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Outcomes of early and interval laparoscopic cholecystectomy for acute cholecystitis at a teaching hospital in Kerala: A prospective observational comparative study

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Abstract

Timing of laparoscopic cholecystectomy, a widely used treatment modality for acute cholecystitis remains controversial. This prospective observational comparative study investigated patient outcomes for early (ELC) and interval laparoscopic cholecystectomy (ILC) in patients with acute cholecystitis admitted to the General Surgery Department at a tertiary care centre in Thrissur, Kerala, between December 2018 and June 2020. Of 67 patients, 34 were assigned to ELC and 33 to ILC groups and followed up for 2 weeks post-surgery. Patient characteristics, clinical features, investigations, intra operative details and post operative outcomes were tabulated. Comparison of age was statistically analyzed using student's 't' test, demographics and morbidity data using Fisher's exact test/ Chi-square test and length of hospital stay using Mann Whitney U test. Mean age was significantly higher in the ILC group. 66% of study participants were females with a higher proportion of females observed in the ILC group. Post-surgical complications were not significantly higher in ELC group compared to ILC group. Total length of hospital stay was significantly longer in the ILC group than in ELC group (10.2 ±4.5 vs. 7.1 ±3.0) days, p value: 0.001). Duration of hospital stay for the laparoscopic cholecystectomy procedure taken separately, was longer in ELC group comparatively, 7 ±3.01 versus 4 ±-2.38, (p value: <0.001). There was no mortality. It was observed in the present study that ELC is preferable to ILC for acute cholecystitis with added benefit of shorter hospital stay. Further large randomized trials would be valuable to make recommendations for future management.

Keywords: acute cholecystitis; laparoscopic cholecystectomy; hospital stay; conversion rate

Introduction

Acute cholecystitis, a frequently seen acute surgical disease is a potential life-threatening condition, which if not treated early may lead to gangrenous (GC) and perforated cholecystitis [1]. Laparoscopic cholecystectomy (LC) has emerged as the preferred treatment option for acute cholecystitis and can be performed during the initial attack as an early laparoscopic cholecystectomy (ELC), from 24 hours up to 7 days after either the onset of symptoms or the time of diagnosis. In others, it can be performed later as an interval cholecystectomy (ILC), 2-3 months after the initial attack has subsided [1]. Meta-analysis and randomized controlled trials have shown early surgery (within 24 to 72 hours) is beneficial as compared to delayed cholecystectomy, with lower mortality rates, complication rates, incidence of bile duct injury, conversion to open surgery as well as hospital stay and costs [2].

However, some studies have reported that ELC for acute cholecystitis is associated with higher intra operative and post operative complications [3], as well as high conversion rate compared to delayed intervention [4]. This is a cause for concern [4] and there is significant variation in clinical practice worldwide [5]. On the

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contrary, Lo et al reported that delayed LC has a tendency toward a higher conversion and complication rate besides prolonged total hospital stay [6].

Hence, the exact timing and potential benefits, of LC for acute cholecystitis continue to be controversial [3] and this aspect has been less studied in Kerala. The present study therefore investigated the patient outcomes following ELC and ILC in acute cholecystitis. The study compared duration of hospital stay, operative procedure difficulty, complications, morbidity and mortality between the two study groups, which would help us understand the advantages if any, in performing ELC in a tertiary centre in Kerala. This study we hope would help determine the appropriate timing of surgical intervention in acute cholecystitis in the local population.

Methodology

A prospective observational comparative study was conducted from December 2018 to June 2020, at a tertiary care centre in Thrissur, Kerala. The study included all patients presenting to the Department of General Surgery aged 19 to 65 years, diagnosed to have acute cholecystitis based on clinical features, laboratory investigations and ultrasonographic criteria. CT scan and MRI were done when indicated. Pregnant patients, those with biliary pancreatitis, a previous history of CAD/ CVA, taking clopidogrel and/ or unfit for anesthesia were excluded from the study.

Based on an earlier publication, "Early versus delayed laparoscopic cholecystectomy for acute cholecystitis: a comparative study" by Siddiqui et al [7], the sample size calculated with 95% confidence level and 80% power; was 20 in each group. During the defined study period, all cases satisfying the inclusion criteria were included.

Patients were recruited in this prospective observational study after getting written informed consent and ethical clearance. The patients were graded according to Acute Cholecystitis Tokyo Guidelines 2018 as mild, moderate and severe disease [8] and they were assigned to either ELC or ILC groups based on their time of presentation after onset of symptoms, clinical condition and treating surgeon's judgment. ELC patients underwent surgery within 1week of onset of symptoms. In the ILC group, surgery was performed after an initial period of conservative management followed by an interval of 6 to 8 weeks. Conservative management included nil orally, nasogastric aspiration, intravenous fluids, IV antibiotics, analgesics and antispasmodics as deemed necessary.

