



Laparoscopic Cholecystectomy for Acute Cholecystitis: Is the Surgery Still Safe beyond the 7-Day Barrier?

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Abstract

Background The optimal timing for early laparoscopic cholecystectomy (ELC) in patients with acute calculous cholecystitis (ACC) is still controversial. The aim of this study was to assess the outcomes of ELC in patients with delayed presentation.

Methods Retrospective analysis of 381 patients who underwent ELC for ACC between January 2010 and September 2018. Included patients were classified into two groups according to the timing of surgery from the onset of symptoms: group 1 (G1) within the first 7 days and group 2 (G2) beyond 7 days.

Results There were no significant differences regarding conversion rate (G1 8.6% vs. G2 11.8%; $p = 0.527$), operative time (G1 100 min [75–120] vs. G2 120 min [71–150]; $p = 0.060$), bile duct injuries (G1 0.3% vs. G2 0%; $p = 1$), major postoperative complications (G1 11% vs. G2 5.9%; $p = 0.557$), reoperation rates (G1 1.4% vs. G2 0%; $p = 1$), length of stay (G1 4 days [3–7] vs. G2 5 days [3–7]; $p = 0.539$), readmissions (G1 3.7% vs. G2 5.9%; $p = 0.633$) and costs (G1 6035 € [3693–8330] vs. G2 7243 € [4921–11,336]; $p = 0.395$).

Conclusion ELC may be considered for patients with ACC who can tolerate surgery with more than 1 week of symptom duration.

Keywords Acute cholecystitis · Laparoscopic cholecystectomy · Early laparoscopic cholecystectomy · Delayed laparoscopic cholecystectomy

Introduction

Acute calculous cholecystitis (ACC) is the most common complication of gallstone disease and previous guidelines have defined a severity grading system (Tokyo Guidelines 2013, or TG13).¹ Laparoscopic cholecystectomy (LC) is currently the most accepted treatment for ACC, although the optimal timing of surgery from symptom onset remains controversial. Several prospective studies have demonstrated that same-admission early LC (ELC)² for ACC is safe when compared with delayed LC (DLC)^{2–6} in terms of morbidity, with decreased hospital length of stay (LOS) and costs, minimising the risks of relapse. The ‘golden 72-hour rule’ from symptom

onset was proposed as a safe period for the timing for ELC⁷, and the TG13 endorsed this recommendation in their guidelines.⁸ With increased experience in advanced laparoscopic surgery, ELC beyond 72 h has been proposed, and several randomised controlled trials (RCT) have demonstrated its safety in terms of morbidity and mortality within the first 7 days,⁹ with decreased hospital LOS. Finally, for the first time, the Tokyo Guidelines 2018 (TG18) has proposed ELC for patients who can tolerate surgery regardless of the symptom duration.¹⁰

The aim of the present study was to assess the outcomes and costs of ELC beyond the first 7 days of symptoms.

Methods

Patients and Characteristics

This is a single-institution retrospective observational study of patients who underwent ELC for ACC. The data included consecutive patients operated on from January 2010 to September 2018 with the following inclusion criteria: (1) diagnosis of ACC defined according to the Tokyo Guidelines

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criteria (including local signs with Murphy's sign and right upper quadrant mass/pain/tenderness and systemic signs with fever, elevated C-reactive protein and elevated white blood cell count);^{1, 10, 11} (2) ELC performed during the index admission for an ACC; and (3) surveillance up to minimum of 30 postoperative days. Exclusion criteria were (1) presence of another concomitant acute biliary pathology (cholangitis, choledocholithiasis and acute pancreatitis), (2) acute cholecystitis not related to a gallstone aetiology (like acalculous cholecystitis and biliary malignancy) and (3) previous abdominal surgical procedures.

This study was approved by the Research Ethics Board from our centre.

