# The suitable time of laparoscopic cholecystectomy after endoscopic retrograde cholangiopancreatography in gallstone-disease-associated choledocholithiasis

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**Purpose**
To establish the feasibility, complications, and outcome of different time intervals between endoscopic retrograde cholangiopancreatography (ERCP) and laparoscopic cholecystectomy (LC) in the management of choledocholithiasis.
**Patients and methods**
This study was carried out on 60 patients who were randomized by systematic randomization into three equal groups according to the interval between ERCP and LC defined as short (3 days or less), medium (4–60 days), or long (60 days or more). All patients have undergone ERCP with sphincterotomy followed by elective LC. Patients' age, sex, history of previous acute cholecystitis, acute pancreatitis and jaundice, abdominal ultrasonography findings, serum bilirubin, alkaline phosphatase, gamma-glutamyl transferase levels, ERCP findings, time interval between ERCP and LC, conversion rate, median operative time, intraoperative complications, hospital stay, and postoperative complication rates were collected.
**Results**
There was no statistically significant difference between the demographics of the patients, the preoperative history, laboratory data or ultrasonographic findings in the three groups. The density of encountered adhesions intraoperatively, median operation time, and median postoperative hospital stay in groups 2 and 3 were significantly higher than those of group 1. Other intraoperative and postoperative complications or conversion showed no statistically significant difference.
**Conclusion**
Early cholecystectomy after ERCP within 72 h has better outcomes, probably due to less inflammatory processes following ERCP than in groups II and III.

**Keywords:**
cholecystectomy, endoscopic retrograde cholangiopancreatography, time interval

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## Introduction

Choledocholithiasis occurs in 10–15% of patients with symptomatic gallstone disease. Common bile duct (CBD) stones should be removed to avoid complications such as acute pancreatitis and cholangitis [1].

Traditional surgical treatment of CBD stones includes intraoperative cholangiography followed by choledochotomy with stone extraction and T-tube placement. This procedure was simpler and more straightforward since the guidelines for open CBD exploration are clearly defined [2].

The current options available for gallstone-disease-associated choledocholithiasis have been changed because of the advent of laparoscopic techniques and instrumentation. The management at the time of laparoscopic cholecystectomy (LC) includes preoperative endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic sphincterotomy, intraoperative ERCP, postoperative ERCP, laparoscopic transcystic CBD exploration, and laparoscopic choledochotomy with CBD exploration [3].

There is a debate about the ideal management for CBD stones; ERCP and LC versus single-stage laparoscopy, postoperative ERCP versus laparoscopic choledochotomy, and preoperative versus postoperative ERCP [4].

The laparoscopic CBD exploration is still not widely used because of the longer operative time, needed advanced experience, and expensive equipment [5].



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ERCP remains the best tool for treating CBD stones but the ideal timing of ERCP with respect to LC is not clearly defined [6].

The interval between ERCP and LC may vary from days to month [7].

The time effect on operation and operation outcome that elapsed between ERCP and LC is not well known [6].

It has been found that intropeative and postoperative complications and conversion to open surgery are more frequent in LC post-ERCP. However, the mechanisms underlying this pattern have not been identified [4].

In view of the above, the study was performed to demonstrate the best time interval between ERCP and LC in the management of patients with cholecystocholedocholithiasis.

## Patients and methods

This prospective, randomized controlled study was carried out on 60 patients with gallstone-disease-associated choledocholithiasis, who were simply randomized by the closed envelope method in which a comparison was held between three groups of patients presented with choledocholithiasis. This study was approved by the Institutional Review Board of Zagazig University Hospitals. The selected patients were randomly classified into three different groups of treatment according to the interval between ERCP and LC defined as short (3 days or less), medium (4–60 days), or long (60 days or more). ERCP with sphincterotomy was performed for all patients followed by elective LC.

From the inpatient we registered neither who have had complications related to ERCP, acute cholecystitis, cholangitis, pancreatitis, previous upper abdominal operation, history of peritonitis nor history of ERCP.