Vital signs and clinical features of all the patients were monitored regularly for signs of worsening and any new developments. Standard 4 port laparoscopic cholecystectomy was performed and a Sub hepatic abdominal drain placed when it was indicated i.e., Gangrenous Gb, Pyocele of Gb, Perforated Gb with purulent collection or dense hypervascular adhesions with possibility of bleeding and bile leak later. Intra-operative findings were noted in both the groups and indications for conversion of laparoscopic cholecystectomy to open procedure with details recorded. Patients were followed up for a period of 2 weeks after discharge for any complications. Primary outcomes of the ELC and ILC groups with regard to length of hospital stay and secondary outcomes which included need for sub-total cholecystectomy, conversion to open procedure, intra-operative findings such as presence of pus, gangrene GB, spillage of stones and/ or bile, bleeding, injury, post operative complications like bile leak, wound infection and septic complications, length of ICU stay and mortality were recorded using a data collection form and entered in MS excel.

Statistical analysis

Age was summarized as mean and SD, while gender, severity grading of cholecystitis and presence of co-morbidities were summarized as frequency with proportion. Age was compared across the groups using Students't' test while the remaining exposure variables were compared using either Chi-square test or Fisher's exact test. Outcomes of the ELC and ILC groups were summarized as frequency with proportion and compared using Fisher's exact test.

Primary outcome of length of hospital stay in ELC and ILC groups was summarized as mean (SD) and median (IQR). Mann Whitney U test was used to compare this outcome between the two groups. The secondary outcomes of operative procedure and its modifications, intra-operative findings, course in hospital, complications, length of ICU stay and mortality were also summarized and compared in a similar manner. Data extracted using a data collection form and entered in MS excel. The data was analyzed using SPSS version 25 and p value less than 0.05 was considered significant.

Results

Comparison of the characteristics, clinical features and lab investigations of the study groups

A total of 67 cases satisfying the inclusion criteria were recruited for this study. Thirty-four cases were included in the ELC group and 33 in ILC group. The mean age for the ELC group was 50.85 ± 12.3 while that of the ILC group was 44.0 ±14.8 and this difference in mean

age between the groups was found to be statistically significant (p value 0.043). Patients in the ELC group presented earlier, with the mean day of presentation being 3.09 days after onset of symptoms as compared to 3.82 days for the ILC group and this difference between the two groups was statistically significant (p value 0. 004) (Table 1).

Table 1: Age distribution and day of presentation after onset of symptoms (N=67).

Groups	*n*	*Age (Years)*		*t value*	*p value*	*Day of presentation to emergency department (Days)*			*p value*
		Mean	*SD*			*Mean*	*SD*	*Median (IQR)*	
ELC	34	50.85	12.31	2.064	0.043	3.09	0.83	3 (4-2)	0.004
ILC	33	44.0	14.78			3.82	1.15	4 (5-3)	

The study population had more females (66%) overall and the ILC group had a greater proportion of females as compared to ELC group though this gender difference between the two groups was not statistically significant. Other socio-demographic variables and co morbidities were comparable across the study groups (Table 2). Fever and Murphy's sign was documented for the first and second visit separately for all the cases. It was observed that, in comparison, more patients during the initial hospitalization in ILC group than ELC group had fever (42.4% vs 23.5%), though not statistically significant. Even though patient's in the ILC group were found to have higher WBC counts as compared to the ELC group, the difference was not significant statistically. In comparison to the ILC group, more patients in the ELC group had increased CRP values, and this difference between the two study groups was statistically significant. When the severity grading of acute cholecystitis was compared between groups, the ELC group had a smaller proportion of mild grade cases (79.4% vs 87.9%). In addition, it was noted that ELC group also included 5 (14.7%) moderate and 2 (5.9%) severe cases of acute cholecystitis. However, the difference in severity of acute cholecystitis between the two groups was not statistically significant.

Table 2: Comparison of socio-demographic characteristics, clinical features and lab investigations in the two groups (N=67).

