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Acute Cholecystitis best timing of Laparoscopic Cholecystectomy

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Abstract

Introduction: Acute cholecystitis is not uncommon surgical disease. Laparoscopic cholecystectomy is the method of choice of surgical treatment. The appropriate time of laparoscopic cholecystectomy remains a debatable issue in the treatment of acute cholecystitis.

Patients and methods: A total of 50 patients presented with acute cholecystitis were divided into two groups according to time elapsed between onset of symptoms and operation. Group 1 patients underwent surgery within 72 hours of onset of symptoms. Group 2 patients underwent surgery after 72 hours of onset of symptoms till about 10 days. The overall primary outcome of laparoscopic cholecystectomy included conversion rate, complication rate, mortality rate and secondary outcomes including operative time and postoperative hospital stay.

Results: As regard to outcome only one patient in the group 1 and 3 in group 2 required conversion to open surgery because of difficulty in dissection at Calot's triangle. Complications were recorded in 12 (24%) of the cases; 2 (9%) and 10 (36%) patients in group 1 and 2, respectively. No significant difference in morbidity detected between both groups. Both preoperative and total hospital stays were significantly shorter in group 1. No mortality recorded in both groups. Univariate logistic analysis showed that age, diabetes, and complicated acute cholecystitis were significant factors associated with a higher rate of postoperative complications. In the multivariate model, diabetes and leucocytosis $\geq 18x10^9/L$ were the only parameters of statistical significance in estimating the risk of complicated acute cholecystitis.

Conclusion: Although the proper time of laparoscopic cholecystectomy for acute cholecystitis doesn't seem to affect the perioperative outcomes, but delaying surgery due to any patient or physician factors will increase the preoperative and total hospital stay. So, it is ideal to operate as early as possible during the same admission.

Keywords: Acute cholecystitis, early laparoscopic cholecystectomy

Introduction

Acute cholecystitis considered to be one of the most common diseases in surgical practice with high socioeconomic impact [1]. The treatment modalities of acute cholecystitis have changed dramatically during the last three decades [2]. New guidelines (Tokyo Guidelines) for diagnosis, assessment, and treatment have recently been published [3] and also revised [4, 5]. Open cholecystectomy was performed on patients suffering from acute cholecystitis until the late 1980s.

At the beginning of laparoscopic era, acute cholecystitis was considered as a relative contraindication to laparoscopic cholecystectomy. In the present time, laparoscopic cholecystectomy is regarded as effective and safe procedure for acute cholecystitis since experience and proficiency have grown over the last two decades. Recent publications did not reported significant elevation of surgical morbidity or mortality after laparoscopic cholecystectomy in patients with acute cholecystitis. Actually, some current literature does not recommend open surgery anymore in this group of patients [6, 8] and laparoscopic cholecystectomy is gaining more and more popularity in the treatment of acute cholecystitis [1].

However, about one third of all cholecystectomies are still performed through laparotomy incision [9, 11]. Certainly, there is a disparity between the recommendation for laparoscopic cholecystectomy and the daily practice where a significant proportion of acute cholecystitis patients are treated by open cholecystectomy. The main obstacle for laparoscopic cholecystectomy in acute cholecystitis patients might be the fear of conversion to open cholecystectomy.

Several authors have demonstrated that conversion to open cholecystectomy significantly lengthens the time of the procedure and hospital stay and increases complications [7, 12]. Moreover, from a surgical point of view, a conversion from laparoscopic cholecystectomy to open cholecystectomy can easily be considered as an individual "failure" of the individual surgeon, and supporters of the laparoscopic approach strive to achieve the lowest conversion rate [8, 13]. However, open cholecystectomy represents a common incident in surgical practice involving a considerable number of patients.

