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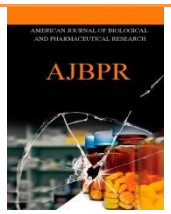

A COMPARATIVE ANALYSIS OF EARLY VERSUS DELAYED LAPAROSCOPIC CHOLECYSTECTOMY FOR ACUTE CHOLECYSTITIS

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ABSTRACT

The aim of this study was to compare the results of laparoscopic cholecystectomy in patients of acute cholecystitis having symptoms for less than five days with those having symptoms for more than five days. 87 patients with diagnosis of acute cholecystitis, admitted to a tertiary care hospital for laparoscopic cholecystectomy were recruited for the study. They were randomly assigned either to early laparoscopic cholecystectomy within five days of presentation of symptoms (n = 43) or to initial conservative treatment followed by delayed laparoscopic cholecystectomy after five days (n = 44). The groups were matched for age, sex, BMI and pre-existing diseases. The pre-anesthetic regimen, anesthesia procedure and laparoscopic technique were uniform. The primary efficacy parameters were measure of conversion rate and post-operative complications in the two groups. Duration of operation, duration of hospital stay, microbial sensitivity pattern of bile were the secondary parameters. 87 patients in all completed the study. There was no statistically significant difference between the groups in regard to conversion rates. (early, 21% versus delayed, 30%, $p > 0.05$). Post-operative pain as scored by VAS did not show significant differences between the groups at any time point. However, significant difference was observed in duration of operation (< 1hr in 86% of early group patients vs 68.1% of delayed group, $p < 0.05$) and in the duration of post-operative hospital stay (< 3 days in 58.1% of early group patients vs 25% of delayed group, $p < 0.05$). Statistical significance was seen in requirement of drains between the two groups (early, 11.65% versus delayed, 41%, $p < 0.05$). There was not much of a difference between the early and the delayed groups in terms of success of laparoscopic cholecystectomy in acute cholecystitis, except for shorter hospital stay, less time of surgery and fewer requirements for drains in the early group. Thus it may be concluded that early laparoscopic cholecystectomy for acute cholecystitis is a safe and feasible offering additional benefit of shorter hospital stay with less operative time.

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INTRODUCTION

The appropriate timing of laparoscopic cholecystectomy in acute cholecystitis is debatable because of the fear of higher rate of morbidity and

conversion from laparoscopic cholecystectomy to open cholecystectomy [1-3]. Nowadays many surgeons are advocating early operative intervention in acute cholecystitis with safe outcome [4-6]. The aim of this study was to compare theresults of laparoscopic cholecystectomy in patients of acute cholecystitis having symptoms for less than five days with those having symptoms for more than five days [7].

MATERIALS AND METHODS

Patient screening and recruitment were carried out at the Surgery inpatient department of a tertiary care hospital in Kolkata during the period October 2011 to April 2012. Eighty seven patients of either sex in the age group 20-50 years with a clinical diagnosis of acute cholecystitis and in need of laparcopic cholecystectomy, were selected for the study. Patients were evaluated following the pre-determined inclusion and exclusion criteria. Written informed consent was mandatory for participation in the study. Necessary ethical clearance was obtained from the Institutional Ethical Committee.

Diagnosis of acute cholecystitis was based on a combination of clinical criteria: acute right upper quadrant tenderness, temperature exceeding 37.5C, Total Leucocyte count greater than 11,000/mm^3 and ultrasonographic criteria of thickened edematous distended gallbladder, presence of gallstones, pericholecystic fluid collection. Patients with previous upper abdominal surgery, coexisting common bile duct stones, or significant medical disease rendering them unfit for laparoscopic surgery were not included in the study.

Sample size

This was determined on the basis of –(patients admitted and willing to participate in the study)---

Study design

This is a unicentric, open-labeled, randomized controlled study with two parallel treatment arms. The selected 87 patients were randomly assigned to two groups, the 'early' group (n=43) or the 'delayed' group(n=44). Simple randomization was accomplished by a computer-generated numbers list and allocation sequence was concealed by a third party. In the early group, laparoscopic cholecystectomy was performed within five days of onset of symptoms, whereas in the delayed group, conservative treatment with intravenous fluids and antibiotics was given. (*Ceftriaxone 1gm IV 12 hrly*). The patients in the delayed group underwent elective laparoscopic cholecystectomy five days or later after the onset of acute episode. Subjects were assessed in the post-operative period. The baseline assessment was done 6 hours after operation. The first follow-up was done after 24 hrs and third after another 24 hours.

