% power (type II error of 1%), 5% marginal error (type I error for z value = 0.05) and 20% dropout rate, the sample size for each arm was 32, with total number of subjects of 64. Approval was obtained from the hospital’s medical research ethics committee (ID No: 201715–4749) and written consent was obtained from all the patients. This study also received a research grant of MYR 3000.00 (USD 709.72) for the purchase of indocyanine green dye, from UMMI Surgical, a distributor of Karl Storz Endoscopy System in Malaysia. This study was registered with ClinicalTrials.gov, NCT 04228835.

Patients were randomly assigned to two arms; ICG fluorescence cholangiography assisted laparoscopic cholecystectomy (ICGFC-LC) and conventional laparoscopic cholecystectomy (LC), using computer-generated block randomization. Patients in the ICGFC-LC group received an intravenous bolus of 2.5 mg of ICG in the preoperative holding area before induction of anaesthesia. All surgeries were performed using standard four ports technique. Near infrared light camera by Karl Storz Endoscopy was used for the ICGFC-LC group. The laparoscope captured fluorescent images via a foot pedal trigger and switched back to white light when the pedal was triggered the second time. The near infrared light camera was utilized intermittently during dissection of Calot’s triangle until critical view of safety was achieved. All surgeries were performed by a single surgeon who had four years of post-graduate surgical experience. Cases which necessitated conversion to open cholecystectomy or laparoscopic subtotal cholecystectomy were excluded from the statistical analysis as laparoscopic CVS was not established in these cases.

The data collected included patient characteristics, indication for surgery, time of ICG administration, time of identification of CVS and post-operative complications. Duration of identification of CVS was defined as time from gallbladder retraction until the time of successful establishment of CVS. In each case, difficulty of dissection of Calot’s triangle during the surgery was arbitrarily rated by the surgeon, from level 1 to 4. Higher amount of gallbladder adhesions, inflammation of the gallbladder and scarring at Calot’s triangle were given a higher level of difficulty. Intraoperative surgical difficulty was also scored using the scoring system devised by Japan-Korea-Taiwan expert Delphi consensus on surgical difficulty during laparoscopic cholecystectomy (Appendix 1).

Statistical analysis was performed using IBM SPSS version 20. Continuous variables were expressed as mean ± standard deviation (SD). Differences in categorical variables between groups were tested using Student’s t test, chi-square test, or Fisher’s exact test. Pearson’s correlation coefficient was used to measure the correlation between difficulty score based on Delphi consensus and the time to establishment of CVS.

3. Results

A total of 72 patients were recruited. In the final analysis, only 30 patients in ICGFC-LC arm, and 33 patients in LC arm were included. The exclusions for the ICGFC-LC arm were due to subcutaneous extravasation of the ICG at the intravenous catheter site, intraoperative gallbladder perforation during surgery, difficult gallbladders necessitating subtotal cholecystectomies and two conversions to open surgery. Three of the patients in the LC group needed conversion to open cholecystectomy. This is depicted in the following consort diagram (Diagram 1).

The mean age of the study population was 50 ± 14 years. The majority were females (67%). Ethnic distribution recorded 46% Malay, 30% Chinese followed by 24% of Indian descent. The mean Body Mass Index (BMI) of the study population was 26.2 ± 5.3. Both groups did not differ statistically in terms of distribution of age, ethnicity, gender, BMI, indication for surgery and presence of previous abdominal surgery (Table 1).

Most of the cases (46%, n = 29/63) had a level 2 difficulty arbitrary scoring Calot’s triangle dissection. 25% (n = 16/63) of the cases were level 1 while 21% (n = 13/63) were level 3 and only 8% (n = 5/63) of cases were level 4. The mean time to identification of CVS was 22.3 min for ICGFC-LC group and 22.8 min for LC group. With a difference of only 0.5 min earlier in the ICG fluorescence cholangiography group, this is not statistically significant. Across all difficulty levels, the time of identification of CVS was earlier with the help of fluorescence cholangiography. This was most pronounced in difficulty level 4: 42.0 ± 8.5 in ICGFC-LC group versus 46.3 ± 14.4 in LC group. The statistical calculation made in the subgroup analysis showed that the difference was not significant (Table 2).