Many studies have specified risk factors associated with conversion to open cholecystectomy in laparoscopic cholecystectomy for acute cholecystitis [14, 15]. Commonest risk factors include age [13], male gender [7, 13], obesity [13, 18], delayed surgical intervention [16], large and impacted gallbladder stones [17, 18], severe comorbidities [13], previous surgery [18], gangrenous cholecystitis [19], urgent surgery [20, 21], and preoperative high level of serum C-reactive protein (CRP) [22, 23]. Interestingly enough, few studies frankly examined characteristics and outcome of the patients who underwent open cholecystectomy [9, 17, 20, 24].

There is little helpful evidence for decision making in patients suffering from acute cholecystitis. The key question revolves every surgeon, "open or cholecystectomy laparoscopic," usually far from being answered. It is not fully determined who might benefit from a laparoscopic approach in spite of calculated risk for open cholecystectomy and who will be benefited from it.

Patients and Methods

Patients

Fifty patients with acute cholecystitis fulfilling the inclusion criteria of the study underwent laparoscopic cholecystectomy. The data were collected prospectively from June 2014 to May 2016. Patients were divided in two groups according to time elapsed between onset of symptoms and operation. Group 1 patients underwent surgery within 72 hours of onset of symptoms. Group 2 patients underwent surgery after 72 hours of onset of symptoms till about 10 days.

Only patients with acute calcular cholecystitis were included in the study. Patients were considered having acute cholecystitis according to the updated Tokyo Guidelines 2013 (TG13) which described diagnostic criteria (Table 1) and surgical treatment (Table 2) for acute cholecystitis according to the grade of severity, the timing, and the procedure used for cholecystitis. [25] Patients with suspected gall bladder malignancy, CBD stones, cholangitis, pancreatitis, unclear timing of symptom onset and unfit patients for general anesthesia were excluded.

Data sheets for patients, containing demographic, pre-operative, per-operative, and post-operative findings, were prospectively generated into computerized database using non-randomized consecutive sampling.

Demographic & preoperative patient characteristics' data including age, sex, body mass index (BMI, kg/m^2) and comorbidities as defined by the American Society of Anesthesiologists (ASA) at the time of surgery were retrieved for each patient, history of acute cholecystitis, and history of abdominal operation. Temperature, Murphy's sign, palpable gallbladder mass, severity grading of acute cholecystitis according to Tokyo guidelines 2013 and laboratory results.

All patients underwent proper history taking, meticulous clinical examination, and laboratory testing [complete blood count, serum bilirubin (total, direct, and indirect), plasma albumin, liver enzymes (alkaline phosphatase, SGOT, and SGPT), prothrombin time and concentration, blood glucose, serum creatinine, blood urea, serum amylase, and lipase]. Ultrasonography of the abdomen establishes the diagnosis of gallstones or abnormalities of the gallbladder wall (Table 3). [26] CT and MRI abdomen (Table 4) was done in equivocal cases [26]. After admission to the hospital supportive care starts immediately, which includes intravenous fluid therapy, correction of electrolyte, control of pain, and antibiotics. A detailed informed written consent was obtained from all patients. Each patient was informed about the procedure details with the possibility of conversion to an open procedure, and expected complications.

The operative data were macroscopic findings of acute cholecystitis (simple or complicated acute cholecystitis which includes; empyema, gangrenous or perforated gallbladder), and amount of adhesions to the gallbladder. Operative time was taken from time of initial skin incision to time of skin closure.

Postoperative data included rate of conversion, complications (bleeding, biliary tract injury, biliary leak, jaundice, intra-abdominal sepsis, wound infection and respiratory infection), management in the intensive care unit (ICU), reoperation, postoperative ERCP, postoperative morbidity and mortality and hospital stay were recorded for each case.

The overall primary outcome of laparoscopic cholecystectomy included conversion rate, complication rate, mortality rate and secondary outcomes including operative time and postoperative hospital stay.

Methods

Since the introduction of laparoscopic cholecystectomy, it has not been advocated for acute cholecystitis. However, due to the introduction of the critical view of safety by Strasberg *et al*. for the dissection of Calot's triangle (Fig. 1), the development of new techniques, and the improvements made to the instruments used for endoscopic surgery, laparoscopic cholecystectomy is now considered as a safe surgical technique when it is performed by expert surgeons [27].

