



A COMPARATIVE STUDY BETWEEN EARLY AND DELAYED LAPAROSCOPIC CHOLECYSTECTOMY IN POST ERCP PATIENTS FOR CHOLEDOCHOLITHIASIS

Surgery

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ABSTRACT

Background: Recently, the early period for LC following stone extraction via endoscopic retrograde cholangiopancreatography (ERCP) has been accepted in terms of conversion rates, bile duct injury, deep surgical wound infections, length of hospital stay and cost. The present research hypothesised that early planned laparoscopic cholecystectomy after endoscopic sphincterotomy prevents recurrent biliary complications and reduces operational morbidity and hospital stay and the purpose of our study is to look for advantages of early cholecystectomy over late laparoscopic cholecystectomy.

Objectives: To compare and study the outcomes of early laparoscopic cholecystectomy and delayed interval laparoscopic cholecystectomy in terms of recurrent biliary events, difficulty in surgery, rate of conversion to open cholecystectomy and duration of hospital stay

Materials and Methods: A Comparative prospective observational study was conducted where All patients above 18 years old with choledocholithiasis with or without cholelithiasis/cholecystitis/mild pancreatitis according to RANSON's scoring admitted in JSS hospital, mysuru with choledocholithiasis post ERCP stenting/sphincterotomy during the study period were included in the study. Statistical analysis was performed using SSPS (Statistical Package For Social Sciences) software version 18.

Results: The mean age the Early cholecystectomy group was 47.73 ± 12.31 and Delayed cholecystectomy group was 44.50 ± 12.30 . 23.3% were males and 76.7% were female in early Cholecystectomy group and 36.7% were males and 63.3% were females in Delayed Cholecystectomy group Chief complaint observed among the Early Cholecystectomy group was Pain abdomen (83.3%), whereas its was 100% among the Delayed Cholecystectomy group. 76.7% of the Delayed Cholecystectomy group showed positive murphy sign in late cholecystectomy group. In present study, mean duration of surgery in early cholecystectomy group was 37.33 ± 8.97 minutes and in delayed cholecystectomy group was 52.66 ± 17.15 minutes. The mean duration of hospital stay in early cholecystectomy group was 29.5 ± 15.01 hours and in delayed cholecystectomy group was 60.80 ± 29.45 hours. Parental analgesia was needed for 1.06 ± 0.25 days in early cholecystectomy group and 1.9 ± 0.92 days in delayed cholecystectomy group. There was statistically significant difference between the mean duration of surgery, hospital stay and parental analgesia among the study groups ($P < 0.05$). During follow up period of 6 months, 19 had Biliary events in the delayed cholecystectomy group compared to 2 in the Early cholecystectomy group. This finding was statistically significant as the p value calculated to be < 0.05 .

Conclusion: ELC provides better morbidity results, as well as a clear trend toward lower mortality and fewer injuries to the main bile duct.

KEYWORDS

INTRODUCTION

Since antiquity, gallstones were known and found during Egyptian mummy autopsies. After a first successful open cholecystectomy in 1882, the first laparoscopic cholecystectomy was performed in 1985 by Eric Muhe, a German surgeon. Gallstone disease arises from a dynamic genetic-environmental relationship. This is supported by a decrease in the occurrence of gallstone identification in citizens from various metropolitan regions with different food regimens, levels of physical activity and hygiene. The typical gallstone pathways include cholesterol hypersecretion, alteration of bile salt, cholesterol absorption and hypokinesia of the gallbladder contributing to supersaturation and nucleation of the bile cholesterol.¹ The occurrence of CBD stones in cases of cholelithiasis is roughly 3.4%-15%.²

Choledocholithiasis is primary or secondary. Secondary choledocholithiasis is more common due to stones occurring in gallbladder and then migrating to CBD via cystic duct. These secondary bile stones are 75% cholesterol stones and 25% black pigment stones. Main bile duct stones originate in the bile ducts and are more common in Asian cultures. These stones contain less cholesterol and high bilirubin content relative to secondary stones. These stones contribute to biliary stasis and bacteria.³