Both groups were comparable in terms of intraoperative difficulty level and Delphi consensus difficulty scoring. Using the Delphi consensus on scoring of surgical difficulty during laparoscopic cholecystectomy, the score was normally distributed with a mean score of 7.5 and standard deviation of 5.1. When difficulty scores using the Japan-Korea-Taiwan expert Delphi consensus were analysed, the higher score indicated the interval that needed a longer duration to identify CVS. This is reflected by positive Pearson correlation coefficients (r value). However, the r value between the two groups were not significantly different (Table 3).

No major complications of common bile duct or hepatic duct injury occurred in this study. There were only minor complications of 2 superficial surgical site infections (SSI) in the ICGFC-LC group while the LC group had 1 superficial SSI and 1 umbilical haematoma. The superficial SSIs were treated successfully with wound dressing and antibiotics. The umbilical haematoma was small and resolved spontaneously.

4. Discussion

This is the first study undertaken to objectively investigate the application of fluorescence cholangiography in facilitating and...
shortening the time to identification of CVS comparing it to conventional white light laparoscopic cholecystectomy. An ideal primary end point would be differences in bile duct injury and conversion to open cholecystectomy, when using ICGFC-LC. However, this is not feasible because a large sample size is required for sufficient power due to their inherent low incidence rate. Previous studies have only evaluated time to identification of cystic duct and common bile duct without full dissection to achieve CVS. Buchs et al and Thomas et al reported a reduction of total operative time with the use of fluorescence cholangiography in robotic single site laparoscopic cholecystectomy. However, total operative time can be affected by many confounding factors and does not accurately represent the added advantage of fluorescence cholangiography. Schols et al reported earlier identification of common bile duct and cystic duct of 10 min and 11 min respectively in prospective patients using ICGFC. Recently, Lehrskov et al published their findings comparing fluorescence and x-ray cholangiography using visualization of biliary structures and time spent as outcome measures.

Our study was designed with time of identification of CVS as the primary objective because this parameter serves as a surrogate for easier dissection of Calot’s triangle, which fluorescence cholangiography can offer. The extrahepatic ducts appear in fluorescent blue or green when viewed using infra-red imaging and allows more confident dissection of the Calot’s triangle to achieve CVS (Fig. 1). This can often be challenging with the presence of fibrosis and scarring. A more confident dissection will thus result in a shorter time of surgery. The clinical importance of shorter surgery is a reduction in cost, and it allows more patients to be listed in each operating theatre list. In our hospital, where there is a long waiting list for laparoscopic cholecystectomy, a saving of 10 min for each case would cumulatively allow 40 min of theatre time saving (average of 4 cases in a 9 h long operative theatre list) and would potentially allow the increase from four to five cases of laparoscopic cholecystectomies per operative theatre day. It would also lead to cost saving of an estimated MYR 230.00 (USD 55.00) per patient for every 10 min saved, as the utilization cost of the operating theatre in our hospital is MYR 1400.00 (USD 331.20) per hour. The cost of a bottle of indocyanine green fluorescence dye in Malaysia is MYR 270.00 (USD 62.20) could be shared among 5 patients per operative day list. The total saving for each patient after deduction of the shared ICG is MYR 176.00 (USD 40.00).

Confidence in dissection of Calot’s triangle to achieve critical view of safety is also crucial for surgical training and safety. However, there is a lack of literature on assessing confidence in surgical training for laparoscopic surgery. Indocyanine green could be a tool in improving confidence of dissection among surgical trainees and new surgeons by providing a roadmap during dissection to avoid important extrahepatic biliary structures. Mercado et al described the “Vanishing Calot” where the inflammation between the gallbladder and the common hepatic duct is so intense, it obliterates the Calot’s triangle. This is often mistaken for Mirizzi Syndrome by unsuspecting junior surgeons. The authors have found that intense inflammation causes traction of the main duct during dissection and could lead to bile duct injury. ICGFC could prevent these complications by accurately identifying the common hepatic duct and cystic duct prior to dissection as the inflammatory tissue around the Calot would not illuminate. Decision could then be made early to change the approach of surgery, for example, performing a subtotal cholecystectomy instead. ICG FC has also been shown to be useful in identifying subvesical and aberrant bile ducts during cholecystectomies in several case reports. This allowed the operating surgeon to avoid injury to the aberrant ducts and detect intraoperative bile leak at the gallbladder bed.