Under general anesthesia a typical four port laparoscopic cholecystectomy technique was used. In the presence of a phlegmon (Fig. 2A), or gangrenous gallbladder (Fig. 2B) the omentum, duodenum and colon were dissected off by blunt and sharp dissection to expose the gallbladder. Watchful dissection of the hepatocystic triangle was performed using usually a diathermy hook (Fig. 3A) as well as blunt dissection with a suction irrigator (Fig. 3B) for identification of the cystic duct and artery within the Calot's triangle (Fig. 4A). The cystic duct milked proximally with a Maryland dissector (Fig. 4B) followed by clipping & division of cystic artery (Fig. 5A) and duct (Fig. 5B). The gallbladder dissected off from its bed (Fig. 6A) and extracted through the epigastric port within a retrieval bag (Fig. 6B). Statistical analysis of the data was performed using Statistical Package for the Social Sciences (SPSS), version 20 and Log Xact (version 10; Cytel Software Corp., Cambridge, MA).

Table 1. Diagnostic criteria for acute cholecystitis [2013 Tokyo Guidelines (TG13)] [25].

A. Local signs of inflammation etc.
(1) Murphy's sign, (2) RUQ mass/pain/tenderness
B. Systemic signs of inflammation etc.
(1) Fever, (2) elevated CRP, (3) elevated WBC count
C. Imaging findings characteristic of acute cholecystitis
Suspected diagnosis: One item in A + one item in B Definite diagnosis: One item in A + one item in B + C

* Acute hepatitis, other acute abdominal diseases, and chronic cholecystitis should be excluded.

* RUQ, right upper abdominal quadrant; CRP, C-reactive protein; WBC, white blood cell.

* Elevation of CRP level (3 mg/dl or more)

Table 2: Severity assessment criteria for acute cholecystitis [2013 Tokyo Guidelines (TG13)] [25].

"Grade I" (mild) acute cholecystitis does not meet the criteria of "Grade III" or "Grade II" acute cholecystitis. Grade I can also be defined as acute cholecystitis in a healthy patient with no organ dysfunction and mild inflammatory changes in the gallbladder, making cholecystectomy a safe and low-risk operative procedure
"Grade II" (moderate) acute cholecystitis is associated with any one of the following conditions:
1. Elevated WBC count (>18,000/mm3) 2. Palpable tender mass in the right upper abdominal quadrant 3. Duration of complaints >72 h 4. Marked local inflammation (gangrenous cholecystitis, pericholecystic abscess, hepatic abscess, biliary peritonitis, emphysematous cholecystitis)
"Grade III" (severe) acute cholecystitis is associated with dysfunction of any one of the following organs/systems:
1. Cardiovascular dysfunction (Hypotension requiring treatment with dopamine ≥5 μg/kg per min, or any dose of norepinephrine) 2. Neurological dysfunction (Decreased level of consciousness) 3. Respiratory dysfunction (PaO2/FiO2 ratio <300) 4. Renal dysfunction (Oliguria, creatinine >2.0 mg/dl) 5. Hepatic dysfunction (PT-INR >1.5) 6. Hematological dysfunction (Platelet count <100,000/mm3)

Table 3: Ultrasonographic diagnostic criteria for acute cholecystitis [26].

Ultrasonography findings:
• Sonographic Murphy sign (tenderness elicited by pressing the gallbladder with the ultrasound probe) • Thickened gallbladder wall (>4 mm; if the patient does not have chronic liver disease and/or ascites or right heart failure) • Enlarged gallbladder (long axis diameter >8 cm, short axis diameter >4 cm) • Incarcerated gallstone, debris echo, pericholecystic fluid collection • Sonolucent layer in the gallbladder wall, striated intramural lucencies, and Doppler signals.

