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A Comparative Study between Early versus Delayed Laparoscopic Cholecystectomy in Cases of Acute Calcular Cholecystitis

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Abstract: Background: Gall bladder disease is among the leading causes for hospital admission for acute abdomen among adults and the most common indication for abdominal surgery in the elderly. Gallstones are common and present as acute calculus cholecystitis (ACC) in 20 % of patients with symptomatic disease, with wide variation in severity. In developed countries, 10–15 % of the adult population is affected by gallstones. **Objectives:** The aim of this study is to prospectively compare between early and delayed laparoscopic cholecystectomy as a management of acute calcular cholecystitis along with their operative and post-operative outcomes. **Patients and Methods:** This is a prospective randomized study conducted on thirty (30) patients presenting to Ain-Shams University hospitals with acute calcular cholecystitis starting from December 2018 to July 2019. Included patients will be randomized, by opening one of two (2) sealed envelopes at the time of admission. Patients will be divided into two groups, fifteen (15) patients each: Group (A): will undergo laparoscopic cholecystectomy during the first 72 hours, Group (B): will undergo laparoscopic cholecystectomy after 6 to 8 weeks (after complete resolution of the acute attack). An informed consent will be taken from all the patients sharing in the study about the procedure they will have. **Results:** The mean operative time in the early group was more than the mean operative time in the delayed group. The conversion rate to open cholecystectomy in the early group was less than the conversion rate in the delayed group. The mean total hospital stay in the early group was less than the mean total hospital stay in the delayed group. Finally, the overall complications in the early group was less than complications occurred in the delayed group. **Conclusion:** Laparoscopic cholecystectomy can be performed safely for acute cholecystitis, with acceptable low conversion and complication rates. Early timing of laparoscopic cholecystectomy in relation to the onset of gall bladder inflammation may reduce the conversion rate and the total complication rate. The morbidity of laparoscopic cholecystectomy for patients with acute cholecystitis is not reduced by a long period of initial conservative treatment. For surgeons with adequate experience, the optimal timing of laparoscopic cholecystectomy for treatment of acute cholecystitis is within 72 hours of admission.

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1. Introduction

Gall bladder disease is among the leading causes for hospital admission for acute abdomen among adults and the most common indication for abdominal surgery in the elderly **(Ukkonen et al., 2015).**

Gallstones are common and present as acute calculus cholecystitis (ACC) in 20 % of patients with symptomatic disease, with wide variation in severity. In developed countries, 10–15 % of the adult population is affected by gallstones **(Shaffer, 2005).**

Acute cholecystitis (AC) is one of the important causes of abdominal pain on presentation to the emergency department. Early diagnosis and treatment of AC has a positive effect on morbidity and mortality **(Yokoe et al., 2012).**

Acute cholecystitis is usually diagnosed based on the presence of non-characteristic local and/or systemic inflammatory findings and/or the result of ultrasonographic examination **(Sekimoto et al., 2007).**

Although there are no specific diagnostic criteria for AC, if it is seen at an advanced stage, it may lead to mortality. The grading of AC is necessary for not only defining the severity of AC but also planning early or elective cholecystectomy **(Miura et al., 2013).**

Cholecystectomy has since long been the therapy of choice for elective treatment of patients with symptomatic gallstone disease **(Chang et al., 2009).**

The standard treatment for symptomatic cholecystitis associated with gallstones is cholecystectomy. Laparoscopic cholecystectomy (LC)

has replaced conventional open cholecystectomy and has become the gold standard of treatment for acute cholecystitis (AC). In recent years, laparoscopic surgery has been confirmed to be preferable to open surgery in elective cholecystectomy cases. Open cholecystectomy (OC) used to be preferred because of the technical difficulties and the high complication rates associated with LC. However, several studies have shown that LC is safe and can be recommended as a form of cholecystectomy **(Teoh et al., 2007).**

Laparoscopic cholecystectomy (LC) is an important approach for treating acute cholecystitis nowadays. Issued data indicated that approximately 917,000 and >50,000 LCs were annually performed to treat acute cholecystitis in the United States and England, respectively **(Wu et al., 2015).**

