



# Evaluation of early versus delayed laparoscopic cholecystectomy in acute calculous cholecystitis: a prospective, randomized study

Gaurav Gupta<sup>1</sup>, Ajay Shahbaj<sup>2</sup>, Dharmendra Kumar Pipal<sup>1</sup>, Pawan Saini<sup>3</sup>, Vijay Verma<sup>4</sup>, Sangeeta Gupta<sup>5</sup>, Vibha Rani<sup>6</sup>, Seema Yadav<sup>7</sup>

<sup>1</sup>Department of General Surgery, All India Institute of Medical Sciences, Gorakhpur, India

<sup>2</sup>Department of General Surgery, Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana (Ambala), India

<sup>3</sup>Venkateshwar Institute of Medical Sciences, Gajraula, India

<sup>4</sup>Department of General Surgery, Dr SN Medical College, Jodhpur, India

<sup>5</sup>Department of Physiology, All India Institute of Medical Sciences, Gorakhpur, India

<sup>6</sup>Department of Gynaecology and Obstetrics, All India Institute of Medical Sciences, Gorakhpur, India

<sup>7</sup>Department of Anaesthesiology, JNU Medical College and Hospital, Jaipur, India

**Purpose:** Uncertainty exists about whether early laparoscopic cholecystectomy (LC) is an appropriate surgical treatment for acute calculous cholecystitis. This study aimed to compare early vs. late LC for acute calculous cholecystitis regarding intraoperative difficulty and postoperative outcomes.

**Methods:** This was a prospective randomized study carried out between December 2015 and June 2017; 60 patients with acute calculous cholecystitis were divided into two groups (early and delayed groups), each comprising 30 patients. Thirty patients treated with LC within 3 to 5 days of arrival at the hospital were assigned to the early group. The other 30 patients were placed in the delayed group, first treated conservatively, and followed by LC 3 to 6 weeks later.

**Results:** The conversion rates in both groups were 6.7% and 0%, respectively ( $p = 0.143$ ). The operating time was  $56.67 \pm 11.70$  minutes in the early group and  $75.67 \pm 20.52$  minutes in the delayed group ( $p = 0.001$ ), and both groups observed equal levels of postoperative complications. Early LC patients, on the other hand, required much fewer postoperative hospital stay ( $3.40 \pm 1.99$  vs.  $6.27 \pm 2.90$  days,  $p = 0.006$ ).

**Conclusion:** Considering shorter operative time and hospital stay without significant increase of open conversion rates, early LC might have benefits over late LC.

**Keywords:** Acute cholecystitis, Gallstones, Laparoscopic cholecystectomy, Treatment outcome

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## Corresponding author

Dharmendra Kumar Pipal

Department of General Surgery, All India Institute of Medical Sciences, 301 Orchid Green Mohaddipur, Gorakhpur 273008, Uttar Pradesh, India

Tel: +91-9602541730

E-mail: dr.dharmendrapipal2007@gmail.com

ORCID:

<https://orcid.org/0000-0002-3483-0403>

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## INTRODUCTION

Whether laparoscopic cholecystectomy (LC) should be performed early (within 3–6 days of pain) or late (3–6 weeks after

conservative treatment) for acute calculous cholecystitis is unclear [1]. A few studies advocate early LC, performed within 7 days of symptoms. The second option is conservative therapy followed by cholecystectomy 3 to 6 weeks later. Institutional in-

frastructure, surgical expertise of the operating surgeon, and the patient's general condition all influence these approaches.

The causes of difficult early LC in acute cholecystitis include edema, adhesions with surrounding structures, distended gallbladder, friability of the gallbladder wall and calot regions, ambiguous ductal and vascular anatomy, infection, and high vascularity. Therefore, such circumstances entail a higher conversion rate to an open procedure and injury to the biliary tree, resulting in enhanced patient morbidity.