Table 4: CT and MRI diagnostic criteria for acute cholecystitis. [26]

Computed tomography (CT) findings:
• Thickened gallbladder wall • Pericholecystic fl uid collection • Enlarged gallbladder • Linear high-density areas in the pericholecystic fat tissue.
Magnetic resonance imaging (MRI) findings:
• Pericholecystic high signal • Enlarged gallbladder • Thickened gallbladder wall.

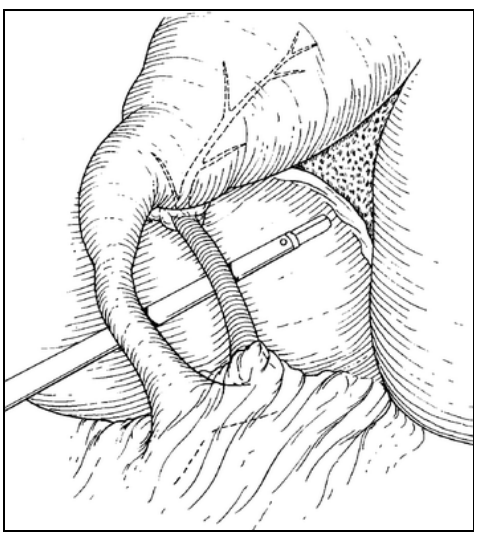

Fig 1: Creation of a critical view of safety. Calot's triangle is dissected free of fat and fibrous tissue and the lower end of the gallbladder is dissected off the liver bed. It is not necessary to expose the common bile duct. The critical view of safety is now the ultimate standard to prevent bile duct injury during laparoscopic cholecystectomy. Failure to create this view is an indication for conversion to open cholecystectomy [26].

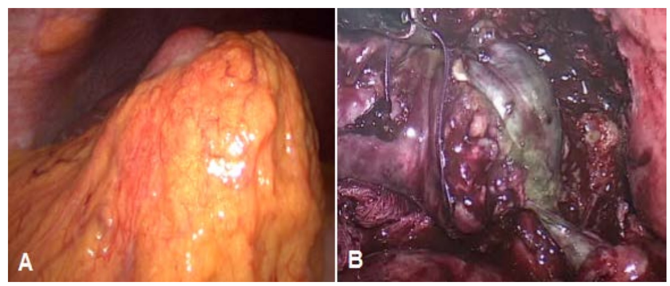

Fig 2: Acute cholecystitis forming phlegmon (A), and gangrenous cholecystitis (B).

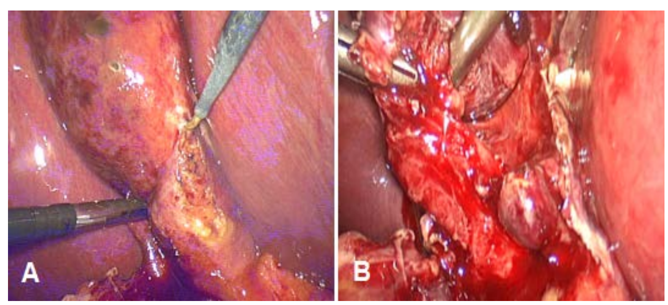

Fig 3: Dissection of Calot's triangle by diathermy hook (A), and by suction irrigator (B).

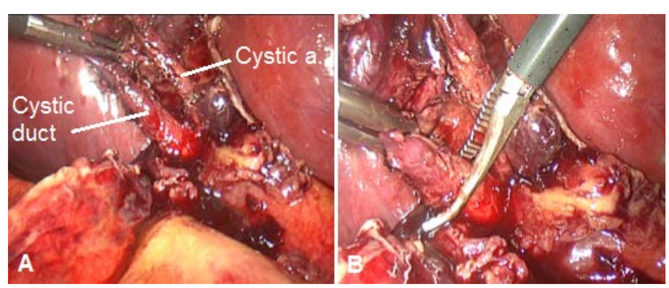

Fig 4: Critical view of safety (A), milking of cystic duct (B).