The population studied was consistent with our local demographics. There are more female patients with biliary disease or complications requiring surgery, which is similar to published findings. The age of the patients undergoing surgery and the indications were consistent with existing data. The rate of conversion to open cholecystectomy in this study was 7%, which is comparable to reported rates of 5–10%. 
A single surgeon assessed the difficulty of the surgery to reduce bias. Although an arbitrary scoring was used, it was not without reference. The operating surgeon used the parameters of intraoperative adhesions, gallbladder appearance and fibrosis or scarring at the Calot’s as reference for deciding on the level of difficulty for Cholecystectomy. As the decision was arbitrary, the parameters were not individually broken down and analysed. There is currently no validated scoring system which addresses the difficulty of the whole surgery. The Japan-Korea-Taiwan expert Delphi consensus describes overall intraoperative difficulty from gallbladder retraction until the visualization of CVS as the key step in laparoscopic cholecystectomy. Devised and validated scoring systems such as the Japan-Korea-Taiwan Delphi consensus redefined difficulty of surgery to reduce time to CVS may not be demonstrated due to the experience and capability of the surgeon in identifying important biliary structures even without the aid of fluorescence cholangiography. Secondly, fluorescent light emitted by ICG has limited tissue penetration of 5–10 mm thickness.12 The light emitted may not penetrate through tissues of patients with thick peritoneal fat or patients with peritoneal scarring secondary to inflammation. This may affect visualization of biliary structures in the intra-abdominal inflammation, mild scarring at Calot’s triangle.
reached critical view of safety. The timing of administration of ICG may also affect the visualization during surgery. In a review of optimal timing of administration of ICG during fluorescence cholangiography, Zarrinpar et al recommended at least 45 min prior to visualization, and also concluded that a longer time interval resulted in better visualization. In our study, the mean time of ICG injection to skin incision is 58 min ± 23. The operating surgeon found that the visualization of the fluorescent biliary structures was adequate for interpretation. The operating surgeon noticed more confidence in dissection of the Calot’s triangle with the use of ICGFC. This provided a descriptive advantage in laparoscopic cholecystectomy rather than time based. The operating surgeon felt reassured during the transaction of cystic duct as the junction of the cystic duct – common hepatic duct was visualized clearly before transaction. This avoided the anxiety and risk of biliary complications such as tenting of cystic duct – common hepatic duct junction during clipping. The surgeon also found that fluorescence cholangiography helped in identification of important structures in a patient who eventually underwent subtotal cholecystectomy, thus avoiding bile duct injury. These factors are important especially for surgeons in training and general surgeons who are not comfortable with biliary anatomy in patients with acute or chronic inflammation.

Although our study did not show statistical advantage in the use of ICGFC for establishing CVS, it did show that ICG FC was safe and clinically not inferior. The use of ICG did not affect the total operative time in this study as the ICG was given preoperatively before induction but it did marginally increase the cost of treatment due to the use of the ICG fluorescent dye.

There were a few limitations in our study. First, this was a single centre experience. Although the use of a single surgeon in this study had the advantage of minimizing operator bias, the experience of other surgeons and centres should also be explored for this novel technique to be accepted widely. Secondly, the sample size calculated for this study was based on a preliminary pilot study that detected 9.7 min of difference in time to identification of CVS. To detect a smaller difference, a bigger sample size is required.

A multicentre study with a larger sample size maybe more representative and examine the use of ICGFC in biliary injury as well. An ongoing multicentre randomised controlled trial comparing time to identification of CVS with or without NIRF-C is currently being carried out in Netherlands. Further studies exploring the use of ICG fluorescence cholangiography in the training and teaching of laparoscopic cholecystectomy among surgical trainees are recommended. The authors feel that this novel technique has great potential in shortening the learning curve for laparoscopic cholecystectomy among surgical trainees and junior surgeons. Further studies should also be done on the potential use of ICGFC in time reduction and cost saving when operating on difficult gallbladders.

5. Conclusion

This is the first study conducted to evaluate reduction in time to identification of CVS using fluorescence cholangiography comparing to conventional white light laparoscopic cholecystectomy. Although earlier studies showed that the use of ICG fluorescence cholangiography resulted in earlier identification of biliary structures, this study showed that it did not translate into statistically or clinically significant earlier achievement of CVS. In the subgroup analysis, the highest difference of time to identification of CVS was found in difficulty level four. This may have potential benefit in surgical training and cost reduction but needs further investigation in view of small sample size of difficult cholecystectomies in this study. The use of ICGFC was safe, with no significant complications encountered in this study. In conclusion, we recommend the use of fluorescence cholangiography when it is feasible, especially for anticipated difficult cholecystectomies and in surgical training. However, further studies with larger sample size is needed.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Study grant: UMMI Surgical – Karl Storz Distributor (Malaysia)
APPENDIX 1. Difficulty score