Early cholecystectomy is accepted as a standard treatment for acute calculous cholecystitis to prevent not only ductal, vascular, and duodenal injuries but also morbidity, mortality, and prolonged hospitalization [2]. The benefits of early LC have been questioned by Cuschieri et al. [3] as it is associated with increased intraoperative difficulty and the ensuing operative consequences, leading to a higher conversion rate (5%–35%) and longer durations of hospitalization. Therefore, it was advocated by a few studies to manage with conservative treatment and perform LC later in acute calculous cholecystitis [2–8]. However, deferring cholecystectomy increases gallstone-related complications and prolongs hospitalization. A few studies have advocated early LC as a safe alternative to open cholecystectomy for acute calculous cholecystitis [4–6,9]. The fundamental benefit of early cholecystectomy is that it provides definitive treatment during the same hospitalization, avoiding the problem of failed conservative treatment and complications such as empyema, gangrene, and perforation. For individuals with acute cholecystitis, the 2013 Tokyo Guidelines and the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) guidelines recommend early LC within 24 to 72 hours of diagnosis [10].

The present study aimed to evaluate whether early or delayed LC is the preferable operative intervention for acute cholecystitis by analyzing the intraoperative difficulty, rate of conversion, duration of surgery, postoperative complications, and duration of hospitalization.

## MATERIALS AND METHODS

This was a prospective, randomized, two-arm clinical study of 60 patients. The sample size was based on a study conducted by Ozkardeş et al. [11] in 2014. The study was conducted from December 2015 to June 2017 at the Department of General Surgery, Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana (Ambala), Haryana, India.

The clinical signs and symptoms (acute pain in the right hypochondrium or epigastrium with associated tenderness, temperature of  $\geq 37.5^{\circ}\text{C}$ ; and total leukocyte count of  $10 \times 10^9/\text{L}$ ) and ultrasonographic findings (thick, edematous, or distended gallbladder; positive Murphy's sign during ultrasound imaging; the presence of gallbladder stones with surrounding fluid collection)

were used to diagnose acute cholecystitis. Patients aged  $\geq 18$  years with a diagnosis of acute calculous cholecystitis were included. Patients were randomly divided, using a computer-generated list, into the 'early' (group A) and 'delayed' groups (group B). Group A underwent LC within 3 to 5 days, while group B received intravenous hydration and antibiotics (cephalosporins, amikacin, and metronidazole). Conservatively treated patients underwent LC after 3 to 6 weeks. No patients dropped out/withdrew from the study. One patient who failed conventional treatment underwent emergency open cholecystectomy, and intention-to-treat analysis was taken. No patient required percutaneous drainage.

To remove interventional bias, all cases were surgically treated by surgeons with more than 10 years of experience. The operational difficulty level was assessed by the Cuschieri scale [3]: grade 1 cholecystectomy, simple and uncomplicated; grade 2, medium difficulty, for example, mild cholecystitis, cystic duct or artery obscured by adhesions or fatty tissue, mucocele may be present; grade 3, difficult cholecystectomy due to gangrenous cholecystitis, shrunken fibrotic gallbladder, severe cholecystitis, subhepatic abscess formation, Hartman pouch adherent to the common hepatic duct, cases in which the cystic duct or artery is difficult or impossible to dissect, or liver cirrhosis with portal hypertension; and grade 4, conversion to open surgery required.

## Exclusion criteria

Patients with surgical jaundice and proximal common bile duct (CBD) stones larger than 1.5 cm in diameter, which were difficult to treat endoscopically before laparoscopic surgery, malignancies, acute biliary pancreatitis, previous upper abdominal surgery, coagulopathy, spreading peritonitis, and those who were not fit for surgery were excluded from the study.

## Statistical analysis

The IBM SPSS version 22.0 (IBM Corp., Armonk, NY, USA), a statistical data processing and analysis software package, was used to process the collected data. The comparisons between the two groups were performed using the Student t-test for continuous variables and the chi-square test for categorical variables. In the statistical analysis of the test findings, statistical significance was set at  $p < 0.05$ .

## RESULTS

In this study, the mean age in group A was  $44.60 \pm 14.96$  years; in group B, it was  $46.37 \pm 9.23$  years. Maximum numbers of cases in both groups (26.7% in group A and 30.0% in group B) were present in the 38 to 47-year age subgroup. The patients in group A were relatively young (Table 1).