All patients were assessed clinically and abdominal ultrasonography (US) was also performed. Routine laboratory investigations were performed including serum bilirubin, alkaline phosphatase, amylase, alanine aminotransferase, aspartate aminotransferase, and gamma-glutamyl transferase levels. Informed consent was obtained from the patients.

The indications for ERCP include elevated serum bilirubin level, elevated alkaline phosphatase, elevated gamma-glutamyl transferase, dilated CBD (≥8 mm), and/or stones in the CBD on US examination.

The patient was kept Nil per os (NPO) for 8 h before the procedure. Prophylactic antibiotic with cefazolin sodium and intravenous 500 mg of metronidazole was given before ERCP. All patients were sedated with 10 mg intravenous dormicum. Surgery was performed under general anesthesia. All operations were performed by the same operation team.

### Endoscopic retrograde cholangiopancreatography technique

ERCP was carried out by using Pentax ED-3410 with video display, which is a side-viewing instrument that allows accurate visualization of the ampulla of Vater. Cannulation of ampulla of Vater and then sphincterotomy was performed by the sphincterotome contained cautery wire. The cautery wire was exposed for a length of 20–30 mm near the tip. After deep bile duct cannulation, the sphincterotome was retracted until one-half to two-thirds of the wire length was exposed outside the papilla. The length of the incision ranged from 0.5 to 1 cm. Then a guidewire was inserted through the cannula by which a balloon catheter was positioned for stone extraction.

Radiologic images were taken using a Digital C-arm fluoroscopy (Philips Pulsera model, Philips, Bothell, Washington; USA) which provided real time imaging of the biliary tree.

### Laparoscopic cholecystectomy technique

LC was performed by using the standard 4-trocar technique. Placement of the umbilical trocar was done after insertion of a Verres needle. Blunt dissection of the cystic duct and cystic artery was done according to the standard technique. Drain was inserted only in patients with difficult dissection or ruptured gallbladder. The operative time was calculated from the start of the incision until placement of the last suture.

### Postoperative follow-up

ERCP findings, time interval between ERCP and LC, conversion rate, median operation time, intraoperative complication, postoperative complication rates, and median postoperative hospital stay were collected.

### Statistical analysis

Collected data were tabulated. Numerical data were expressed by the mean±SD and categorical data were expressed as number and percent. Student's $t$ test was used to compare numerical data and $\chi^2$ test was used to

compare categorical data. *P* value was considered to be significant if it was less than 0.05.

## Results

This study was conducted from February 2014 to June 2017. Sixty patients with suspected choledocholithiasis who were referred to the Department of General Surgery, Zagazig University Hospitals were included in this study. All included patients were managed by ERCP followed by LC. The enrolled patients were divided into three groups (each=20 patients) according to the interval between the ERCP and LC: group 1with short interval (3 days or less), group 2 with medium interval (4–60 days), and group 3 with long interval (60 days or more).

The patients in the study were in the third and fourth decades, and women were predominant (63.3%). History of acute cholecystitis and jaundice was predominant in group 1 (18 and 16 patients, respectively) (Tables 1 and 2).

### Preoperative laboratory data were similar in the three groups

Preoperative US showed dilated CBD in the three groups that were ranging 10.6±2 in group I, 10.8±3.2 in group II, and 11.2±2.4 in group III, with no significant difference between the three groups (*P*=0.7) (Tables 3 and 4).

**Table 1 Distribution of age and sex**

| | *N*=60 |
|---|---|
| Age (years) | |
| Mean±SD | 38.5±11.8 |
| Range | 20–65 |
| Sex [*n* (%)] | |
| Male | 22 (36.7) |
| Female | 38 (63.3) |

Predominant female sex (63.35%) and ages mostly in the 30 and 40 s.

ERCP failed to extract CBD stone in two cases in group I, one case in group II, and two cases in group III, with no significant difference between the three groups (*P*=0.8) (Table 5).

There were significant adhesions of types 3 and 4 found in the intermediate and long interval groups with lower grade adhesions in group 1 (*P*=0.04) (Table 6).