Choledocholithiasis diagnosis originates from symptomatology, laboratory studies, and ultrasound (US) findings. Each of these variables has low sensitivity and specificity for choledocholithiasis. Abdominal ultrasound, the most widely used initial diagnostic technique for suspected biliary stones, is 25-60% sensitive and 95-100% specific.⁴

In 1968, ERCP was introduced as a diagnostic method for treating biliary and pancreatic diseases.⁵ With the advent of endoscopic sphincterotomy, ERCP is now developed as a therapeutic method with 90% sensitivity and 98% specificity.⁶ ERCP stone extraction is

effective 80% - 90% of the time using sphincterotomy and balloon catheter techniques or Dormia basket stone retrieval.⁷ Pancreatitis is ERCP's most common complication. ERCP-induced pancreatitis is characterised as new or exacerbated abdominal pain with serum amylase, which reaches the upper limit of normal at 24 hours after the procedure and requires at least two days of hospitalisation.⁸ Long term complications include papillary stenosis, cholangitis and recurrent choledocholithiasis.⁹

Laparoscopic cholecystectomy (LC) is considered gold standard for treatment of symptomatic cholelithiasis.¹⁰ Recently, the early period for LC following stone extraction via endoscopic retrograde cholangiopancreatography (ERCP) has been accepted in terms of conversion rates, bile duct injury, deep surgical wound infections, length of hospital stay and cost.¹¹ According to recent studies, the overall outcome is better if Laparoscopic Cholecystectomy is performed early (< 72 hours).¹² There was a significant rate of conversion to open cholecystectomy in cases performed after 6 weeks, than within the first week after ERCP.¹³

The present research hypothesised that early planned laparoscopic cholecystectomy after endoscopic sphincterotomy prevents recurrent biliary complications and reduces operational morbidity and hospital stay and the purpose of our study is to look for advantages of early cholecystectomy over late laparoscopic cholecystectomy.

Methodology:

Study design: Comparative prospective observational study

Study population : patients admitted in JSS hospital, mysuru with choledocholithiasis post ERCP stenting/sphincterotomy

INCLUSION CRITERIA

All patients above 18 years old with choledocholithiasis with or without cholelithiasis/cholecystitis/mild pancreatitis according to RANSON's scoring.

EXCLUSION CRITERIA:

1. Patients with severe acute pancreatitis and cholangitis
2. Patients deemed not fit for surgery with co-morbidities

This research included all patients with laparoscopic cholecystectomies after ERCP for CBD stones.

The research omitted patients with carcinoma gall bladder, common bile duct strictures, post-ERCP pancreatitis, related comorbidities (with anaesthesia contraindication), coagulopathy, end-stage liver disease, prior upper abdominal surgery.

Normal four port Laparoscopic cholecystectomy was performed after ERCP in CBD stone cholelithiasis patients.

Following ERCP, patients were divided into two groups. Patients in Category A had early laparoscopic cholecystectomy within 3 days of ERCP, whereas patients in Category B had late laparoscopic cholecystectomy after 3 days of ERCP.

Before the study, all baseline investigations were performed including CBC, RFT, LFT, Electrolytes, S. Amylase, blood sugar, blood grouping, coagulation profile, serology, etc. Various imaging studies including CXR, USG, CT (if needed), MRCP (In case USG is inconclusive). Outcomes were compared based on operating time open cholecystectomy conversion, transfusion-related intraop bleeding, hospital stay and postop complications such as infection, CBD injury, pancreatitis.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS (Statistical Package For Social Sciences) software version 18. Parametric data have been measured as means and standard deviations. Nonparametric data are measured as frequencies and percentages. Continuous data have been analyzed using paired t test and non-continuous data by Fisher's exact test.