Socio-demographic variables	*Study groups*				*p value**
	ELC (n=34)		*ILC (n-=33)*		
	n	*%*	*n*	*%*	
Gender					
Male	16	47.1	9	27.3	0.094
Female	18	52.9	24	72.7	
Comorbidities					
Present	13	38.2	15	45.5	0.549
Absent	21	61.8	18	54.5	
Clinical features and lab values					
Positive Murphy`s Sign	17	50	13	39.4	0.383
Hyperthermia (Fever)	8	23.5	14	42.4	0.123
Elevated WBC Count	25	75.8	30	90.9	0.099
Elevated CRP values	32	94.1	25	75.8	0.045
Acute cholecystitis grade					
Mild	27	79.4	29	87.9	
Moderate	5	14.7	4	12.1	0.500#
Severe	2	5.9	0	0	

*Chi-square test # Fisher exact test

Outcomes of the surgery

Hospitalization among the study population

Total period of hospitalization (including both admissions taken together) and the median period of stay in the hospital were higher for ILC cases 10.2 ±4.5 days as compared to the ELC group 7.1 ±3.0 days. This

difference in the total duration of hospital stay between ELC and ILC groups was found to be statistically significant. However, it was also found that the length of hospital stay for the laparoscopic cholecystectomy procedure taken separately, was longer in the ELC group than that in the ILC group (i.e. second visit alone after exclusion of the initial period of hospitalization for conservative management) (7.1 ±3.0 versus 4.3±2.38), with a statistically significant p value of 0.001(Table 3).

Table 3: Comparison of length of hospital stay in the two groups for laparoscopic cholecystectomy (ELC vs ILC II visit) (N=67).

Total hospital stay					
Groups	n	Mean	SD	Median (IQR)	p value*
ELC	34	7.12	3.01	7(4.5-7.5)	0.001
ILC	33	10.21	4.46	9.5(7.25-11.0)	
Length of hospital stay for laparoscopic cholecystectomy procedure (ELC vs ILC group second admission)					
Groups	n	Mean	SD	Median (IQR)	p value*
ELC	34	7.12	3.01	7(4.5-7.5)	<0.001
ILC	33	4.30	2.378	4(6.6-3.2)	

* Mann Whitney U Test

Secondary Outcomes of surgery like, subtotal cholecystectomy, conversion to open cholecystectomy, bile leak, septic complications and ICU admissions though slightly higher in the ELC group as compared to the ILC group were not statistically significant (Table 4). There was no mortality in our study.

Table 4: Secondary outcomes among the study population compared across the two groups (N=67).

Variables	*Study groups*				*p value**
	ELC (n=34)		*ILC (n-=33)*		
	n	*%*	*n*	*%*	
Post-operative complications					
Bile leak	3	8.8	1	3.0	0.614
Conversion to open cholecystectomy	3	8.8	0	0	0.239
Wound infection	1	2.9	1	3	1.00
Septicaemia	2	5.9	1	3	0.572
ICU Admission	4	11.8	2	6	0.413

*Chi-square test

Discussion

The present study compared the length of hospital stay, complications and other outcomes between the two treatment modalities for acute cholecystitis a commonly encountered condition in surgical practice. With the introduction of newer armamentarium and improvement in surgical expertise, acute cholecystitis is being increasingly dealt with by laparoscopic cholecystectomy, early in the disease. However, the potential hazards of serious complications and a high conversion rate ranging from 6% to 35% remains a chief concern [9, 10].

In the present study, females made up 66% of the study population. Patients in the ELC group were older and had higher CRP values as compared to the ILC group, both of which were statistically significant. CRP a well-known acute phase reactant improves diagnostic accuracy in the evaluation of severe or gangrenous cholecystitis and facilitates early surgical intervention [11, 12]. The greater proportion of patients with elevated CRP values in the ELC group in our study, indicated that more patients with severe acute cholecystitis underwent early laparoscopic cholecystectomy. This was in concordance with findings of Andrei et al who showed that fit patients with severe acute cholecystitis and higher values of CRP should have their operation performed earlier in order to provide better quality of care and to reduce cost of health care [13].

Patients in the ELC group presented earlier, with the mean day of presentation being 3.09 days after onset of symptoms as compared to 3.82 days for the ILC group and this difference between the two groups was statistically significant (p value 0.004). In our study, patients who presented early and underwent surgery within 96 hours of the onset of their disease experienced shorter hospital stay, less complicated procedures, lower morbidity and better outcomes. Kolla et al found early laparoscopic surgery performed within 72 to 96 h of the onset of symptoms offers definitive treatment at initial admission and avoids the problems of failed conservative management and recurrent symptoms [10]. It is also associated with a shorter hospital stay which offers a major economic benefit [9]. Furthermore, studies investigating surgical timing and operative difficulty have shown that LC was less difficult and of a shorter duration when performed within 72 h of the onset of acute cholecystitis [14, 15].

