No 72-hour pathological boundary for safe early laparoscopic cholecystectomy in acute cholecystitis: a clinicopathological study

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Abstract

Background The pathological boundary of acute cholecystitis (AC) between early edematous and late chronic fibrotic inflammation beyond 72 h is well-described. Early laparoscopic cholecystectomy (ELC) is safe in AC but the timing still remains controversial. The aim of this study was to analyze the impact of the duration of symptoms on clinical severity, pathology and outcome in patients who underwent laparoscopic cholecystectomy (LC) for AC during the urgent admission.

Methods A retrospective analysis of a prospectively collected database of 61 patients who underwent LC for AC over a 6-month period was performed.

Results Of 61 patients 21 (34.43%) received ELC at <72 h and 40 (65.57%) received late LC (LLC) at >72 h. Clinically in the ELC group the majority were mild and in the LLC group the majority were moderate and severe in severity grading as per Tokyo guidelines (P<0.001). Surgical findings and histopathology showed no significant difference in the distribution of simple, phlegmonous and gangrenous cholecystitis between both groups (P=0.94). The majority were completed by a standard four port technique and only one required subtotal cholecystectomy. There was no significant difference between operating time, return to normal activities or hospital stay between both groups. There were no conversions to open cholecystectomy, no wound infections, no intra-abdominal collections, no biliary tract injury or mortality in either group.

Conclusions The degree of inflammatory change in AC is not dependent on time. LC can be safely performed in AC regardless of timing with a standardized surgical strategy in experienced units.

Keywords Acute cholecystitis, laparoscopic cholecystectomy, subtotal cholecystectomy, pathology acute cholecystitis, 72 hour boundary

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Introduction

Laparoscopic cholecystectomy (LC) has long been the gold standard for the treatment of patients with symptomatic gallstones. With increasing experience in laparoscopic surgery a number of centers have reported on the use of LC for acute cholecystitis (AC) suggesting that it is technically feasible and safe. Several prospective randomized trials have established the superiority of early over delayed intervention [1-6].

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A factor complicating the assessment of outcomes of early treatment in these trials is that "early" has been variably defined as anywhere from 24 h to 7 days after either the onset of symptoms or the time of diagnosis. However, current literature suggests that early laparoscopic treatment for AC should be within 72 h from onset of symptoms defining a rigid 72 h boundary. The effect of delay in "early" beyond the 72 h boundary is not clear in the literature as these groups have not been effectively tested in the existing randomized controlled trials. But there have been a number of reports on the impact of delay beyond the 72 h boundary and despite initial reservations regarding increase in the conversion rate and morbidity, increasing newer reports are emerging of safety of LC in AC regardless of timing [7,8].

Most of these studies in the literature have not analyzed the difference clinically and pathologically between the early and late stages of AC despite speculations on the possible role of the pathological course of AC changing from an early

edematous to a more chronic fibrotic phase of inflammation beyond 72 h making surgery more technically demanding.

In our institution, we have adopted a policy of performing a LC during the initial urgent admission for AC regardless of timing. The aim of this study was to analyze prospectively the impact of the duration of symptoms on clinical severity, pathology and outcome in patients who underwent LC for AC during the urgent admission.

Patients and methods

We conducted a retrospective analysis of a prospectively collected database of 61 consecutive patients who underwent LC for AC during the emergency admission for AC from July 2012 to December 2012 at Bhatia Hospital Mumbai, India. The diagnosis was made by the diagnostic criteria for AC according to the Tokyo guidelines, i.e. presence of any one local symptom or sign (Murphy's sign, pain or tenderness in right upper quadrant, mass in right upper quadrant), one systemic sign (fever, leukocytosis, increased C-reactive protein) and a confirmatory finding on an imaging test (ultrasonography/hepatobiliary scintigraphy). Ultrasonographic evidence included the presence of gallstones, thickened gallbladder wall, pericholecystic fluid, and/or sonographic Murphy's sign and no evidence of a dilated ductal system. Patients were then clinically graded for severity into mild, moderate or severe by severity grading for AC according to Tokyo guidelines. All the patients diagnosed as AC received LC as soon as possible within 24 h of admission regardless of the time since the onset of symptoms. Patients with Mirizzi syndrome, previous upper abdominal surgery, choledocholithiasis, cholangitis, acute pancreatitis and patients treated conservatively and readmitted for elective or delayed LC 6-12 weeks later were excluded from this study. Histopathological confirmation of AC by pathologists was obtained for all patients.