The pain was the consistent symptom found in both groups followed by nausea, dyspepsia, and vomiting (Table 2). Physical signs such as pallor and icterus were not significantly different between the two groups, but Murphy's sign did show a significant difference ( $p < 0.001$ ). Laboratory findings such as hemoglobin, total leukocyte count, and bilirubin (total, direct, and indirect) were not different between the groups (Table 2). Ultrasonic findings regarding the number of stones were insignificant, but pericholecystic adhesions and fluid collections were seen significantly more often in group A than in group B (13 [43.3%] vs. 5 [16.7%], respectively;  $p = 0.018$ ). In addition, the gallbladder wall was significantly thicker in group A than in group B (10 [33.3%] vs. 2 [6.7%], respectively;  $p = 0.006$ ) (Table 2).

Before surgery, endoscopic retrograde cholangiopancreatography was performed in three of the early group (10.0%) and four of the delayed group (13.3%). They had an obstruction from a small stone (less than 1.5 cm) in the distal CBD.

As for intraoperative findings, all patients (100%) in group A and nine patients in group B (30.0%) had distended gallbladders. As shown in Table 3, group A had more adhesions than did group B (22 [73.3%] vs. 13 [43.3%]). However, in the delayed group, the adhesions were denser than those in the early group, and some patients had fibrosis around the gallbladder.

The conversion rate to open surgery was not significantly different (two patients in group A only [6.7%],  $p = 0.143$ ). Twenty-

three patients in group A (76.7%) and seven in group B (23.3%) had a drain placed ( $p < 0.001$ ). Difficulty experienced during surgery did not significantly differ between the groups (grade 1, 7 [23.3%] vs. 12 [40.0%]; grade 2, 19 [63.3%] vs. 17 [56.7%]; grade 3, 4 [13.3%] vs. 1 [3.3%];  $p = 0.309$ ) (Table 3). Twenty-two patients in group A (73.3%) and 12 in group B (40.0%) required more than

**Table 1.** Patients' demographics

Variable	Group A	Group B	p value
No. of patients	30	30	
Sex, male:female	8:22	14:16	0.180
Age (yr)	44.60 ± 14.96	46.37 ± 9.23	0.009
18–27	5 (16.7)	1 (3.3)	
28–37	6 (20.0)	6 (20.0)	
38–47	8 (26.7)	9 (30.0)	
48–57	3 (10.0)	13 (43.3)	
58–67	5 (16.7)	1 (3.3)	
>68	3 (10.0)	0 (0)	
Previous medical history			
DM or HTN	5 (16.7)	2 (6.7)	0.222
Surgery	13 (43.3)	4 (13.3)	0.006

Values are presented as number only, mean ± standard deviation, or number (%).

Group A, the group treated with laparoscopic cholecystectomy (LC) within 3 to 5 days of arrival at the hospital; group B, the group first treated conservatively, and followed by LC 3 to 6 weeks later.

DM, diabetes mellitus; HTN, hypertension.

**Table 2.** Preoperative clinical manifestations

Variable	Group A	Group B	p value
No. of patients	30	30	
Symptom <sup>a)</sup>			
Pain	30 (100)	30 (100)	>0.999
Dyspepsia	15 (50.0)	12 (40.0)	0.434
Nausea	17 (56.7)	12 (40.0)	0.190
Vomiting	15 (50.0)	2 (6.7)	<0.001
Fever	5 (16.7)	2 (6.7)	0.222
Cough	2 (6.7)	2 (6.7)	>0.999
Sign <sup>a)</sup>			
Pallor	9 (30.0)	8 (26.7)	0.774
Icterus	6 (20.0)	8 (26.7)	0.540
Murphy's sign	26 (86.7)	6 (20.0)	<0.001
Hemoglobin (g/dL)			0.739
<10	5 (16.7)	6 (20.0)	
>10	25 (83.3)	24 (80.0)	
Total leucocyte counts (cells/μL)			0.311
4,000–11,000	23 (76.7)	27 (90.0)	
>11,000	7 (23.3)	3 (10.0)	
Total bilirubin (mg/dL)			0.071
≤1.2	23 (76.7)	28 (93.3)	
>1.2	7 (23.3)	2 (6.7)	
Direct bilirubin (mg/dL)			0.129
≤0.3	24 (80.0)	28 (93.3)	
>0.3	6 (20.0)	2 (6.7)	
Ultrasonography finding			
Single calculus	9 (30.0)	4 (13.3)	0.110
Multiple calculi	21 (70.0)	26 (86.7)	0.110
Adhesions	13 (43.3)	5 (16.7)	0.018
Increased gallbladder wall thickness	10 (33.3)	2 (6.7)	0.006

Values are presented number only or number (%).