RESULTS:

The mean age the Early cholecystectomy group was 47.73 ± 12.31 and Delayed cholecystectomy group was 44.50 ± 12.30 . 23.3% were males and 76.7% were female in early Cholecystectomy group and 36.7% were males and 63.3% were females in Delayed Cholecystectomy group. Distribution based on ASA Grade, Grade 1 (86.7%), Grade 2 (13.3%) in the Early group, and in Delayed Cholecystectomy, Grade 1 (86.7%), Grade 2 (3.3%), Grade 3 (10%). Chief complaint observed among the Early Cholesyctectomy group was Pain abdomen (83.3%), whereas its was 100% among the Delayed Cholecystectomy group. 76.7% of the Delayed Cholecystectomy group showed positive murphy sign in late cholecystectomy group. 36.7% of the Early cholecystectomy group presented with tenderness in Right Hypochondrium, and 23.3% in the Delayed group presented with tenderness in right Hypochondrium. 30% of patients had co-morbidities in early Cholecystectomy group and 20% of patients in late Cholecystectomy had co-morbidities such as arthritis, chronic kidney disease, diabetes mellitus, hypertension, hypothyroidism, bronchial asthma and osteoporosis. GGT and TLC levels were found to have statistically significant difference among the two study groups ($P < 0.05$). 10% of cases had contracted bladder, 23.3% had distended bladder in early cholecystectomy group. 6.7% of cases had contracted bladder, 66.7% of cases had distended bladder, 26.7% had pericholecystic fluid collection and 20% of cases had impacted stone at neck of bladder in Delayed Cholecystectomy group seen with ultrasonography. The mean wall thickness in early cholecystectomy group was 4.13 ± 0.50 and in Delayed Cholecystectomy group was 7.83 ± 1.96 . Pericholecystic adhesions were seen in 16.7% of cases in early cholecystectomy group and 20% had mucocoele, 3.3% had empyema and 80% had pericholecystic adhesions in delayed cholecystectomy intra-operatively. The wall of gall bladder was normal in all patients in early cholecystectomy group whereas in delayed cholecystectomy group, 43.3% had edematous friable wall, 3.3% had gangrenous wall, 40% had normal wall and 13.3% had thick and fibrosed wall. There was statistically significant difference between gall bladder wall intra-operatively among the study group ($P < 0.05$). 86.7% of cases had simple GB bed dissection and 13.3% had bleeding in early cholecystectomy group whereas in delayed cholecystectomy group, 56.7% had simple dissection, 36.7% had

bleeding and 6.7% had perforation intra-operatively which was statistically significant (P value < 0.05). All the patients in early cholecystectomy group had clipped and divided cystic duct whereas in delayed cholecystectomy group, 70% of cases had clipped & divided cystic duct, 10% had sutured divided cystic duct and 20% had tied & divided cystic duct which was found to be statistically significance between cystic duct status intra-operatively (P value < 0.05). In early cholecystectomy group, 83.3% of cases had clear calot's triangle, 3.3% had frozen and 13.3% had not clear calot's anatomy whereas in delayed cholecystectomy group, 26.7% of cases had clear, 30% had frozen and 43.3% had not clear calot's anatomy intra-operatively which was statistically significant among the study groups ($P < 0.05$). Although difficulty in identifying the calot's triangle seems to be equal in both groups, we believe that more experience and skills of the surgeon may bring down the complication rate in both early and delayed groups. No drain was used in all patients of early cholecystectomy group where as 16.7% of cases in late cholecystectomy group used drain which was statistically significant ($P < 0.05$). No drain was used in all patients of early cholecystectomy group where as 16.7% of cases in delayed cholecystectomy group used drain which was statistically significant ($P < 0.05$). In present study, mean duration of surgery in early cholecystectomy group was 37.33 ± 8.97 minutes and in delayed cholecystectomy group was 52.66 ± 17.15 minutes. The mean duration of hospital stay in early cholecystectomy group was 29.5 ± 15.01 hours and in delayed cholecystectomy group was 60.80 ± 29.45 hours. Parenteral analgesia was needed for 1.06 ± 0.25 days in early cholecystectomy group and 1.90 ± 0.92 days in delayed cholecystectomy group. There was statistically significant difference between the mean duration of surgery, hospital stay and parenteral analgesia among the study groups ($P < 0.05$). In present study no patient in both the groups were converted into open cholecystectomy surgery. 96.7% of cases in early cholecystectomy group had no complication, 3.3% of cases had post-site infection. In late cholecystectomy group, 80% of cases had no complications, 13.4% had fever, 3.3% each had post-site infection and sub-hepatic abscess. There was no statistical significance between complications post-operatively among the study group ($P > 0.05$). During follow up period of 6 months, 19 had Biliary events in the delayed cholecystectomy group compared to 2 in the Early cholecystectomy group. This finding was statistically significant as the p value calculated to be < 0.05 .