Another controversial topic is the optimal timing of surgery in AC, where one of the issues is whether it should be operated early (i.e., within the first 48 to 96 h) or delayed (within the same hospital stay), depending on the actual practical and logistic circumstances **(Lau et al., 2006).**

Over the years, it has been claimed that AC can be primarily treated conservatively and then followed by delayed elective cholecystectomy. In recent decades, evidence has been gathered to show that early cholecystectomy for AC during the acute hospital stay is safe and cost-effective **(Casillas et al., 2008).**

Traditionally, given the higher rate of morbidity such as bile duct injury, leakage, and conversion to open surgery, the delayed LC (DLC), which is defined as at least 1 week after initial conservative treatment, is commonly adopted in treating acute cholecystitis. However, several clinical studies supported early LC (ELC) (within 7 days of the onset of symptoms) to treat acute cholecystitis **(Zhou et al., 2014).**

Thus, in the late 1980s early surgery for acute cholecystitis had gained popularity. The updated Tokyo Guidelines announced in 2013 by the Japanese Society of Hepato-Biliary-Pancreatic Surgery suggested that early laparoscopic cholecystectomy is the first-line treatment in patients with mild acute cholecystitis, whereas in patients with moderate acute cholecystitis, delayed/elective laparoscopic cholecystectomy after initial medical treatment with antimicrobial agent is the first-line treatment.

A French nationwide registry study has recently shown that operation within 3 days after admission is recommended in patients with acute cholecystitis **(Polo et al., 2015).**

Aim of the work

The aim of this study is to prospectively compare between early and delayed laparoscopic cholecystectomy as a management of acute calcular cholecystitis along with their operative and post-operative outcomes.

2. Patients and Methods

Patients

This is a prospective randomized study conducted on thirty (30) patients presenting to Ain-Shams University hospitals with acute calcular cholecystitis starting from December 2018 to July 2019.

Included patients will be randomized, by opening one of two (2) sealed envelopes at the time of admission.

Patients will be divided into two groups, fifteen (15) patients each.

Group (A): will undergo laparoscopic cholecystectomy during the first 72 hours.

Group (B): will undergo laparoscopic cholecystectomy after 6 to 8 weeks (after complete resolution of the acute attack).

An informed consent will be taken from all the patients sharing in the study about the procedure they will have.

Inclusion Criteria:

1) Adult patients (males and females) above 16 years of age.
2) Symptoms and signs of acute cholecystitis.

Exclusion criteria:

1) Patients under 16 years of age.
2) Pregnant females during their third trimester.
3) Patients with previous major abdominal surgeries or midline exploratory surgeries.

Methods

Pre-operative assessment:

1- Clinical assessment:

Good history taking (including history of previous attacks of acute cholecystitis and history of jaundice), together with full general and local examination.

A. General: full general examination was done for all patients, focusing on:

- Vital data (Fever).
- Complexion (Jaundice).
- Cardio-vascular fitness.
- Respiratory fitness.

B. Local: full abdominal examination was done for all patients focusing on:

- Right hypochondrial tenderness.
- Scars of previous operations (mainly in the upper abdomen).
- Abdominal wall hernias.

2- Imaging investigations:

- Pelviabdominal ultrasound will be needed for diagnosis.
- MRCP will be used in certain cases.

- General preoperative imaging as chest x- ray, ECG and echocardiogram (if needed).

3- Laboratory investigations:

Complete blood count, coagulation profile (PT, PTT, INR), kidney function tests (BUN, serum creatinine), liver function tests (ALT, AST), total bilirubin, direct bilirubin, alkaline phosphatase and gamma glutamyl transferase (if needed).

All patients received the following line of treatment on admission:

- Nothing per mouth (N.P.O) which continued for the early group (A) till the time of the operation which ranged from 30 to 60 hours, while nothing per mouth for the delayed group (B) continued till the attack subsided and symptoms improved (no fever, tachycardia or leucocytosis) which ranged from 24 to 58 hours after admission.
- Intra venous fluids (500 cm Glucose 5% every 8 hours, 500 cm Ringer solution every 12 hours and 500cm Normal Saline every 24 hours).
- Broad spectrum third generation cephalosporins antibiotic injection 1gram every 12 hours for 5 days.
- All patients in both groups received analgesic in the form of sodium diclofenac (Voltaren) 75 mg every 12 hours with antispasmodic injection for 24 hours and was given narcotic as Pethidine 50mg when needed.