Surgical procedure

The pre-anesthetic regimen, anesthesia procedure and laparoscopic technique were uniform in all subjects. Pre-medication was done with ondansetron 4mg IV, fentanyl 2µg/kg IV, glycopyrrolate 0.2mg IV and midazolam 1mg IV. Anesthesia was induced with propofol 2-2.5 mg/kg IV. Succinylcholine hydrochloride 2mg/kg IV was used as muscle relaxant for facilitation of tracheal intubation. Muscle relaxation was maintained by intermittent bolus dose of atracurium. Anesthesia was maintained with nitrous oxide and isoflurane in oxygen.
Laparoscopic cholecystectomy was performed under general anesthesia with four punctures of the abdomen which is the usual technique in this hospital. Abdomen was insufflated with CO_2 using a Veress needle through a supraumbilical incision. Four laparoscopic ports were used: two 10-mm ports (one umbilical 10-mm port for the optical system and one epigastric port for the dissector/suction device) and two 5-mm ports (one at the midclavicular line along the right subcostal margin and one in the right flank). Release of adhesions and exposure of Calot's triangle were first undertaken. The cystic pedicle was dissected to isolate the cystic duct and the artery separately which were then clipped and divided. The gallbladder was dissected off its bed with a monopolar cautery hook. At completion of the surgery, the gallbladder was extracted through the epigastric incision. Hemostasis was achieved in gallbladder bed, and after a thorough saline lavage, a suction drain was placed if clinically indicated and the incisions closed. Bile sample was collected and sent for culture/sensitivity report. On completion of surgery, neuromuscular block was reversed using neostigmine 0.05-0.07 mg/kg IV and atropine 0.02 mg/kg IV. All patients received diclofenac sodium 75 mg IM after end of surgery.

Study activities and efficacy assessment

At the baseline assessment done 6 hrs after operation, the subjects were clinically examined and assessed for post-operative complications, if any. Pulse rate, blood pressure, respiratory rate and temperature were recorded. Patient's pain perception was recorded as the VAS score on a 10 cm line*. Inj Ceftriaxone 1gm 12 hrly was changed to Cefuroxime 500mg BD once patient was allowed oral feeding. Pain relief was obtained by intramuscular diclofenac injection, which was changed to tablet administration once patient was allowed oral intake of fluids. At each of the subsequent assessments, clinical examination was done, VAS score of pain perception was noted and adverse events if any were elicited through history and physical examination. The patients were discharged when drain (if any) was removed and he/she was taking nutrition orally.

Study parameters

The primary efficacy parameters for the study were measured in terms of conversion rate to open cholecystectomy, and post-operative complications like fever, infection, pain in the two groups. The secondary parameters were duration of operation, duration of post-operative hospital stay and microbial sensitivity pattern of bile.

Safety monitoring

Information on adverse events, reported spontaneously by the subject or noted by the investigators during the follow-up assessments was recorded.

Statistical analysis

Statistical analysis was performed using paired t-test and chi-square test. A p-value less than 0.05 were considered statistically significant. Microsoft office 2003 excel sheet was used for analysis.

RESULTS

A total number of 87 patients were randomized in two groups. 43 patients in early group and 44 patients in the delayed group completed the study. The differences in demographic features, clinical and laboratory findings between the two groups were not statistically significant [Table 1].

The primary efficacy parameter for this study, namely the conversion rate to open cholecystectomy was 21% (n=9) in early group compared to 30% (n=13) in the delayed group. This was not statistically significant (p = 0.355). The reasons for conversion in the early group were distorted anatomy, bleeding, bile duct injury. In the delayed group dense adhesions and choledocoduodenal fistula were the reasons. The results of other primary efficacy parameters i.e. post-operative complications like fever(*OR=0.6; R.R=0.68; 95% CI 0.17-2.49 in early group vs OR 1.5; RR 1.47; 95%CI=0.4-5.9 in delayed group*), port infection (*OR=0.8; RR=0.77; 95% CI 0.16-3.57 in the early group vs OR 1.3; RR 1.3; 95%CI 0.28-6.34 in delayed group*) and pain score in the two groups were not statistically significant but relative risks of fever and port infection were slightly higher in the delayed group[Table 2]. The serial change in VAS pain score in the two groups is shown in Table 3. Between groups comparisons of VAS score by Mann-Whitney *U* test showed no significant difference at any time point.

Between groups comparison of the secondary efficacy parameters is shown in Table 4. Microbial sensitivity pattern of bile did not show any growth in any patient. The operating time was < 1 hr in 37 cases (86%) in the early group compared to 21 cases (61.8%) in delayed group (p=0.014) which was significant statistically. Postoperative hospital stay was <3days in 25 cases(58.1%) in the early group compared to 11 cases (25%) in the delayed group (p =0.002) hence statistically significant.

REVIEW OF LITERATURE

Laparoscopic cholecystectomy is the gold standard treatment of gall stone diseases and provides advantages over open variant in earlier return of bowel function, less postoperative pain, improved cosmetic outcome, shorter length of hospital stay, earlier return of full activity and decreased overall cost.

Initially acute cholecystitis was a relative contraindication for laparoscopic cholecystectomy. Chung Mua Lo et al[1] found that LC in acute cholecystitisis technically demanding and time consuming but this procedure provides economic advantage of markedly reduced hospital stay. PB Lai et al[2] found that LC was safe and feasible for acute cholecystitis with added advantage of reduced hospital stay.