Table 1: Age distribution

Age distribution (Years)	Early Cholecystectomy		Delayed Cholecystectomy	
	N	%	N	%
21 – 30	4	13.3%	3	10%
31 – 40	4	13.3%	11	36.7%
41 – 50	8	26.7%	7	23.3%
51 – 60	10	33.3%	6	20%
61 – 70	2	6.7%	3	10%
71 – 80	2	6.7%	0	0%
Total	30	100%	30	100%
Mean $\pm$ SD	47.73 ± 12.31		44.50 ± 12.30	

Table 2: Duration of surgery

	Early Cholecystectomy	Delayed Cholecystectomy	P value
Duration of surgery (Mins)	37.33 ± 8.97	52.66 ± 17.15	$< 0.05^*$
Duration of Hospital stay (Hours)	29.50 ± 15.01	60.80 ± 29.45	$< 0.05^*$
Parenteral analgesia (Days)	1.06 ± 0.25	1.90 ± 0.92	$< 0.05^*$

Table 3: Post operative complications

	Early Cholecystectomy		Delayed Cholecystectomy	
	Frequency	Percent	Frequency	Percent
Fever	0	0%	4	13.4%
Nil	29	96.7%	24	80%
Post site infection	1	3.3%	1	3.3%
Subhepatic abscess	0	0%	1	3.3%
Total	30	100%	30	100%

Table 4: Biliary events occurring during a follow up period of 6 months in patients undergoing Early or Delayed LC

	Early Cholecystectomy	Delayed Cholecystectomy	P value
Recurrent CBD stones	1	1	-
Colic pain	1	13	-
Acute cholecystitis	0	5	-
Biliary events	2	19	<0.05*

DISCUSSION:

The present study hypothesized that early planned laparoscopic cholecystectomy after endoscopic sphincterotomy prevents recurrent biliary complications and reduces operative morbidity and hospital stay and the aim of our study is to look for advantages of early cholecystectomy over delayed laparoscopic cholecystectomy.

A prospective comparative observational study was done among 60 patients admitted in JSS hospital, Mysore with cholelithiasis after ERCP stenting.

In present study, majority of patients in early cholecystectomy group belong to age 51 – 60 years (33.3%) followed by 26.7% in 41 – 50 years, 13.3% each in 21 – 30 years and 31 – 40 years, 6.7% each in 61 – 70 years and 71 – 80 years. Majority of patients in delayed cholecystectomy group belong to 31 – 40 years age (36.47%) followed by 23.3% in 41 – 50 years, 20% in 51 – 60 years, 10% each in 21 – 30 years and 61 – 70 years. The mean age of patients in early cholecystectomy group was 47.73 ± 12.31 and in delayed Cholecystectomy group was 44.50 ± 12.30 years which was found statistically not significant (P value > 0.05).

23.3% were males and 76.7% were female in early Cholecystectomy group and 36.7% were males and 63.3% were females in delayed Cholecystectomy group and there was no statistically significant difference was found between gender distribution among the study groups (P > 0.05).

In present study, 83.3% of patients had abdominal pain, and 36.7% had nausea/vomiting in early Cholecystectomy group and 100% of patients had abdominal pain, 13.3% had fever and 20% had nausea/vomiting in delayed Cholecystectomy group. No patient in early Cholecystectomy group had fever.