Intraoperative bleeding occurred in five (8.3%) patients; one (5%) case each in groups 1 and 3; both cases had minimal bleeding from the gallbladder bed that was easily controlled with cautery. Intraoperative bleeding occurred in three (15%) cases in group 2; one had minimal from the bed that was controlled easily with cautery and the other two cases were due to missed posterior cystic branch in one case that was controlled by laparoscopic

**Table 3 Relation between preoperative laboratory data**

| | I (*N*=20) | II (*N*=20) | III (*N*=20) | *F* | *P* |
|---|---|---|---|---|---|
| Bilirubin | 3.1±1.7 | 2.95±1.4 | 3.5±1.8 | 0.65 | 0.5 |
| ALP | 253.5±87 | 228.7±109.4 | 274±110 | 0.97 | 0.38 |
| GGT | 296.2±127 | 330.7±104.5 | 346.1±131 | 0.88 | 0.41 |

Data are presented as mean±SD. The three groups are similar in preoperative laboratory data. ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase.

**Table 4 Relation between preoperative ultrasonographic**

| | I (*N*=20) | II (*N*=20) | III (*N*=20) | $\chi^2$/*F* | *P* |
|---|---|---|---|---|---|
| Gallbladder stone number | 5 (25) | 7 (35) | 4 (20) | 1.19 | 0.55 |
| Gallbladder stone size | 7.15 ±2.5 | 7.2 ±2.9 | 7.4±2.5 | *F*=0.05 | 0.95 |
| CBD stones | 14 (70) | 11 (55) | 12 (60) | $\chi^2$=0.99 | 0.6 |
| CBD diameter | 10.6±2 | 10.8 ±3.2 | 11.2 ±2.4 | *F*=0.3 | 0.7 |

CBD, common bile duct. Data are presented as *n* (%) and mean ±SD. No significant difference between the three groups regarding ultrsonographic findings.

**Table 2 Relation between demographic data and clinical history**

| | I (*N*=20) | II (*N*=20) | III (*N*=20) | *F* | *P* |
|---|---|---|---|---|---|
| Age (years) | | | | | |
| Mean±SD | 38.5±11.8 | 39.1±12.9 | 38.4±11.4 | 0.03 | 0.96 |
| Range | 21–60 | 20–65 | 23–65 | | |
| Sex [*n* (%)] | | | | | |
| Male | 5 (25) | 9 (45) | 8 (40) | $\chi^2$=1.87 | 0.39 |
| Female | 15 (75) | 11 (55) | 12 (60) | | |
| History of acute cholecystitis | 18 (40) | 2 (10) | 7 (35) | $\chi^2$=5.09 | 0.07 |
| History of jaundice | 16 (80) | 14 (70) | 12 (60) | $\chi^2$=1.9 | 0.38 |
| History of pancreatitis | 1 (5) | 0 (0) | 1 (5) | $\chi^2$=1.03 | 0.6 |

History of acute cholecystitis and jaundice were predominant in group I.

clipping and the other due to rapid accumulation of blood together with unclear anatomy necessitated conversion to open surgery (Table 6).

In group 1, LC was attempted in 20 patients and all of them completed laparoscopically. In group 2, LC was attempted in 20 patients, of which two (10%) were converted to open cholecystectomy due to gallbladder bed bleeding (one patient) or dense adhesions in Callot's triangle (one patient) and in group 3, LC was attempted in 20 patients, of which one (5%) patient was converted to open cholecystectomy due to intraoperative CBD injury secondary to accidently discovered Mirizzi syndrome (Table 6).

**Table 5 Stone extraction by endoscopic retrograde cholangiopancreatography**

| | I (*N*=20) [*n* (%)] | II (*N*=20) [*n* (%)] | III (*N*=20) [*n* (%)] | $\chi^2$ | *P* |
|---|---|---|---|---|---|
| Yes | 18 (90) | 19 (95) | 18 (90) | 0.44 | 0.8 |
| No | 2 (10) | 1 (5) | 2 (10) | | NS |

ERCP, endoscopic retrograde cholangiopancreatography. No significant difference between the study groups regarding stone extraction by ERCP (*P*=0.8).