Conversion To Open Cholecystectomy

Conversion to open cholecystectomy should be viewed as a modification of treatment rather than failure. But it certainly reflects the difficulties faced by a surgeon during LC. In a study conducted by Ozkardes *et al* in 2014 60 patients with acute cholecystitis were randomised into early(within 24 hours of admission) or delayed (after 6-8 weeks of conservative management) LC groups. There was no significant difference between rates for conversion to open cholecystectomy. In a metaanalysis by Siddiqui et al[4] published in 2008, 375 patients were included. No significant study heterogeneity or publication bias was found. There was no significant difference in conversion rates in both groups.

Operating Time

In most of the studies found in literatures, it is found that operating time is significantly increased in delayed LC groups. In a study by Gharaibeh KL et al[5], LC done in <72 hrs. vs. >72 hrs was studied. The median operation time was 78±36 minutes, but the operation time for 2nd group was significantly longer.

Post Operative Hospital Stay

Post operative hospital stay and total hospital stay is very much important as it tends to increase the total cost of treatment per patient. Operative cost remains constant as it remains the same in both forms of management. In a metaanalysis by Menahem B,Mulliri A et al[6] published in 2015, nine RCTs were included in a total of 617 who underwent early LC and 603 patients who underwent delayed LC after acute cholecystitis. The mean hospital stay was 5.4 days in the early group and 9.1 days in the delayed group.

Complications of Laparoscopic Cholecystectomy

Complications pertaining to LC are major bleeding, wound infection, bile leak and biliary injury. The pioneering work regarding major complications associated with LC was done by Strasberg and colleagues. Suter M et al[7] found no difference in the overall rate of biliary complications between the patients operated for acute cholecystitis and those who underwent elective surgery.

Table 1. Profile of demographic characteristics, clinical and laboratory data of patients in the groups at admission

Parameter	Early group (n=43)	Delayed group (n=44)	*p* value
Age (years)	35.19 ± 9	33.6 ± 9.3	0.28
Weight (kg)	77.09 ± 7.5	76.95 ± 7.45	0.466
Male:Female	19/24	18/26	0.757
Previous lower abdominal surgery	17	21	0.441
Maximum temperature (ºF)	102.02 ± 0.73	101.95 ± 0.797	0.338
Total leukocyte count (>11,000/mm^3)	14639.58 ± 2243.65	14730.28 ± 2184.407	0.425
Total bilirubin (mg %)	0.87 ± 0.15	0.84 ± 0.14	0.176
Aspartate transaminase (U/l)	32.09 ± 8.03	32.5 ± 6.42	0.397
Alkaline phosphatase (IU/l)	104.74 ± 32.97	103.3 ± 33.88	0.4226

Table 2. Profile of primary efficacy parameters in the two groups

Parameter	Early group (n=43)	Delayed group (n=44)	*p* value
Conversion	9 (21%)	13 (30%)	0.355
Drain	5 (11.6%)	18 (41%)	0.002
CBD injury	1 (2.3%)	1 (2.27%)	0.448
Fever	4 (9.3%)	6 (13.6%)	0.526
Port infection	3 (7%)	4 (9.1%)	0.717

p value ----------by -------Chi Square---------- tests

Table 3. Serial change in visual analog scale (VAS) pain score (mean ± SD)

Group	Baseline	1st follow-up	2nd follow-up
Early group (n=43)	9.05 ± 0.11	7.8 5± 0.14	5.72 ± 0.14
Delayed group (n=44)	9.32 ± 0.11	8.5 ± 0.13	5.75 ± 0.14

Difference between groups was not statistically significant at any time point by Mann-Whitney *U* test

Table 4. Secondary efficacy parameters in the two groups

Parameter	Early group (n=43)	Delayed group (n=44)	*p* value
Operating time (< 1 hr)	37 (86%)	21 (61.8%)	p=0.014
Post-operative stay (< 3 days)	25 (58.1%)	11 (25%)	p= 0.002

p value ----------by ----------Chi square -------- tests

DISCUSSION & CONCLUSION

Both early and delayed *Laparoscopic Cholecystectomy* is feasible and safe in the treatment of *acute cholecystitis* with similar complications profile and no major complications such as bile duct injury.

Delayed cholecystectomy is associated with an overall increased operative time and significantly higher rate of conversion to open surgery, which depicts more technical difficulties faced during delayed laparoscopic surgery for *acute cholecystitis*.

Early cholecystectomy is also superior to delayed surgery in terms of post operative and overall hospital stay with no increased requirement for readmission. Furthermore, a reduction of total hospital stay is a major economic benefit to the current health care system. Thus we conclude that early cholecystectomy should be the procedure of choice in treating *acute cholecystitis*.

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CONFLICT OF INTEREST:

The authors declare that they have no conflict of interest.

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