Group A, the group treated with laparoscopic cholecystectomy (LC) within 3 to 5 days of arrival at the hospital; group B, the group first treated conservatively, and followed by LC 3 to 6 weeks later.

<sup>a)</sup>At the time of presentation.

**Table 3.** Intraoperative parameters

Variable	Group A (n = 30)	Group B (n = 30)	p value
Operative finding			
Adhesions/collection	22 (73.3)	13 (43.3)	0.013
Conversion	2 (6.7)	0 (0)	0.143
Drain	23 (76.7)	7 (23.3)	<0.001
Difficulty			0.309
Simple (grade 1)	7 (23.3)	12 (40.0)	
Medium (grade 2)	19 (63.3)	17 (56.7)	
Difficult (grade 3)	4 (13.3)	1 (3.3)	
Operative time (min)	56.67 ± 11.70	75.67 ± 20.52	0.001

Values are presented as number (%) or mean ± standard deviation.

Group A, the group treated with laparoscopic cholecystectomy (LC) within 3 to 5 days of arrival at the hospital; group B, the group first treated conservatively, and followed by LC 3 to 6 weeks later.

**Table 4.** Postoperative parameters

Variable	Group A (n = 30)	Group B (n = 30)	p value
Analgesic requirement (dose)			0.009
<3	8 (26.7)	18 (60.0)	
>3	22 (73.3)	12 (40.0)	
Drain removal (day)			<0.001
No drain	6 (20.0)	23 (76.7)	
1–3	13 (43.3)	5 (16.7)	
>3	11 (36.7)	2 (6.7)	
Hospital stay (day)			0.211
<5	1 (3.3)	0 (0)	
5–10	22 (73.3)	27 (90.0)	
>10	7 (23.3)	3 (10.0)	
Mean postoperative stay (day)	3.40 ± 1.99	6.27 ± 2.90	0.006

Values are presented as number (%) or mean ± standard deviation.

Group A, the group treated with laparoscopic cholecystectomy (LC) within 3 to 5 days of arrival at the hospital; group B, the group first treated conservatively, and followed by LC 3 to 6 weeks later.

three analgesic doses ( $p = 0.009$ ). The drain was placed for >3 days in 11 patients in group A (36.7%) and only two in group B (6.7%) ( $p < 0.001$ ). Mean postoperative hospital stay was significantly shorter in group A than group B (3.40 ± 1.99 days vs. 6.27 ± 2.90 days,  $p = 0.006$ ) (Table 4). The overall hospital stay for the early and delayed groups was 5.07 ± 2.19 and 8.07 ± 3.17 days, respectively.

## DISCUSSION

In this prospective randomized study, we observed that early LC had the advantage in terms of shorter operation time and hospital stays without significant increase of open conversion rate and intraoperative difficulty level.

Historically, acute cholecystitis due to stone was managed optimally with a span of 6 to 8 weeks with antibiotics in view of inflammatory resolution to avoid ductal and vascular injury. However small and retrospective, many clinical trials have shown the advantage of early LC over the delayed one in terms of short hospital stay and cost with a similar estimate of associated morbidity and mortality [12–16].

Acute calculous cholecystitis is one of the digestive system's most prevalent acute hepatobiliary disorders. Numerous studies have attempted to demonstrate less rigorous and cost-effective treatments [17,18]. The complexity of the structure, size, and multiplicity of stones are the factors limiting their nonsurgical management. These nonsurgical methods include oral desaturation of stones using ursodeoxycholic acid, contact disintegration, and extracorporeal lithotripsy techniques. The incidence of gallstones increases with age, from 4% in the third decade of life to 27% in the seventh [19].