LC was performed randomly by five specialists with more than 10 years of experience in laparoscopic surgery and they usually operated with comparable speed. The standard 4-port operative technique (retrograde cholecystectomy) was used for all LCs. A 30-degree angled scope was used for best operative view. Intraoperative pathological findings of simple, phlegmonous or gangrenous cholecystitis was recorded. In the presence of a phlegmon, the omentum, duodenum and colon were dissected off by blunt dissection with a suction cannula tip to expose the gallbladder. When the gallbladder was distended it was first aspirated and decompressed using an aspiration needle or direct insertion under vision of a 5 mm trocar cannula. The gallbladder was manipulated carefully. Dissection was performed using mostly monopolar diathermy (occasionally harmonic) as well as blunt suction cannula tip dissection with intermittent use of the suction to obtain a clear operative field to identify structures within the Calot's triangle and create a safety window prior to clipping and dividing the cystic artery and duct. A subtotal cholecystectomy was only exceptionally performed when safe Calot's triangle dissection

was not possible and majority of the LC were completed by the standard technique as described. All specimens were bagged before removal. Saline lavage and good suctioning of gallbladder fossa and subhepatic region was performed for all. A drain was left postoperatively if necessary. No intraoperative cholangiography was performed during LC.

Data recorded included demographic details, clinical findings and severity, counts, liver function tests, radiological findings, timing of cholecystectomy, duration of surgical procedure, conversion rate, complication rate, mortality and length of hospital stay. Patients with AC were divided into two groups according to the time between the onset of symptoms and the operation during the emergency admission: 1) those operated within 72 h of symptom onset (early LC group, ELC); and 2) those operated on beyond 72 h of symptom onset (late LC group, LLC).

In those operated beyond 72 h, LC was delayed because of patient delay and/or physician delay. In some cases admission for AC was delayed due to patient's decision. Some of the patients were referred late by physicians because of delays in confirming the diagnosis either at outpatient clinics or after admission to other departments. The rest were admitted after failure of a trial of conservative treatment.

Statistical analysis was performed with SPSS 14.0 software (SPSS, Chicago, IL, USA). The results of the study were expressed as mean ± standard deviation (SD) for quantitative variables and number (percentages) for categorical variables. Continuous data were compared using Student's t test; and categoric data were compared with Pearson's chi square test. Values of $P<0.05$ were considered statistically significant.

Results

This study comprised 61 patients with AC who underwent LC. Of the 61 patients 21 (34.43%) received ELC and 40 (65.57%) LLC. In the ELC group the median time from symptom onset to operation was 48 h with a range of 24-72 h and in the LLC group median time from symptom onset to surgery was 11 days with a range of 4-20 days. In the ELC group the distribution of males and females were 14.3% and 85.7% respectively and in the LLC group the distribution of males and females were 40% and 60% respectively. Co-morbidities in the patients included 16 patients with presence of comorbidities of which 10 patients had diabetes mellitus, 10 had hypertension, 2 had hypothyroidism, 1 had chronic renal failure and 1 had asthma. There were 54 patients of ASA grade 1, 7 patients with ASA grade 2 and none were of ASA grade 3 or 4.