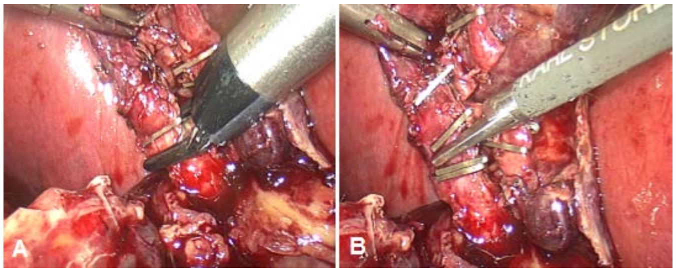

Fig 5: Clipping and division of cystic artery (A) and duct (B).

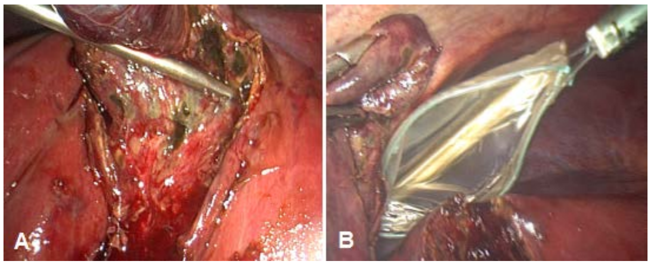

Fig 6: Dissection of gallbladder from liver bed (A), and extraction of gallbladder within a retrieval bag (B).

Results

During study period laparoscopic cholecystectomy performed within 72 hours of onset of symptom in 22 patients (44%) [Group 1] and after 72 hours in 28 patients (56%) [Group 2]. Demographic and preoperative patient characteristics were summarized in Table 5.

On analysis of the clinical severity, patients were classified according to Tokyo guidelines 2013 as mild [17 (89.5%)], moderate [1 (5.3%)], and severe [1 (5.3%)] in the group 1 and mild [0 (0%)], moderate [30 (96.8%)], and severe [1 (3.2%)] in the group 2. This difference between both groups was statistically significant (p = 0.012).

Comorbidities were documented in 28 patients; of which 10 patients had diabetes mellitus, 6 had hypertension, 2 had ischemic heart disease, 6 had asthma, 6 had hepatic diseases, 22 had BMI ≥ 30. There were 12 patients of ASA grade 1, 36 patients with ASA grade 2 and 2 patients with ASA grade 3. There was no statistically significant difference between both groups with respect to previous history of acute cholecystitis, history of abdominal operation, fever >38 °C, Murphy's sign, palpable gallbladder mass, leucocytosis > 18x10^9/L and comorbidities (p > 0.05) (Table 6).

Intraoperatively, 40 cases had non-complicated acute cholecystitis, 5 had empyema, 3 had gangrenous cholecystitis and 2 had perforated gallbladder. This difference between both groups was not statistically significant. Also, gallbladder adhesions were seen in 41 cases. The difference between both groups was insignificant statistically (p value<0.05) (Table7).

As regard to outcome only one patient in the group 1 and 3 in group 2 required conversion to open surgery because of difficulty in dissection at Calot's triangle. The statistical difference between the two groups was insignificant.

Complications were recorded in 12 (24%) of the cases; 2 (9%) and 10 (36%) patients in group 1 and 2, respectively. There was no significant difference in the rate of complications between both groups (Table 8). Both preoperative and total hospital stays were significantly shorter in group 1. No mortality recorded in both groups.

Univariate logistic analysis showed that age, diabetes, and complicated acute cholecystitis were significant factors associated with a higher rate of postoperative complications. The timing from the onset of acute cholecystitis to cholecystectomy was not a significant predictor of postoperative complications (Table 9).

In the multivariate model, diabetes (OR 5.84; 95 % CI 2.10-44.82; *p* = 0.044), and leucocytosis ≥18x10^9/L (OR 8.60; CI 1.94-56.22; *p* = 0.036) (Table 10) were the only parameters maintained statistical significance in estimating the risk of complicated acute cholecystitis.