Operative Details:

1- Preparation and Positioning

2- Insertion of ports and creation of pneumoperitoneum

3- Dissection of the cystic pedicle

4- Dissection of the gallbladder from its liver bed

5- Extraction of the gallbladder

In this study, when conversion to open cholecystectomy was necessary (due to difficult dissection at Calot's triangle) a right subcostal incision was performed, the area was isolated with packs, the neck of the gallbladder was grasped with sponge holding forceps, the cystic artery was divided between ligatures, the cystic duct was then ligated and divided, the gallbladder was dissected from its liver bed, then was removed, haemostasis assured and the abdominal wall was closed in layers.

Post-operative evaluation:

Post-operative workup and follow up

1- All patients received intra-venous fluids for only 12 hours followed by oral fluids and soft diet.

2- All Patients received intravenous third generation cephalosporin for 1 day postoperatively every 12 hours.

3- The patients were discharged after removal of the drain and when they were open bowel and tolerating oral intake.

4- The patients were followed during the hospital stay then regularly until complete recovery for signs of post-operative complications as intra-peritoneal bleeding or biliary injury (including tachycardia, hypotension, jaundice and gallbladder bed collection detected by follow up abdominal ultrasound). This was followed by a visit 1 week later for follow up to detect of any late complications.

5- All patients were followed up for any complications at site of incision including wound infection and port site hernia.

The post-operative outcome of the surgery on both groups of patients will be evaluated.

Statistical analysis

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 20. The qualitative data were presented as number and percentages while quantitative data were presented as mean, standard deviations and ranges when their distribution found parametric. So, the p-value was considered significant as the following: $P > 0.05$: Non- significant, $P < 0.05$: Significant, $P < 0.01$: Highly significant.

3. Results

Table (1): Comparison between patient's criteria and co- morbidities of group (A) and group (B)

	Group (A)	Group (B)	P Value
Age (years)	47.8 ± 11.46	48.9 ± 10.67	0.788
Sex (M: F)	6: 9	4: 11	0.439
D.M.	2	2	1.000
Hypertension.	5	6	0.704

There were five patients in group (A) having hypertension and their blood pressure was controlled prior to surgery while in group (B) there were six patients having hypertension.

Table (2): History of biliary colic in both groups

Biliary colic in history		Groups					
		Group A		Group B		Total	
		N	%	N	%	N	%
No		12	80	13	86.7	25	83.3
Yes		3	20	2	13.3	5	16.7
Total		15	100	15	100	30	100
Chi-square	X^2	0.240					
	P-value	0.624					

In group (A) three patients gave history of previous attacks of biliary colic while in group (B) two patients gave history of previous attacks of biliary colic.

Table (3): Comparison between lab. Investigations and U/S findings in group (A) and group (B).

	Group (A)		Group (B)		P value
	Number of patients.	%	Number of patients.	%	
WBC >11.000/ml	10	66.7	8	53.3	0.456
Thick GB wall	10	66.7	9	60	0.704
Distended GB	13	86.7	11	73.3	0.361
Pericholecystic coll.	2	13.3	2	13.3	1.000

The correlation between the two groups showed that 66.7% of cases of group (A) had thick gallbladder wall, while 60% of cases of group (B) had thick gallbladder wall and the difference between them is not significant. Distended gallbladder was found in 86.7 % of cases in group (A) and 73.3% of cases in group (B) and the difference between the two groups is not significant. Finally, pericholecystic fluid collection was found in 13.3 % of cases in group (A) and also in 13.3 % of cases in group (B).