The median operation time in group 1 (39.5±15.5) was significantly shorter than the other two groups. The groups were found to be similar with no significant difference in gallbladder appearance, intraoperative gallbladder rupture, intraoperative bleeding, and conversion rate (Table 6).

Postoperative wound infection was reported in seven (11.7) cases as follows: one (5%) case in group I, four (20%) cases in group II, and two (10%) cases in group III. The wound infection paralleled two events, rupture gallbladder and conversion. Postoperative collection was reported only in one (1.7%) case in the whole study in group II due to difficult laparoscopic dissection with intraoperative rupture gallbladder reported; postoperative fever and right shoulder pain persists for 3 days and US showed turbid collection and US-guided drainage was done. The hospital stay in days was significantly lower in group I, 1.5±0.6, while in group II it was 2±0.8, and in group III it was 2.75±2.3 (*P*=0.03). The three groups showed no significant statistical difference with respect to postoperative pain, wound infection, and collection. We reported neither postoperative CBD injury nor mortality (Table 7).

**Table 6 Intraoperative findings and complications**

| | I (*N*=20) | II (*N*=20) | III (*N*=20) | $\chi^2$ | *P* |
|---|---|---|---|---|---|
| Adhesions | | | | | |
| Type 1 | 11 (55.0) | 5 (25.0) | 3 (15.0) | | |
| Type 2 | 8 (40.0) | 6 (30.0) | 7 (35.0) | | |
| Type 3 | 1 (5.0) | 8 (40.0) | 9 (45.0) | 15.52 | 0.04* |
| Type 4 | 0 (0.00) | 1 (5.0) | 1 (5.0) | | |
| Visceral injury | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 | 1 |
| Intraoperative bleeding | 1 (5) | 3 (15) | 1 (5) | 1.75 | 0.4 |
| Gallbladder rupture | 1 (5) | 2 (10) | 1 (5) | 0.54 | 0.76 |
| Intraoperative CBD injury | 0 (0) | 0 (0) | 1 (5) | 2.03 | 0.36 |
| Conversion | 0 (0) | 2 (10) | 1 (5) | 2.11 | 0.34 |
| Operative time [mean±SD (median)] | 39.5±15.5 | 54.7±23 | 57.3±19.1 | 4.7 | 0.012* |

CBD, common bile duct. There were significant difference regarding adhesions type (*P*=0.04) and operative time (*P*=0.12). *significance difference P<0.05.

**Table 7 Postoperative findings**

| | I (*N*=20) [*n* (%)] | II (*N*=20) [*n* (%)] | III (*N*=20) [*n* (%)] | $\chi^2$ | *P* |
|---|---|---|---|---|---|
| Postoperative CBD injury | 0 (0) | 0 (0) | 0 (0) | 0 | 1 |
| Postoperative collection | 0 (0) | 1 (5) | 0 (0) | 2.03 | 0.36 |
| Postoperative wound infection | 1 (5) | 4 (20) | 2 (10) | 2.26 | 0.3 |
| Postoperative pain | | | | | |
| Type 1 | 12 (60) | 5 (25) | 10 (50) | | |
| Type 2 | 7 (35) | 10 (50) | 8 (40) | 6.7 | 0.1 |
| Type 3 | 1 (5) | 5 (25) | 2 (10) | | |
| Hospital stay (mean±SD) | 1.5±0.6 | 2± 0.8 | 2.75±2.3 | 3.61 | 0.03* |
| Range | 1–3 | 1–4 | 1–10 | | |
| Mortality | 0 | 0 | 0 | 0 | 1 |

CBD, common bile duct. There is significant difference between the three groups regarding hospital stay (*P*=0.03) with shorter hospital stay in group I.

## Discussion

The presence of CBD stone significantly increases the morbidity, mortality, and costs of patients with gallstones [8].

The obvious goal of treatment in choledocholithiasis is to remove the stones with the fewest number of interventions, lowest cost, and least morbidity [4].

Postponing LC after ERCP makes it difficult to be performed due to the possibility of adhesions at the area of Calot's triangle, besides the risk of second-time anesthesia [9].