Patients diagnosed with ACC were treated with empiric antibiotic therapy (AT) according to guidelines:^{12, 13} for grade I ACC, AT was discontinued within 24 h after ELC and it was extended for 4–7 days if specific conditions were present (perforation, gangrenous/emphysematous changes, pericholecystic abscess or gallbladder necrosis). Grade II or grade III ACC was treated with AT during 4–7 days after ELC. If bacteraemia by gram-positive cocci was present, AT was prolonged for at least 2 weeks. LC was performed with a standard four-trocar technique,¹⁴ achieving the critical view of safety as described by Strasberg et al.¹⁵ A right subcostal incision was performed if conversion to open surgery was required. All interventions were performed either by surgical residents supervised by a consultant specialist surgeon with experience in minimally invasive surgery or by the consultant surgeon. During the study period, five consultant surgeons, each with more than 3 years of experience as specialists, were involved in the procedures. An on-call resident was always involved in the procedures, performing either a part or the entire intervention under the supervision of the consultant. The residents on call were senior trainees who had performed an average of 50 LC each.

All resected gallbladder specimens were confirmed as ACC at histopathological examination.

The included patients were divided into two groups according to the timing from onset of symptoms, defined by the Tokyo Guidelines 2018 as above specified (right upper quadrant mass/pain/tenderness and systemic signs with fever): in group 1 (G1), ELC was performed within the first 7 days of symptoms, and in group 2 (G2), with more than 7 days of evolution. Duration of symptoms was assessed according to the earliest symptom referred by patients.

Data Collection

Our database included the following variable: age, gender, Charlson comorbidity index,¹⁶ previous episodes of ACC, previous abdominal surgeries, duration of symptoms, severity grade of ACC,¹ laboratory findings (including liver panel), anaesthetic risk score (American Society of

Anesthesiologists classification-ASA),¹⁷ date of surgery, operative details (approach, duration and intraoperative events), complications within 30 first postoperative days (including reoperations, mortality and readmissions), LOS, duration of AT and total cost of hospitalisation (€). Intraoperative events recorded were iatrogenic bile duct injury, major bleeding (> 500 ml) and trocar injuries during ELC.

All postoperative complications were recorded according to the Clavien-Dindo classification,¹⁸ infectious complications were described in accordance with the CDC (Centers for Disease Control) definitions.^{19, 20}

Statistical Analysis

Descriptive data were expressed as counts and proportions for categorical variables; continuous variables were presented as median with interquartile range. Statistical analysis was performed using the χ^2 test or the exact Fisher test for comparison of categorical variables and the Student's *t* test or the Mann-Whitney *U* test for continuous variables. The differences were considered significant at a two-sided *p* value of < 0.05. All statistical analyses were performed using SPSS® 23.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Patient's Characteristics and Operative Details

We included 381 patients: 347 (91.1%) in G1 and 34 (8.9%) in G2. Table 1 shows the baseline characteristics and operative details. There were no significant differences for age (G1 63 years [47–75], G2 55 years [40–74]), male sex (G1 54.2%, G2 58.8%), comorbidity index (G1 2 [0–4], G2 2 [0–4]) and ASA classification (ASA I–II: G1 79.8%, G2 70.6%).

We detected higher values of leucocyte count in G1 ($p = 0.020$), alanine transaminase ($p = 0.011$) and alkaline phosphatase ($p = 0.014$) in G2 without clear clinical relevance. G2 had a higher percentage of grade II severity: 46.4% vs. 91.2% ($p < 0.001$) as per the definition of ACC by TG13¹ which describes grade II cholecystitis as patients with symptom duration of > 72 h.

Regarding operative details, there were no significant differences in conversion rate to open surgery: 8.6% in G1 vs. 11.8% in G2. G2 had a longer median operative time: 100 min [75–120] in G1 vs. 120 min [71–150] in G2, with no significant differences. The overall rate of intraoperative complications was 2.1% (G1 2% vs. G2 2.9%), including one bile duct injury in G1 (0.3%) which was treated intraoperatively with primary choledochorrhaphy (biliary leak was not present in the postoperative course). There were no intraoperative deaths.