Table (4): Intraoperative modifications in group (A) and group (B)

	Group (A)		Group (B)		
	Number of Patients	%	Number of Patients	%	P value
Conversion	1	6.7	2	13.3	0.543
GB decompression	11	73.3	3	20	0.003
Widening of epigastric port	2	13.3	2	13.3	1.000

The correlation between the two groups showed that there is statistically significant difference in favor of group (B) as regard gallbladder decompression and there is no difference as regard widening of epigastric port.

Table (5): Intraoperative and postoperative complications in group (A) & group (B)

	Group (A)		Group (B)		
	Number of patients.	%	Number of patients.	%	P value
Bleeding	1	6.7	0	0	0.309
Wound infection	2	13.3	2	13.3	1.000
Bile leak	1	6.7	0	0	0.309
Collection	1	6.7	2	13.3	0.543
Jaundice	0	0	1	6.7	0.309
Post. op. complications	3	20	5	33.3	0.409

Postoperative complications occurred in 3 cases of group (A) while postoperative complications occurred in 5 cases of group (B).

Table (6): Total hospital stay in group (A) & group (B)

Groups	Hospital stay					P-value
	Range			Mean	± SD	
Group A	3.5	-	6	4.80	± 0.91	<0.001
Group B	7	-	12	9.20	± 1.61	

The correlation between the two groups showed that there is statistically significant difference in favor of group (A) denoting that surgery in the early group is more economic because of less hospital stay.

4. Discussion

Acute cholecystitis is the most common cause of hospitalization for gastrointestinal disease. Although cholecystectomy is the definitive management, the timing of surgery in relation to the first episode of acute cholecystitis remains an area of considerable practice variation. Operative intervention is either undertaken early on first presenting admission or, may be delayed some 6 to 8 weeks after initial nonoperative management to allow the acute inflammation to settle **(De Mestral et al., 2013).**

Several randomized controlled trials have shown that early laparoscopic cholecystectomy (within up to 7 days of symptom onset) is associated with a shorter total hospital length of stay and a similar rate of conversion to an open procedure, when compared with delayed cholecystectomy **(Yamashita et al., 2013).**

Furthermore, early surgery precludes the risk of recurrent gallstone-related symptoms, estimated to affect nearly 20% of patients. However, despite this evidence and expert consensus supporting early laparoscopic cholecystectomy, rates of early surgery remain variable. Because concern remains that rare but devastating complication such as major bile duct injury or death may occur more frequently in the setting of emergency surgery on an acutely inflamed gallbladder **(Greenstein et al., 2012).**

This study included thirty patients with acute calcular cholecystitis, the patients were classified into two groups each group consisted of fifteen patients:

Group (A): underwent laparoscopic cholecystectomy in the first 72 hours from the onset of symptoms after initial period of conservative treatment.

Group (B): underwent delayed interval laparoscopic cholecystectomy in six to eight weeks after initial period of conservative treatment.

In this study, the male to female ratio in the early group was 6: 9, while the male to female ratio in the delayed group was 4: 11.

According to **Sushant et al. (2013)** the male to female ratio in the early group was 4: 26, while the male to female ratio in the delayed group was 2: 28.

In this study, the range of age of patients with acute cholecystitis in the early group was 30 to 65 years with a mean age of 47 ± 11.46 years, and the range of age of patients with acute cholecystitis in the delayed group was 32 to 70 with a mean age of 48.9 ±10.67 years.

In consistent with **Eldar et al. (2005)**, the range of the age of patients with acute cholecystitis going to laparoscopic cholecystectomy was 18 to 92 years with a mean of 62 ± 15 years.

According to **Greenwald et al. (2010)** the mean of age of patients with acute cholecystitis undergoing laparoscopic cholecystectomy was 49.6 ± 17.3 years. The extreme of age of patients in the study of **Eldar et al. (2005)** may explain the higher rate of conversion to open cholecystectomy which was 24%. While according to **Greenwald et al. (2010)** the mean of age of patients was 49.6 years which is close to our mean of age of patients that is why the rate of conversion to open cholecystectomy in **Greenwald et al. (2010)** was 13%. While the rate of conversion in our study was 10% (1 case in the early group out of 15 patients and 2 cases in the delayed group out of 15 patients).