The total number of patients in our study was 60 patients, 22 (36.7%) men and 38 (63.3%) women. The ages in this study ranged between 20 and 65 years. The sex distribution in this study showed that cholecystocholedocholithiasis was predominant in women with a woman to man ratio of about 3 : 2. This was in agreement with Stanley *et al.* [10] who found that the gallstones and CBD stones were more common in women.

The most common decades of life for the development of cholecystocholedocholithiasis in this study were the fourth and fifth decades (40%) of our patients. This was in some agreement with Stanley *et al.* [10] and Topal *et al.* [11] who reported that the gallstones and CBD stones were more common in the fourth to fifth decades of life.

Jaundice was the most common complaint reported in 42 patients followed by a history of acute cholecystitis in 17 patients and then history of acute pancreatitis in two patients. Disturbance of liver functions was detected in 86.7% of our patients.

Freitas *et al.* [12] and Yang *et al.* [13] reported that majority of patients with CBD stones have abnormal liver function tests.

Abdominal US showed gallstones in all patients. Dilatation of CBD with stones inside was detected in 56 patients only. This denotes that US is highly accurate for the detection of gallstones (100%), but less accurate for the detection of CBD stones (93%). Costi *et al.* [14] found that the sensitivity of US for the detection of gallstones and CBD stones was 80–100% and 30–90%, respectively.

Liu *et al.* [15] reported that the sensitivity of US for detecting CBD stones was 55–91%.

Magnetic resonance cholangiopancreatography (MRCP) is very helpful in the diagnosis of CBD stones in patients who had equivocal results on abdominal US. MRCP has an excellent overall sensitivity of 95% and a specificity of 97% for demonstrating CBD stones with no significant differences between it and endoscopic US in the detection rate of CBD stones [16,17].

We gave preoperative intramuscular injection of vitamin K 10 mg twice daily for 3 days for patients with slightly prolonged Prothrombin time (PT). This was also reported by Leon *et al.* [18] who denoted that vitamin K deficiencies are common in patients with obstructive jaundice.

Prophylactic broad-spectrum antibiotic (cefoperazone sodium) has potential use as it covers common biliary flora. It was given intravenously in a dose of 1 g immediately before the procedure and continued for 1–3 days for patients with intraoperative gallbladder rupture or CBD injury. This also was supported by Bratzler *et al.* [19] but disagreed with Banerjee *et al.* [20] who denoted that antibiotic prophylaxis is not recommended before any operative intervention when obstructive biliary tract disease is not suspected.

Isoflurane undergoes less hepatic metabolism [19]. So, it was our anesthetic drug of choice for all of our patients.

This study was carried out on 60 patients who were randomized by systematic randomization into three equal groups according to the interval between ERCP and LC defined as short (3 days or less), medium (4–60 days), or long (60 days or more).

We did a comparison between the three groups regarding intraoperative and postoperative complications, conversion rate, operative time, and hospital stay.

The intraoperative adhesions in group I were mainly of types 1 and 2 11 (55%) and eight (40%), respectively. In group II, five (25%) of type 1, six (30%) of type 2, eight (40%) of type 3, and one (5%) of type 4. In group III, three (15%) of type 1, seven (35%) of type 2, nine (45%) of type 3, and one (5%) of type 4 ($P$=0.04). This favors group I with less dense adhesions prevailed and this goes with the results of Salman *et al.* [5].

Regarding intraoperative bleeding, five (8.3%) patients were reported. Only one (5%) case in each group I and group III and were minimal bleeding from the

gallbladder bed that was easily controlled with cautery. Three (15%) cases of intraoperative bleeding in group II, one with minimal bleeding from the bed and was cauterized and the other two cases were due to the missed posterior cystic artery branch, one that was controlled by laparoscopic clipping and the other due to rapid accumulation of blood together with unclear anatomy necessitated conversion to open surgery and this was one of the two (5%) converted cases in the whole study.