Table 1 Cohort characteristics

	Total (n = 381)	Group 1 (n = 347)	Group 2 (n = 34)	p value
Age (years), median (IQR)	62 (47–74)	63 (47–75)	55 (40–74)	0.870
Male sex, n (%)	208 (54.6)	188 (54.2)	20 (58.8)	0.604
Charlson comorbidity index, median (IQR)	2 (0–4)	2 (0–4)	2 (0–4)	0.915
Diabetes mellitus, n (%)	68 (17.8)	65 (18.7)	3 (8.8)	0.150
Previous episode of ACC, n (%)	29 (7.6)	24 (6.9)	5 (14.7)	0.163
Previous intraabdominal surgery, n (%)	98 (25.7)	89 (25.6)	9 (26.5)	0.917
ASA classification				0.207
ASA I–II, n (%)	301 (79)	277 (79.8)	24 (70.6)	
ASA III–IV, n (%)	80 (21)	70 (20.2)	10 (29.4)	
Symptom duration, median (IQR)	3 (1–4)	2 (1–4)	10 (8–14)	< 0.001
Laboratory characteristics on admission				
Leukocyte count (cells/mm ³), median (IQR)	13,860 (10,950–17,230)	14,090 (11,160–17,370)	11,760 (8787–14,655)	0.020
Total bilirubin (mg/dl), median (IQR)	0.8 (0.5–1.3)	0.8 (0.6–1.3)	0.6 (0.4–1.1)	0.269
Aspartate aminotransferase (U/l), median (IQR)	24 (18–42)	24 (18–42)	27 (22–35)	0.435
Alanine transaminase (U/l), median (IQR)	25 (16–47)	24 (15–47)	35 (21–50)	0.011
Alkaline phosphatase (U/l), median (IQR)	83 (62–113)	79 (61–110)	103 (83–150)	0.014
Gamma-glutamyl transpeptidase (U/l), median (IQR)	42 (23–100)	40 (23–97)	56 (37–132)	0.076
Severity grade				< 0.001
Mild cholecystitis (grade I), n (%)	160 (42)	160 (46.1)	0 (0)	
Moderate cholecystitis (grade II), n (%)	192 (50.4)	161 (46.4)	31 (91.2)	
Severe cholecystitis (grade III), n (%)	29 (7.6)	26 (7.5)	3 (8.8)	
Surgery characteristics				
Conversion to open, n (%)	34 (8.9)	30 (8.6)	4 (11.8)	0.527
Resident as principal surgeon, n (%)	299 (78.5)	276 (79.5)	23 (67.6)	0.107
Operative time (min), median (IQR)	100 (75–120)	100 (75–120)	120 (71–150)	0.060
Intraoperative cholangiography, n (%)	16 (4.2)	15 (4.3)	1 (2.9)	1
Intraoperative common bile duct exploration, n (%)	10 (2.6)	8 (2.3)	2 (5.9)	0.222
Intraoperative complication, n (%)	8 (2.1)	7 (2)	1 (2.9)	0.530
Bleeding (> 500ml), n (%)	5 (1.3)	4 (1.2)	1 (2.9)	0.375
Bile duct injury, n (%)	1 (0.3)	1 (0.3)	0 (0)	1
Hollow viscus injury (trocar), n (%)	1 (0.3)	1 (0.3)	0 (0)	1
Intraoperative mortality, n (%)	0 (0)	0 (0)	0 (0)	–

ASA, American Society of Anesthesiologists; IQR, interquartile range

A similar number of patients across both groups had intraoperative cholangiogram or common bile duct exploration.