In this study, the duration of acute symptoms in the early group ranged from 16 to 54 hours with mean of 35.6 ± 11.17 hours and the range of duration of acute symptoms in the delayed group was 12 to 60 hours with mean of 36.6 ± 14.38 hours.

In the same line with **Kolla et al. (2004)** the range of duration of acute symptoms in early group was 35.1 ± 19.1 hours and the range of duration of acute symptoms in delayed group was 36.1 ± 24.7 hours.

In this study, the white blood cell count was found to be more than 11.000/ml in 10 cases in the early group and 8 cases in the delayed group. According to **Sushant et al. (2013)** white blood cell count was found to be more than 11.000/ml in 18 patients out of 30 patients and 15 patients out of 30 patients respectively.

Ultrasound is usually the initial screening examination for biliary colic, and is also sensitive for the detection of acute cholecystitis and gallbladder stones. It is widely available and relatively inexpensive. Ultrasound is extremely sensitive for the detection of gall stones, gall bladder wall thickening and pericholecystic fluid collection and permits an assessment of the location patient's pain in relation to the gall bladder **(Hirota et al., 2007).**

In this study, abdominal ultrasound findings in the early group were thickened gall bladder wall in 10 patients out of 15 patients (66.7%) and thickened gall bladder wall in 9 patients out of 15 (60%) patients in the delayed group. Distended gall bladder was found in 13 cases in the early group (86.7%) and 11 cases in the delayed group (73.3%) also pericholecystic collection was found in 2 cases (13.3%) in the early group as well as in the delayed group.

According to **Kolla et al. (2004)** abdominal ultrasound findings in the early group were thickened gall bladder wall in 60% of the patients and thickened gall bladder wall in the delayed group was found in

55% of the patients. Distended gall bladder was found in 85% of the patients from the early group and in 75% of the patients from the delayed group, also pericholecystic collection was found in 15% of the patients from the early group and the same in the delayed group.

In the current study, the operative time in the early group was ranged from 55 to 140 minutes with a mean of 95.3 ± 14.75 minutes and the operative time in the delayed group was ranged from 45 to 106 minutes with a mean of 75.3 ± 12.4 minutes. The relatively longer operative time in the early group could be explained by time taken for dissection of adhesions, difficulty of grasping the gall bladder and some modifications as aspiration of the gallbladder.

According to **Sushant et al. (2013)** the mean operative time in the early group was 65.78 minutes and the mean operative time in the delayed group was 56.83 minutes, according to **Kolla et al. (2004)** the mean operative time in the early group was104.3 ± 44 minutes and the mean operative time in the delayed group was 93 ± 45 minutes.

In this study, the conversion rate to open cholecystectomy in the early group was 6.7% (1 case due to difficulty of dissection in Calot's triangle and intraoperative bleeding). And the rate of conversion to open cholecystectomy in the delayed group was 13.3 % (2 cases due to difficult dissection of Calot's triangle due to presence of dense adhesions obscuring the normal anatomy).

In a similar study, **Gutt et al. (2013)** showed that the conversion rate to open cholecystectomy was 9.9% in the early group while the rate of conversion to open cholecystectomy was 11.9% in the delayed group. On the other hand, the rate of conversion to open cholecystectomy according to **Kolla et al. (2004)** was 25% in both early and delayed group.

The pathophysiological basis for these results lies in understanding the progression of the acute inflammatory process. Early in the course of acute cholecystitis, the inflamed, edematous tissues are often helpful in delineating tissue planes. As inflammatory process continues these normal tissue planes are replaced by fibrotic adhesions that make dissection difficult **(Greenwald et al., 2010).**

In this study gall bladder decompression was indicated in 11 cases in the early group (73.3%) and 3 cases in the delayed group (20%), According to **Sushant et al. (2013)** gall bladder decompression was needed in 15 cases out of 30 in the early group (50%) and in 3 cases out of 30 in the delayed group (10%).

As regard widening of epigastric port site during extraction of the gall bladder in this study it was needed in 2 cases in the early group (13.3%) and also in 2 cases in the delayed group (13.3%), according to **Gutt et al. (2013)**. Widening of epigastric port site was needed in 10.2% of cases in the early group in 6% of cases in the delayed group.