Table 5: Demographics and Preoperative Patients' Characteristics

	Group 1		Group 2		p-value
	N (22)	44%	N (28)	56%	
Age (y), mean±SD	41±12		34±18		0.420
Gender					0.816
Male	7	32%	9	32%	
Female	15	68%	19	68%	
Previous Acute Cholecystitis		0.682			
No	20	91%	25	89%	
Yes	2	9%	3	11%	
History of Abdominal Operation					0.640
None	19	86%	26	93%	
Upper	2	9%	1	3.5%	
Lower	1	5%	1	3.5%	
Temperature					0.486
< 38ºC	8	36%	12	43%	
≥ 38ºC	14	64%	16	57%	
Murphy's Sign					0.662
Absent	4	18%	3	11%	
Present	18	82%	25	89%	
Palpable Gallbladder Mass					0.814
Absent	12	55%	13	46%	
Present	10	45%	15	54%	
WBC					0.680
< 18 x 10^9/L	14	64%	16	57%	
≥ 18 x 10^9/L	8	36%	12	43%	
Clinical Severity Grading					0.012*
Tokyo grade I	14	64%	6	21%	
Tokyo grade II	5	23%	20	72%	
Tokyo grade III	3	13%	2	7%	

Table 6: Patients' comorbidities.

	Group 1		Group 2		p-value
	N (22)	44%	N (28)	56%	
Diabetes					0.482
Absent	18	82%	22	79%	
Present	4	18%	6	21%	
Hypertension					0.626
Absent	19	86%	25	89%	
Present	3	14%	3	11%	
Ischemic Heart disease					0.860
Absent	21	95%	27	96%	
Present	1	5%	1	4%	
Asthma					0.460
Absent	20	91%	24	86%	
Present	2	9%	4	14%	
Hepatic					0.312
Absent	19	86%	25	89%	
Present	3	14%	3	11%	
BMI					0.416
< 30	12	55%	16	57%	

≥ 30	10	45%	12	43%	
ASA					0.680
ASA I	5	22.5%	7	25%	
ASA II	16	73%	20	71%	
ASAIII	1	4.5%	1	4%	

Table 7: Operative findings

	Group 1		Group 2		p-value
	N (22)	44%	N (28)	56%	
Acute cholecystitis					0.482
Non complicated	19	86.5%	21	75%	
Complicated					
Empyema	2	9%	3	11%	
Gangrenous	1	4.5%	2	7%	
Perforated	0	0%	2	7%	
Gallbladder Adhesions					0.260
Absent	7	32%	2	7%	
Present	15	68%	26	93%	
Median oper. time (min)	94		102		0.628

Table 8: Morbidity and mortality

	Group 1		Group 2		*p*-value
	N (22)	44%	N (28)	56%	
Conversion to open	1	4.5%	3	11%	0.420
Total complications	2	9%	10	36%	0.226
Severe bleeding	0	0.0%	1	3.5%	0.860
Biliary tract injury	0	0.0%	0	0.0%	-
Jaundice	0	0.0%	1	3.5%	1.000
Intra-abdominal collection	1	4.5%	2	7%	1.000
Wound infection	0	0.0%	2	7%	0.822
Respiratory infection	1	4.5%	2	7%	0.720
Other complications	0	0.0%	2	7%	0.818
Postoperative ICU	1	4.5%	4	14%	0.460
Postoperative ERCP	0	0.0%	2	7%	0.688
Reoperation	0	0.0%	1	3.5%	0.812
Hospital stay					
Preoperative stay(d), median	1.2		3.8		0.086*
Postoperative stay(d), median	2.6		5.2		0.220
Total Stay(d), median	2.8		8.9		0.024*
Mortality	0	0.0%	0	0.0%	-

Table 9: Univariate analysis of risk factors for postoperative complications**.**

	Postoperative Complications				
	Absent		Present		*p-value*
	N (38)	76%	N (12)	24%	
Age	42±64		62±12		0.046*
Diabetes	2	20%	8	80%	0.062*
Complicated AC	3	30%	7	70%	0.088*

Table 30: Multivariate analysis of risk factors for complicated acute cholecystitis.