Postoperative Outcomes

Table 2 summarises the postoperative complications within the first 30 days. The rate of major postoperative complications (Clavien-Dindo \geq 3a) was 10.5%: 11% in G1 vs. 5.9% in G2. The bile leakage rate was 2.6% in G1 vs. 2.9% in G2. Cardiovascular, respiratory or renal complications were not significantly different between the groups. Both groups had similar percentages of infectious complications: incisional site infection was 3.7% in G1 vs. 2.9% in G2; organ/space (intra-abdominal) infection was 2.3% in G1 vs. 2.9% in G2. The

groups also had a similar median duration of AT: 5 days [3–7] in G1 vs. 5 days [3–10] in G2. Five patients, all in G1, underwent reoperation: two patients had acute abdomen and subsequent urgent laparotomy due to cystic stump leak, one patient had acute haemoperitoneum and one patient had fascial dehiscence and evisceration.

Four patients died: three in G1 (0.9%), representing one patient with myocardial infarction and two patients with multiple organ failure; one death was observed in G2 (2.9%) due to myocardial infarction. The median LOS did not differ: total LOS was 5 days [3–7] in G1 vs. 6 days [4–15] in G2; postoperative LOS was 4 days [3–7] in G1 vs. 5 days [3–7] in G2. Readmission rates were: 3.7% in G1 vs. 5.9% in G2. There were no significant differences

Table 2 Postoperative outcomes (first 30 days)

	Total (n = 381)	Group 1 (n = 347)	Group 2 (n = 34)	p value
Major complications, n (%)	40 (10.5)	38 (11)	2 (5.9)	0.557
Bile leakage, n (%)	10 (2.6)	9 (2.6)	1 (2.9)	1
Haemorrhage, n (%)	6 (1.6)	4 (1.2)	2 (5.9)	0.092
Acute heart failure, n (%)	13 (3.4)	11 (3.2)	2 (5.9)	0.326
Acute myocardial infarction, n (%)	2 (0.5)	1 (0.3)	1 (2.9)	1
Acute respiratory insufficiency, n (%)	22 (5.8)	20 (5.8)	2 (5.9)	1
Acute pulmonary thromboembolism, n (%)	0 (0)	0 (0)	0 (0)	–
Acute kidney injury, n (%)	22 (5.8)	20 (5.8)	2 (5.9)	1
Infectious postoperative complications, n (%)	25 (6.6)	22 (6.3)	3 (8.8)	0.479
SSI – Overall, n (%)	23 (6)	21 (6.1)	2 (5.9)	1
SSI – Incisional, n (%)	14 (3.7)	13 (3.7)	1 (2.9)	1
SSI – Organ/space, n (%)	9 (2.4)	8 (2.3)	1 (2.9)	0.573
Urinary tract infection, n (%)	1 (0.3)	0 (0)	1 (2.9)	0.089
Pneumonia, n (%)	2 (0.5)	2 (0.6)	0 (0)	1
Antibiotic therapy global duration, median (IQR)	5 (3–7)	5 (3–7)	5 (3–10)	0.678
Reoperation, n (%)	5 (1.3)	5 (1.4)	0 (0)	1
Overall mortality, n (%)	4 (1)	3 (0.9)	1 (2.9)	0.313
Total length of stay, median (IQR)	5 (3–7)	5 (3–7)	6 (4–15)	0.142
Postoperative stay, median (IQR)	4 (3–7)	4 (3–7)	5 (3–7)	0.539
Readmission, n (%)	15 (3.9)	13 (3.7)	2 (5.9)	0.633
Cost (€), median (IQR)	6040 (3709–8486)	6035 (3693–8330)	7243 (4921–11,336)	0.395

IQR, interquartile range; SSI, surgical site infection

for the median total cost (€) of hospitalisation: G1 6035 [3693–8330] vs. G2 7243 [4921–11,336].