The mean of age of patients undergoing ELC was 48.67±12.07 years and LLC was 54.30±15.73 years and was comparable on analysis with no statistically significant difference. There was also no statistically significant difference in leukocytosis (ELC 9,450.00±3,155.64 vs. LLC 9,337.25±4,132.01) between both groups. On analysis of the clinical severity in the ELC group 17 (81%) were mild, 4 (19%) moderate and none were

Table 1 Analysis of the clinicopathological difference between ELC and LLC

Characteristic	ELC<72 h	LLC>72 h	P value
1. Age (Mean±SD)	48.67±12.07	54.30±15.73	0.157
2. Leukocytosis (Mean±SD)	9,450.00 ±3,155.64	9337.25 ±4,132.01	0.913
3. Clinical type			<0.001
Mild	17 (81%)	4 (10%)	
Moderate	4 (19%)	29 (72.5%)	
Severe	0 (0%)	7 (17.5%)	
4. Pathological type			0.943
Simple	13 (61.9%)	23 (57.5%)	
Phlegmonous	6 (28.6%)	13 (32.5%)	
Gangrenous	2 (9.5%)	4 (10%)	

ELC, early laparoscopic cholecystectomy; LLC, late laparoscopic cholecystectomy

severe and in the LLC group 4 (10%) were mild, 29 (72.5%) moderate and 7 (17.5%) severe by severity grading as per the Tokyo guidelines and this difference in distribution between both groups was statistically significant (P<0.001). Surgical findings and histopathology confirmed acute simple cholecystitis in 13 (61.9%), phlegmonous cholecystitis in 6 (28.6%) and gangrenous cholecystitis in 2 (9.5%) of the ELC group and acute simple cholecystitis in 23 (57.5%), phlegmonous cholecystitis in 13 (32.5%) and gangrenous cholecystitis in 4 (10%) of the ELC group. This distribution between both groups was comparable with no statistically significant difference (P=0.94), (Table 1).

The majority were completed by the standard 4-port technique (retrograde cholecystectomy) with special care and only one patient required subtotal cholecystectomy performed with suture closure of the stump with a drain in place. On analysis of the outcome in both groups there was no statistically significant difference in the operating time [ELC 69.52 (40-130 min) vs. LLC 70.62 (35-120 min)], return to normal activities (ELC 2.90±0.83 days vs. LLC 3.65±2.15 days), hospital stay (ELC 3.02±0.87 days vs. LLC 4.03±2.24 days) between both

groups. There were no conversions to open cholecystectomy, no wound infection, no intra-abdominal collections no biliary tract injury or mortality in either group (Table 2).

Discussion

ELC is considered the treatment of choice for most patients with AC. In randomized and prospective trials [1-6] and their meta-analyses [9-13] comparing ELC with a delayed procedure, performance of an ELC has shown no significant difference in morbidity or mortality or in operative time or conversion rates to open cholecystectomy. Additional advantages of performance of an ELC were a shorter overall hospitalization and that approximately 15-20% of patients planned for a delayed interval LC had persistent or recurrent symptoms requiring intervention before their planned operation [7]. However current literature suggests that ELC for AC should be within 72 h from onset of symptoms defining a rigid 72-h boundary. The effect of delay in "early" beyond 72 hours is not

Table 2 Analysis of the outcome difference between ELC and LLC

Characteristic	ELC<72 h	LLC>72 h	P value
Operation time	69.52±24.94	70.63± 25.04	0.871
Conversion rate	0	0	-
Hospital stay (Mean±SD)	3.02±0.87	4.03± 2.24	0.053
Return to normal activities (Mean±SD)	2.90±0.83	3.65±2.15	0.133
Complications	0 (0%)	0 (0%)	-
Wound infection	0	0	-
BDI	0	0	-
Systemic	0	0	-