Skouras C in "A best-evidence topic" that analyzed 92 papers concluded that ELC for acute cholecystitis is advantageous in terms of the length of hospital stay, is feasible and safe [16]. In our study, we found the total duration of hospital stay for the ILC group was significantly longer than that of the ELC group. We also noted that the duration of hospital stay for the laparoscopic cholecystectomy procedure taken

separately was longer in the ELC group. Our patients in the ELC group had the distinct advantage of shorter hospital stay as the early surgery in this group obviated the need for initial conservative management that was required in the ILC group. Cao et al stated that early LC is clearly superior to delayed LC in acute cholecystitis and the most recent evidence-based practice strongly suggests that early LC should be the standard of care in the management of acute cholecystitis [5].

22 (65%) of our cases who underwent ELC had a more complicated picture, including empyema GB, gangrenous GB, or dense adhesions which made the surgery challenging. Three of these patients required conversion to open procedure. The remaining twelve patients (35%) had only a mildly inflamed distended GB. Three of our study patients who underwent surgery 4 days after onset, required sub-total cholecystectomy and one patient with Mirrizi syndrome developed post-operative bile leak. These patients had significantly elevated CRP levels and the operative difficulty may be explained by the slightly higher proportion of patients with severe inflammation in the ELC group. Kaushik et al concluded in their study that preoperative CRP value is a potent predictor of higher risk for intra operative complications, difficult laparoscopic cholecystectomy and its conversion to open procedure [9]. In addition, Rothman et al showed older age and male gender to be risk factors for increased difficulty of laparoscopic cholecystectomy [17]. It could be plausible to conclude in our study that, there were not many conversions to open surgery overall, given that 66% of the study population were female. However, the comparatively higher conversion rate in ELC group though not statistically significant, could also be attributed to the larger proportion of older age male patients in this group.

In this study, we found that among patients who underwent ILC, the great majority (85%) had a favorable intra-operative finding, but 5 patients (15%) with empyema GB experienced intra-operative technical difficulty and needed prolonged surgery. In our analysis, although we found that the post-operative complications in the ELC group were slightly higher than the ILC group, the difference was not statistically significant. In a systematic review of randomized clinical trials by Gurusamy et al comparing early versus delayed laparoscopic cholecystectomy in acute cholecystitis, there was no significant difference between the two groups in terms of primary outcomes or serious complications [18].

Traditionally, conversion to open surgery encountered in 2-7% has been a marker of difficult LC [19, 20]. Gupta et al reported 2.3% conversions to open cholecystectomy and the most common reason for conversion was acute inflammation with obscure anatomy [21]. In our study, there were no conversions to open procedures in the ILC group, whilst there were three conversions in the ELC group. This difference in conversion rates, however, was not statistically significant. Badal et al and Gurusamy et al also found that the observed difference in conversion rate between early and delayed laparoscopic cholecystectomy was insignificant [10, 18]. Siddiqui et al in their analysis of 4 clinical studies found no significant difference in conversion rates between early and delayed laparoscopic cholecystectomy although the operation time for early laparoscopic cholecystectomy was longer [7].

Chang et al. showed that early laparoscopic cholecystectomy when compared to delayed intervention increases the risk of wound infections but diminishes the likelihood of recurrent cholecystitis. In contrast to the observations of Chang et al [22], the present study had an identical number of wound infections in both groups, which could be attributed to our practice of specimen retrieval utilizing endobag for all our patients.

Although not statistically significant, in our study population there were more patients in the ELC group admitted to the ICU than in the interval cholecystectomy group, as a result of the slightly higher rate of conversion to open surgery, more prolonged procedure, need for post operative ventilator support and better monitoring in this group. This was in contrast to the observations of Sanchez-Carrasco et al who demonstrated that ELC group had a significantly lower proportion of patients needing ICU care as compared to delayed cholecystectomy. Sanchez-Carrasco et al also reported that delayed cholecystectomy group had a higher mortality than the early cholecystectomy group, but the differences were not statistically significant [23]. However, we noted that there was no mortality in our study.

Patients were assigned to ELC and ILC groups according to the time of presentation after onset and their clinical condition. This in addition, was done according to the surgeon's judgment and hence it was impossible to rule out a selection bias. In this study the sample size considered was small and this did not account for the total expense incurred by the patients who were included. Future randomized trials would help prescribe recommendations for management of this commonly encountered acute surgical problem.

Conclusions

Early laparoscopic cholecystectomy should be the preferred treatment and standard of care for acute

cholecystitis as it results in shorter hospital stay and therefore less expensive. This study demonstrated that the acute cholecystitis severity grading, older age, male gender and duration of symptoms determined patient outcomes when comparing the length of hospital stay and morbidity between early and interval laparoscopic cholecystectomy. It may be recommended that early surgical intervention is best undertaken by surgeons with sufficient expertise in view of the likelihood of technical difficulty and increased risk for complications.

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Conflict of interest

Authors declare no conflicts of interest.

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