Discussion

The continuous improvement in laparoscopic procedures has progressively reduced the relative contraindications of surgery in ACC. Although benefits of same-admission LC for patients with ACC have already been detailed meticulously,^{4–6, 9} the optimal timing of ELC has not yet been clearly established. Until a few years ago, the recommendation of performing ELC was limited to the first 72 h from onset because of the possibility of obtaining a higher conversion rate and worse morbidity outcomes.^{7, 21} In relation to this, some authors have argued that the operative difficulty increases proportionally to the days of evolution from the onset of symptoms, with greater inflammatory adhesions in these patients.^{7, 14, 22} However, several studies have demonstrated safety and potential benefits for ELC within the first 7 days of symptoms.^{9, 23} A recent RCT published by Roulin et al.²⁴ showed promising results for ELC in patients with moderate ACC and more than 72 h of symptom duration, without establishing an upper barrier for surgery. However, the median length of symptoms was only 4 days in the ELC group. Very few studies,^{25–27} none RCT, have analysed

the outcomes of ELC in patients who strictly presented with more than 1 week of symptoms. Tan et al.^{26, 27} observed a conversion rate of 21% for patients with more than 7 days of symptoms and higher total LOS for this group, without significant differences regarding median postoperative LOS. In our analysis, no significant differences were detected for conversion rate, morbidity and LOS (both total and postoperative). Regarding operative time, our results show that it could be somewhat higher for patients with delayed presentation. It must be considered that no bile duct injuries were observed in G2, while G1 included one case that required a bile duct repair. These data should therefore be further assessed in a larger RCT. The present study also reports additional results on total days with AT prescribed and the total cost of hospitalisation, with both variables being similar between the groups.

The recently updated TG18¹⁰ have updated their recommendations and proposed, for the first time, ELC for patients who can tolerate surgery regardless of exactly how much time has passed since onset. Our series confirms these data, making us think about the real role of the symptom duration referred by patients due to the non-specific nature. Other possible factors influencing intraoperative difficulty and perioperative morbidity and mortality of ELC have been suggested, including laboratory parameters, radiologic findings or patient characteristics.^{28–31} Male patients with advanced age and higher body mass index

could represent a clinical profile with a higher risk of conversion and postoperative morbidity.^{28, 30, 31} Preoperative laboratory variables associated with higher rates³¹ of conversion to an open procedure include white blood cell count, bilirubin or C-reactive protein; ultrasonographic features are the presence of pericholecystic fluid and impacted stones.³¹ In this way, the Tokyo Guidelines¹⁰ already recommend an exhaustive preoperative evaluation of general condition using Charlson index¹⁶ and ASA performance status¹⁷, which would be the predictive factors within each severity grade of ACC. Future prospective studies should investigate outcomes of LC in specific patients with delayed presentation and determine precise predictive factors for a safe and cost-effective ELC.

Our study has some limitations. It is a retrospective review and it increases the possibility of potential selection bias, although patients' characteristics were similar in both groups. The patients identified within the two groups were based on the specified criterion of symptoms referred from onset, being non-specific criteria due to variable perception. Moreover, the limited size of included patients, especially in G2 could imply a lower power for the detection of small significant differences in postoperative outcomes. In addition to this, the incidence of certain complications was too small to draw conclusions about them. Finally, it must be taken into account that patients with initial non-operative management of ACC with >7 days of symptoms who were operated on several weeks later were excluded from our analysis. Comparison of DLC of patients with ACC with >7 days of symptoms and initial non-operative management with ELC would be an interesting topic for further research.

Conclusion

ELC may be considered for patients with ACC who can tolerate surgery with more than 1 week of symptom duration.

Author Contribution We hereby certify that all listed co-authors were integrally involved in the formation of this manuscript via study conception/design and/or data acquisition and analysis/interpretation. Furthermore, all authors made significant contributions to the drafting or critical revisions of the manuscript, and all authors gave final approval prior to submission for publication.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Abbreviations ACC, acute calculous cholecystitis; ASA, American Society of Anesthesiologists; CDC, Centers for Disease Control; DLC, delayed laparoscopic cholecystectomy; ELC, early laparoscopic cholecystectomy; G1, group 1; G2, group 2; LC, laparoscopic cholecystectomy; LOS, length of stay; RCT, randomised controlled trial; TG13, Tokyo Guidelines 2013; TG18, Tokyo Guidelines 2018

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