ELC, early laparoscopic cholecystectomy; LLC, late laparoscopic cholecystectomy; BDI, bile duct injury
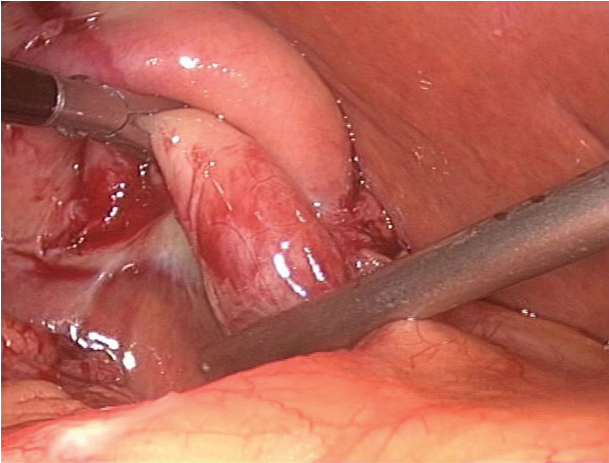
Figure 1 Intraoperative photograph of simple acute cholecystitis
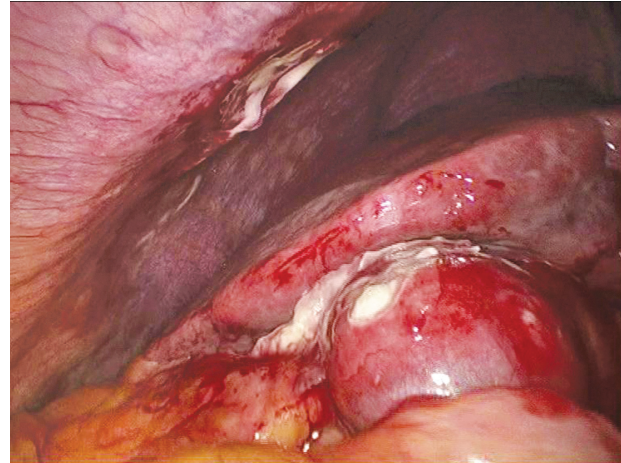
Figure 2 Intraoperative photograph of phlegmonous acute cholecystitis

clear in the literature as this cutoff and these groups have not been effectively tested in the existing randomized controlled trials and it is not known if benefits of the trials of early LC over delayed LC can be projected to this group. A number of initial clinical studies on the impact of delay beyond the 72-h boundary reported increase in the conversion rate and morbidity. However increasing newer reports are emerging of safety of LC in AC regardless of timing [7,8].

The inflammatory response of AC has a well-described pathological course. In the early phase, the stages of hyperemia and edema predominate and this may even facilitate laparoscopic dissection of the Calot's triangle. After 72 h chronic inflammation predominates with adhesions, fibrosis, hypervascularity and necrosis responsible for the difficulty in laparoscopic dissection of the Calot's triangle. However there is not much data on this clinicopathological course as most of the studies in the literature have not analyzed the difference between the early and late stages of AC clinically and pathologically, despite speculations on the possible role of the pathological course of AC changing from an early edematous to a more chronic fibrotic phase of inflammation beyond 72 h making surgery more technically demanding.

In our study, in the ELC group the median time from symptom onset to operation was 48 h with a range of 24-72 h and in the LLC group median time from symptom onset to surgery was 11 days with a range of 4-20 days. The clinical diagnosis of AC was made according to the diagnostic criteria for AC according to the Tokyo guidelines. After the clinical diagnosis of AC was made we clinically graded them into mild, moderate or severe by severity grading for AC according to the Tokyo guidelines [14,15]. On analysis of our data our findings showed that the majority of the patients were clinically moderate and severe in the LLC group and the majority of the patients were mild in severity in the ELC group. The obvious possible interpretation of our findings was that a delayed treatment of AC is associated with increased clinical severity.

During the operations for AC intraoperative pathological findings as per the operating surgeons judgement of extent of