Factors	Adjusted Odds	Confidence interval	*p*-value
Diabetes [a]	5.84	2.10-44.82	0.044*
Temperature ≥ 38° C	4.93	0.33-72.87	0.245
WBC ≥ 18x10^9/L	8.60	1.94-56.22	0.036*

Discussion

Currently, the best timing of laparoscopic cholecystectomy for acute cholecystitis is a matter of controversy. However, many researchers have recommended early same admission laparoscopic cholecystectomy [28, 29].

For various reasons, it is not always feasible to operate on patients admitted with acute cholecystitis urgently because of patient and/or physician delay. The question remains whether there is a difference in outcomes when surgery is performed at any time during the same admission [30].

The main purpose of the present study is to identify the best time for laparoscopic cholecystectomy during acute attach of cholecystitis. Therefore, to certainly answer this question, a relationship between time of operation and outcome should be established. The primary outcomes include rate of conversion, complications and mortality while the secondary outcomes include the duration of surgery and postoperative hospital stay. Also to identify the factors significantly associated with a higher rate of postoperative complications.

The pathological process of acute cholecystitis is considered one of the important issues to understand the extent of the effect of the operative timing of cholecystectomy on the outcomes. According to the operating surgeon, the intraoperative findings of acute cholecystitis were grossly divided to simple and complicated (including empyema, gangrenous cholecystitis, and perforated gall bladder with peritonitis). These findings are associated with the pathological course of acute cholecystitis which starts with edematous stage in the early 72 hours then progress to chronic fibrotic stage [31].

The present study demonstrated that complicated cholecystitis is significantly associated with age, diabetes mellitus, fever > 38° C, palpable gall bladder mass, leucocytosis ≥ 18 X 10^9/L and higher Tokyo severity grades. Similar results were drawn by many literatures which reported that older male patients (age older than 50 years) with history of diabetes, coronary artery disease, leukocytosis greater than 17 X 10^9/L, elevated bilirubin, and gall bladder wall thickness (sonographic) more than 4.5 mm are important risk factors for suspicion of complicated acute cholecystitis. [32, 33] In fact, diabetes and leucocytosis ≥ 18 X 10^9/L rather than time of surgery, are the main predictive factors for complicated acute cholecystitis.

Conversion from laparoscopic to open surgery is required when safe laparoscopic procedure cannot be ensured. It is considered as a sound judgment rather than failure of laparoscopic surgery to avoid complications and reduce morbidity [34]. The overall conversion rate to open cholecystectomy was 8% (4 cases) in the present study [one patient in the group 1 (4.5%) and 3 in group 2 (10.7%)] which is comparable to other studies (range 5-28%). [31, 35, 37] found significant decrease in conversion rate if patients were operated on within 72 hours of symptom onset. Some authors detected no significant association between the conversion rate and time of laparoscopic cholecystectomy [38, 41].

Contrary to expectations, there were no statistically significant difference in conversion rate between both groups. This reflects that the conversion is not time related but depends on the intraoperative patient findings, the surgeon's skills and equipment as well as the surgeon's threshold for conversion [42].

In the literature, the reported complication rate was 10- 32%. The present study complication rate was 24%. [30, 31, 36, 39] Complications developed in 2 patients (9%) in group 1 and 10 (36%) in group 2, and no statistically significant difference was found between groups. In group 1, one patient developed respiratory infection and admitted to the intensive care unit. The patient was managed conservatively with antibiotics. Another one developed intra-abdominal collection and drained with pig-tail catheter. In group 2, one patient complicated by intraoperative bleeding from avulsed cystic artery from its origin from the right hepatic artery which controlled by intracorporeal suturing and blood transfusion. One patient developed jaundice from missed CBD stone and extracted with ERCP. Intra-abdominal fluid collection developed in two patients in group 2 which drained by pig-tail catheter in one patient and open drainage in the other patient. Also wound infection developed in two patients in group 2 which relieved with drainage and antibiotics. Lastly respiratory infection developed in two patients in group 2 and improved on conservative management.