Concerning intraoperative bleeding in the current study it has occurred once in the early group (6.7%) and this lead to conversion to open cholecystectomy and has occurred in no cases of delayed group, according to **Gutt et al. (2013)** intraoperative bleeding has occurred in 3% of cases in each group.

Postoperative wound infection in this study has occurred in 2 cases in the early group (13.3%) and it has also occurred in 2 cases in the delayed group (13.3%). According to **Kolla et al. (2004)** wound infection has occurred in 5% of cases only in the early group and in 10% of cases in the delayed group.

In this study, postoperative bile leak has been noticed in one case in the early group (6.7%) due to slipped clips which was treated with ERCP and stenting and postoperative bile leak has been noticed in no cases in the delayed group. According to **Kolla et al. (2004)** postoperative bile leak has been noticed in 5% of cases in the early group with no bile leak in the delayed group.

In the current study, postoperative collection has been found in one case (6.7%) in the early group and in two cases (13.3%) in the delayed group which were subhepatic and were detected by ultrasound and were treated by pig tail insertion. According to **Gutt et al. (2013)** postoperative collection has been found in 3% of cases in the early group and 8% of cases in the delayed group.

In this study, postoperative jaundice has occured in no cases in the early group and has occured in one case (6.7%) in the delayed group due to missed stone in the common bile duct and treated by endoscopic retrograde cholangiopancreatography and stone extraction. According to **De Mestral et al. (2013)** postoperative jaundice has been occurred in 3.6% of the delayed group and it has been occurred in 1% of the early group.

In this study, the total hospital stay in the early group ranged from 3.5 to 6 days with a mean of 4.8 ± 0.91 days and the total hospital stay in the delayed group (including the number of days spent till the resolution of the acute attack of cholecystitis along with the number of days spent after readmission for laparoscopic cholecystectomy) ranged from 7 to 12 days with a mean of 9.2 ± 1.61 days. According to **Gutt et al. (2013)** the total hospital stay in the early group ranged from 4 to 6 days with a mean of 5.4 days and the total hospital stay in the delayed group ranged from7 to 12 days with a mean of 10.03 days. There is close correlation between our study and **Gutt et al. (2013)** also the total hospital stay in the delayed group was double that in the early group. So early laparoscopic cholecystectomy is more economic.

According to **Kolla et al. (2004)** the mean of total hospital stay in the early group was 4.1 ± 8.6 days and the mean of total hospital stay in the delayed group was 10.1 ± 6.1 days. There was significant decrease in hospital stay in cases having early laparoscopic cholecystectomy when compared to those undergoing delayed laparoscopic cholecystectomy. This result is in harmony with similar several studies in literature.

Finally, further studies with larger samples in this topic could lead us to more accurate results and findings.

Conclusion

- Laparoscopic cholecystectomy can be performed safely for acute cholecystitis, with acceptable low conversion and complication rates.
- Early timing of laparoscopic cholecystectomy in relation to the onset of gall bladder inflammation may reduce the conversion rate and the total complication rate.
- The morbidity of laparoscopic cholecystectomy for patients with acute cholecystitis is not reduced by a long period of initial conservative treatment. For surgeons with adequate experience, the optimal timing of laparoscopic cholecystectomy for treatment of acute cholecystitis is within 72 hours of admission.
- Early laparoscopic cholecystectomy for patients with acute cholecystitis has both medical and socioeconomic benefits and it is the preferred approach in comparison to delayed approach.
- Early cholecystectomy provides better morbidity results, as well as a clear trend toward lower mortality and fewer injuries to the main bile duct. No differences were found in the rate of complications between patients who underwent surgery within the first 72 hours of symptoms and the patients operated on more than 72 hours after the initiation of symptoms. In addition, early cholecystectomy could be of benefit for elderly patients with high comorbidity and lead to a reduction in direct costs due to fewer days of hospital stay. We would recommend delayed cholecystectomy only in cases where acute pancreatitis, choledocholithiasis, or cholangitis cannot be ruled out and those with unacceptable anesthetic risk at the time of diagnosis.

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