inflammation can broadly vary from just simple AC (edematous planes with minimal inflammation) (Fig. 1), to the phlegmonous type (extensive inflammation and adhesions) Fig. 2 and finally to the gangrenous type (patchy to frank gangrene with or without perforation in addition to inflammation and adhesions) (Fig. 3). As per the current understanding of the pathological course of AC these gross pathological findings correlate with the early edematous and the late chronic fibrotic phase of the clinicopathological course of AC. However, in our study on an analysis of the pathological findings, contrary to expectations, our findings showed that the pathological distribution of simple, phlegmonous and gangrenous cholecystitis was not significantly different between the ELC and LLC groups. This clearly suggests that not everyone got the same degree of inflammatory change of the gallbladder and surprisingly the number of days that passed from onset of AC symptoms was not a determining factor. The pathological course of AC is therefore not a time-related event. Numerous studies have shown a number of risk factors affecting the natural history of AC, such
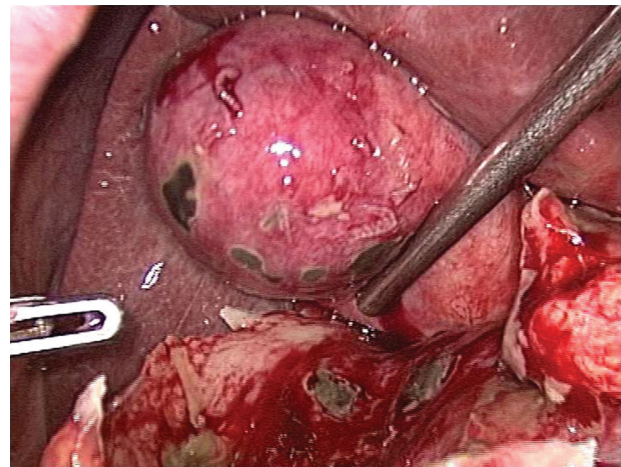
Figure 3 Intraoperative photograph of gangrenous acute cholecystitis

as advanced age, male sex, comorbidity etc., more associated with complicated cholecystitis like gangrenous cholecystitis, perforation and peritonitis, which may explain why the degree of inflammation may not only be time-dependent [16].

Our findings also showed that operation beyond 72 h was not more difficult to perform with no significant difference in operative time completion of almost all LCs with the standard technique and no conversions to open. Of course this could be explained by the fact that patients have a greater chance of a laparoscopically completed standard cholecystectomy if operated on by an experienced surgeon. Many studies have showed that experienced centres have shown better results in terms of conversion rates and morbidity [17]. Improved technique with time could be one of the reasons why newer reports show good outcome regardless of timing of LC in AC in comparison to earlier reports [7,8]. We must emphasize however that the pathologically severe forms of phlegmonous and gangrenous cholecystitis are more technically demanding and should be performed only by a highly experienced surgeon and promptly converted to open cholecystectomy if operative conditions make anatomical identification difficult. All our patients were of ASA grade 1 or 2 and were subjected to operation. We did not have a poor ASA grade patient in this series but do recommend that for those who cannot tolerate general anesthesia then an alternative must be considered as in conservative management for mild cholecystitis and percutaneous cholecystostomy for severe episodes.

In our study there were no complications in all patients and we attribute this to our standardized protocol of bagging, good suctioning and drainage if required. However, because of the small numbers in our study chances of uncommon complications like bile duct injury cannot be ruled out. Data from large, studies suggest that biliary injury is more common when LC is performed on an acutely inflamed gallbladder [18,19]. There was no significant difference in hospital stay and return to normal activities between both groups. The overall hospital stay was not significantly different in the two groups as we managed to operate all the patients diagnosed as AC within 24 h of admission and the delay was because of patient and physician-related factors before admission. Early return to normal activity in both groups was related to laparoscopic procedure which was successfully used in all the patients.

This study was limited because the number of patients studied was small and its retrospective design did not allow randomization of the two groups. There is need for data comparing "early" ELC (<72 h), "late" ELC (>72 h) and interval or delayed LC after 6 weeks by a prospective randomized controlled trial to confirm these findings.

In conclusion, our data shows that though clinical severity of AC increases with time, no pathological boundary exists at 72 h and the degree of inflammatory change is not dependent on time. LC for AC during the urgent admission for AC is safe and associated with a low morbidity and a low conversion rate regardless of timing in units with expertise in laparoscopic surgery. Every effort should be made to operate on all patients with AC during the index admission as soon as the diagnosis is made as clinical severity increases with time.

Summary Box

What is already known:

- LC within 72 h of symptom onset of AC during the urgent admission for AC is safe but LC beyond 72 h may be associated with increase in the conversion rate and morbidity
- The pathology of AC changes from an early edematous to a late chronic fibrotic phase beyond 72 h

What the new findings are:

- LC beyond 72 h of symptom onset for AC during the urgent admission for AC is technically feasible and safe in experienced hands
- There exists no rigid pathological boundary between early edematous and late chronic fibrotic phase at 72 h and the degree of inflammatory change in AC is not only time dependent

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