Bile duct injury is one of the most distressing and critical complications of laparoscopic cholecystectomy. Corrective surgery for bile duct injury has a high morbidity and mortality rate. No patient in our study experienced this complication. Reported bile duct injury rate in early laparoscopic cholecystectomy was 0–5%. On the other hand, because of the small number of patients in the present study likelihood of uncommon complications such as bile duct injury cannot be eliminated in future [43, 44].

Zafar et al., 2015 and Rajcok et al., 2016 identified that complication rate was higher when surgery performed after 72 hours of onset of symptoms. [30, 37] But *Zhu et al., 2012* in china didn't found significant difference regarding wound infection rates between groups and also published that there was no biliary tract injury or biliary leak, and no 30-day readmission rates in both groups [36] *Degrate et al., 2013; Meng et al., 2012; Ohta et al., 2012; and Chandler et al., 2000* didn't found significant association between complication rate and timing of laparoscopic cholecystectomy which was similar to our findings. This is attributed to surgeon experience, operative technique and equipment availability. No mortality was documented in the present study [35, 39, 40, 45].

By reviewing the operative time and hospital stay as the secondary outcomes, findings of the present study showed that operation beyond 72 h up to 10 days was not more difficult to perform with no significant difference in operative time. This is attributed to increasing experience.

Zhu et al., 2012 reported that operating on within 72 hours had a significantly shorter operating time. [36] While *Degrate et al., 2013; Gomes et al., 2013; Ohta et al., 2012 and Meng et al., 2012* didn't find any significant relationship between the length of operation and the timing of laparoscopic cholecystectomy which was similar to the present findings [31, 35, 39, 40].

Furthermore, results of the present study revealed that those operated beyond 72 hours had statistically significant longer preoperative and total hospital stay. While they had insignificantly different postoperative hospital stay in comparison to those operated less than 72 hours.

Degrate et al., 2013 and Zhu et al., 2012 found no significant association between the timing of laparoscopic cholecystectomy and postoperative hospital stay. They identified that the total hospital stay was shorter in the group of <72 hours [36, 39].

Meng et al., 2012 and Ohta et al., 2012 reported that the timing of laparoscopic cholecystectomy has no significant effect on total length of hospital stay in cases with acute cholecystitis [35, 40].

By a univariate analysis, age, diabetes, and surgical findings of acute cholecystitis (including complicated acute cholecystitis) were associated with a higher risk for development of postoperative complications. Most of these factors are already known to be associated with complications *(Degrate et al., 2013; Gorka and Azad, 2013 and Botaitis et al., 2012)* but it is remarkable that the timing of cholecystectomy was not identified as a predictor of postoperative morbidity [39, 46, 47].

In fact, these factors were related with the occurrence of complications, as shown by the multivariate analysis, suggesting that complicated forms of acute cholecystitis rather than the timing of surgery, is the key element that affecting postoperative complications.

Results of the present study couldn't determine any significant association between primary and secondary outcomes in one hand and timing of laparoscopic cholecystectomy within or after 72 hours from symptom onset on the other hand. However, the earlier the operation is performed, the total hospital stay will decrease.

However, we should highlight that the pathologically complicated forms of acute cholecystitis as phlegmonous, gangrenous, empyema and perforated gallbladder are challenging and difficult and should be performed by a highly experienced surgeon and promptly converted to open cholecystectomy if operative conditions make anatomical identification difficult.

In conclusion, although the timing of laparoscopic cholecystectomy for acute cholecystitis doesn't seem to affect the perioperative outcomes, but delaying surgery due to any patient or physician factors will increase the preoperative and total hospital stay. So, it is ideal to operate as early as possible during the same admission. Complicated forms of acute cholecystitis are affected by many variables rather than timing of surgery and can be safely completed with experienced hands as they are technically demanding.

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