In group I, LC was attempted in 20 patients and all of them were completed laparoscopically with conversion rate zero. In group II, LC was attempted in 20 patients, of which two (10%) cases were converted to open cholecystectomy due to gallbladder bed bleeding (one patient) or dense adhesions in Calot's triangle (one patient) and in group III, LC was attempted in 20 patients, of which one (5%) was converted to open cholecystectomy due to intraoperative CBD injury secondary to accidently discovered Mirizzi syndrome.

Bostanci *et al.* [2] found that higher conversion rates (13–16%) were associated with the performance of multiple preoperative ERCPs, but not with the performance of stone extraction on preoperative ERCP, and this suggests that the ERCP procedure itself may have an effect independent of gallstone disease. However, in our study we have excluded cases with multiple ERCP and stone extraction during ERCP has no relation with conversion rate.

Salman *et al.* [3] investigated the effects of the time interval between ERCP and LC on operation outcomes showing conversion rate in patients who had LC within 24–72 h after ERCP was significantly lower compared with the patients who had LC within 72 h to 7 days (2.5 vs. 17.5%) ($P$=0.02).

Hassanen [21] showed that the conversion rate was 5.8% in the early group versus 56.2% in the delayed group ($P$=0.006) but with a small study that included 33 patients.

We also found that post-ERCP time interval and conversion rates were not associated with each other in agreement with that of Bostanci *et al.* [2].

The conversion rate is affected by the skills and learning curve of surgeons who are doing the LC. The surgeons performing LC during their learning curve are associated with a high conversion rate [9]. In the present study, all patients in the three groups were operated upon by a single surgeon. This eliminated the factor of different surgical skills which may affect the incidence of conversion rate.

The median operative time in group I was 39.5 ±15.5 min, in group II 54.7±23 min, in group III 57.3±19.1 with a shorter operative time in group I ($P$=0.012) and this reflects the adhesion score deference in the groups.

The groups were found to be similar with no significant difference with respect to gallbladder appearance, intraoperative gallbladder rupture, and intraoperative bleeding and conversion rate. There was no mortality-related procedure in both groups.

Postoperative wound infection was reported in seven (11.7%) cases as follows: one (5%) case in group I, four (20%) cases in group II, and two (10%) cases in group III. Hassanen [21] found that the incidence of wound infection was detected in one (5.8%) patient in the early group versus five (31.2%) patients in the delayed group ($P$=0.03).We have noted that wound infection paralleled two events, rupture gallbladder, and conversion. Postoperative collection was reported only in one (1.7%) case in the whole study; this was in group II (5%) in a case with difficult intraoperative rupture gallbladder but was completed laparoscopically. The patient experienced postoperative fever and right shoulder pain that persisted for 3 days and abdominal US showed a turbid collection at the gallbladder bed and was completely aspirated.

In this study, the hospital stay in days was in group I (1.5±0.6), group II (2±0.8), and group III (2.75±2.3). The median postoperative hospital stay was statistically significant between the three groups ($P$=0.03) as there were more patients in groups II and III who were converted to open cholecystectomy, longer anesthesia time, and more postoperative complications, such as wound infections, collection, and pulmonary atelectasis and this is consistent with the results of Salman *et al.* [3]. But in contrast Suvikapakornkul *et al.* [22] showed that there was no difference in hospital stay between the single stage and sequential groups.

This work showed that postoperative CBD injury and mortality was zero. The three groups were found to be similar with no significant statistical difference with respect to postoperative pain, wound infection, and collection; this is consistent with the results of Bostanci *et al.* [2] and Salman *et al.* [3].

## Conclusion

Conversion to open surgery and serious intraoperative and postoperative complications did not seem to be affected by the time interval between ERCP and LC. The main difference between the groups were seen in the score of encountered intraoperative adhesions in favor of the short interval group. Shorter operative time and hospital stay was seen in the early group with less cost and earlier return to work, and fewer admissions.

In conclusion, the operation after 72 h was more difficult in patients who undergo preoperative ERCP due to adhesions at Calot's triangle. It is better to perform LC 24–72 h after ERCP.

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**Conflicts of interest**

There are no conflicts of interest.

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