Japan-Korea-Taiwan expert Delphi Consensus on surgical difficulty during laparoscopic cholecystectomy

<table>
<thead>
<tr>
<th>Intraoperative findings that potentially contribute to surgical difficulty</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Factors related to inflammation of the gallbladder</td>
<td></td>
</tr>
<tr>
<td>(a) Appearance around the gallbladder</td>
<td></td>
</tr>
<tr>
<td>1. Fibrotic adhesions around the gallbladder due to inflammation</td>
<td>2</td>
</tr>
<tr>
<td>2. Partial scarring adhesions around the gallbladder</td>
<td>2</td>
</tr>
<tr>
<td>3. Diffuse scarring adhesions around the gallbladder</td>
<td>2</td>
</tr>
<tr>
<td>(b) Appearance of the Calot's triangle area</td>
<td></td>
</tr>
<tr>
<td>4. Sparse fibrotic change in the Calot’s triangle area</td>
<td>4</td>
</tr>
<tr>
<td>5. Dense fibrotic change but no scarring in the Calot’s triangle area</td>
<td>3</td>
</tr>
<tr>
<td>6. Partial scarring in the Calot’s triangle area</td>
<td>4</td>
</tr>
<tr>
<td>7. Diffuse scarring in the Calot’s triangle area</td>
<td>5</td>
</tr>
<tr>
<td>(c) Appearance of the gallbladder bed</td>
<td></td>
</tr>
<tr>
<td>8. Sparse fibrotic change in the gallbladder bed</td>
<td>1</td>
</tr>
<tr>
<td>9. Dense fibrotic change but no scarring in the gallbladder bed</td>
<td>2</td>
</tr>
<tr>
<td>10. Partial scarring in the gallbladder bed</td>
<td>3</td>
</tr>
<tr>
<td>11. Diffuse scarring in the gallbladder bed</td>
<td>4</td>
</tr>
<tr>
<td>(includes atrophic gallbladder with no lumen due to severe contraction)</td>
<td></td>
</tr>
<tr>
<td>(d) Additional findings of the gallbladder and its surroundings</td>
<td></td>
</tr>
<tr>
<td>12. Edematous change around the gallbladder/in the Calot’s triangle area/in the gallbladder bed</td>
<td>1</td>
</tr>
<tr>
<td>13. Easy bleeding at dissection around the gallbladder/in the Calot’s triangle area/in the gallbladder bed</td>
<td>3</td>
</tr>
<tr>
<td>14. Necrotic changes around the gallbladder/in the Calot’s triangle area/in the gallbladder bed</td>
<td>4</td>
</tr>
<tr>
<td>15. Non-iatrogenic, perforated gallbladder wall and/or abscess formation towards the abdominal cavity noted during adhesiolysis around the gallbladder</td>
<td>3</td>
</tr>
<tr>
<td>16. Abscess formation towards the liver parenchyma</td>
<td>4</td>
</tr>
<tr>
<td>17. Cholecysto-enteric fistula</td>
<td>5</td>
</tr>
<tr>
<td>18. Cholecysto-choledochal fistula (included in the expanded classification of Mirizzi syndrome)</td>
<td>6</td>
</tr>
<tr>
<td>19. Impacted gallstone in the confluence of the cystic, common hepatic, and common bile duct (included in the expanded classification of Mirizzi syndrome)</td>
<td>5</td>
</tr>
<tr>
<td>B. Intra-abdominal factors unrelated to inflammation</td>
<td></td>
</tr>
<tr>
<td>20. Excessive visceral fat</td>
<td>2</td>
</tr>
<tr>
<td>21. Inversion the gallbladder in the gallbladder bed due to liver cirrhosis</td>
<td>4</td>
</tr>
<tr>
<td>22. Collateral vein formation due to liver cirrhosis</td>
<td>4</td>
</tr>
<tr>
<td>23. Non-inflammatory (physiological) adhesion around the gallbladder</td>
<td>1</td>
</tr>
<tr>
<td>24. Anomalous bile duct</td>
<td>4</td>
</tr>
<tr>
<td>25. Gallbladder neck mounting on the common bile duct</td>
<td>3</td>
</tr>
</tbody>
</table>

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