Acute cholecystitis was once considered a relative contraindication to LC in the early days of laparoscopic surgery; however, it has recently been demonstrated to be feasible and safe. Numerous studies have documented significant conversion rates for early LC, ranging from 6% to 35% to treat acute cholecystitis [20–25].

Surgical treatment is the gold standard for calculus cholecystitis because nonsurgical approaches have not yielded positive consequences [26]. LC has become the treatment of choice for gallstones during the past two decades. The Endovision system and other technological improvements have played a vital role in its development [27,28].

The time frame for treating acute cholecystitis is highly debatable, although various studies, including meta-analyses, advocate early cholecystectomy.

Falor et al. [14] performed early laparoscopic cholecystitis in 117 patients out of 303 suffering from gallstone pancreatitis within 48 hours of their hospitalization and the rest were managed by the delayed laparoscopic way after their blood investigations came normal. They observed that early LC was safe and associated with shorter hospital stays and less need for endoscopic retrograde cholangiopancreatography.

Regarding intraoperative parameters, the conversion rate in a 2017 study by Khalid et al. [29], which included 188 patients, was 15.5% early vs. 14.4% delayed, and operation time was 64.32 minutes early vs. 58.24 minutes delayed. According to the study of Goh et al. [30] in 2017 which involved 466 patients, the intra-

operative severity was higher ( $p < 0.001$ ) and the median operative time was longer (107 minutes; range, 46–220 minutes) in the early group than the delayed group (95 minutes; range, 25–186 minutes) ( $p = 0.048$ ). Conversion rates were also higher in the early than that in the delayed group (early, 21.4% vs. delayed, 4.9%;  $p = 0.048$ ) [30]. The outcomes of our study are different from those forementioned studies. The delayed group not early group required a longer surgical procedure because the adhesions were denser, including fibrosis and necrosis, and the gallbladder was constricted in some patients. In our study, furthermore, two patients in the early group (6.7%) and none of the delayed group required conversion to open surgery, but this was not statistically significant. As for intraoperative difficulty grade, proportion of the patients showing difficult (grade 3) level was higher in the early group than the delayed group, but this was not statistically significant too.

In a 2014 study including 14,220 patients, de Mestral et al. [31] found that the early group's hospital stay was 1.9 days shorter than that of the delayed group. In a 2015 trial of 502 participants, Pisano et al. [32] observed a hospital stay of 2.5 days shorter in the early group, and no surgical complications were reported in the early group. This finding is in line with our study in terms of shorter mean postoperative and overall hospital stay in the early group.

Injury to the biliary tract was an important monitoring metric for both groups. In 2016 research by Roulin et al. [33], the early surgical patients had a total morbidity rate of 14% (vs. 39% in the delayed group) and favored early LC. In a 2018 study of 72 patients, Jee et al. [34] observed 7.78% vs. 11.76% perioperative problems for early patients. In our study, no patient experienced bile duct injury.

Kao et al. [35] examined 86 early and delayed patients in terms of their hospitalization durations (4 vs. 7 days), the associated costs (9,349 vs. 12,361 Canadian dollars), and found that the total hospital costs were lower in early LC (9,349€ vs 12,361€,  $p = 0.018$ ). However, the cost was not studied in our study.

This study has small number of patients, and sample size calculation was not conducted; instead, we took the sample size from the previously published article dealing with comparing the early and delayed LC. Detailed patients' demographics such as American Society of Anaesthesiologists physical status classification are omitted demonstrating limited underlying diseases. Detailed perioperative complications other than bile injury are not recorded. Lastly, cost analysis was also not performed.

Although early LC required more analgesic doses and longer drain placement, early LC might have benefits over late LC when considering shorter operative time and hospital stay without significant increase of open conversion rates.

## NOTES

### Ethical statements

The study was approved by the Institutional Ethics Committee of Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana (Ambala), Haryana, India (IEC/Project No. /634) and written informed consent was obtained.

### Authors' contributions

Conceptualization, Formal analysis, Methodology, Visualization: GG, AS, DKP

Data curation, Investigation: All authors

Writing—original draft: DKP

Writing—review & editing: DKP

All authors read and approved the final manuscript.

### Conflict of interest

All authors have no conflicts of interest to declare.

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