In present study, murphy's sign was positive in 76.7% of patients in delayed Cholecystectomy. Tenderness in right hypochondrium was present in 36.7% in early Cholecystectomy and 23.3% in delayed Cholecystectomy. Palpable lump was felt in one patient in early Cholecystectomy group and in 36.3% in delayed Cholecystectomy group. In a study done by Alper BO et al¹⁴ showed that among 60 patients, 90% of cases of both the groups showed murphy's sign and all patients had tenderness in right hypochondrium.

In present study, 30% of patients had co-morbidities in early Cholecystectomy group and 20% of patients in delayed Cholecystectomy had co-morbidities such as arthritis, chronic kidney disease, diabetes mellitus, hypertension, hypothyroidism, bronchial asthma and osteoporosis.

In present study, mean biochemical parameters in group with early Cholecystectomy patients was mean total bilirubin 0.88 ± 0.44 , direct bilirubin 0.26 ± 0.12 , indirect bilirubin 0.76 ± 0.88 , ALP 102.23 ± 41.10 , GGT 65.03 ± 62.3 , RBS 113.53 ± 56.91 , TLC 7555 ± 2145.29 , INR 0.91 ± 0.12 and creatinine 1.01 ± 1.34 and in delayed Cholecystectomy was mean total bilirubin 1.53 ± 2.45 , direct bilirubin 0.64 ± 1.54 , indirect bilirubin 0.89 ± 0.93 , ALP 167.23 ± 169.01 , GGT 121.9 ± 146.74 , RBS 114.96 ± 45.27 , TLC 8845.10 ± 5012.93 , INR 0.98 ± 0.13 and creatinine 0.87 ± 0.29 . GGT and TLC levels were found to have statistically significant difference among the two study groups (P < 0.05). In a study done by Rouf et al¹⁵ showed routine blood investigations among the study groups were comparable.

In present study, 10% of cases had contracted bladder, 23.3% had distended bladder in early cholecystectomy group. 6.7% of cases had contracted bladder, 66.7% of cases had distended bladder, 26.7% had pericholecystic fluid collection and 20% of cases had impacted stone at neck of bladder in delayed cholecystectomy group seen with ultrasonography. The mean wall thickness in early cholecystectomy

group was 4.13 ± 0.50 and in delayed cholecystectomy group was 7.83 ± 1.96 .

In present study, pericholecystic adhesions were seen in 16.7% of cases in early cholecystectomy group and 20% had mucocele, 3.3% had empyema and 80% had pericholecystic adhesions in delayed cholecystectomy intra-operatively. Although difficulty in identifying the calot's triangle seems to be equal in both groups, we believe that more experience and skills of the surgeon may bring down the complication rate in both early and delayed groups. No drain was used in all patients of early cholecystectomy group where as 16.7% of cases in late cholecystectomy group used drain which was statistically significant (P < 0.05). In a study done by Rohit Prasad et al¹⁶ showed 16% in early and 12% in delayed cholecystectomy groups were converted into open surgery.

In present study, mean duration of surgery in early cholecystectomy group was 37.33 ± 8.97 minutes and in delayed cholecystectomy group was 52.66 ± 17.15 minutes. The mean duration of hospital stay in early cholecystectomy group was 29.5 ± 15.01 hours and in delayed cholecystectomy group was 60.80 ± 29.45 hours. Parental analgesia was needed for 1.06 ± 0.25 days in early cholecystectomy group and 1.9 ± 0.92 days in late cholecystectomy group. There was statistically significant difference between the mean duration of surgery, hospital stay and parental analgesia among the study groups (P < 0.05). R.A. Pyne [1969]¹⁷ in his study found that the average duration of hospital stay to be around to be 16 days for delayed cholecystectomy. I.Ahmed [1992] in his study found that the average duration of hospital stay in early cholecystectomy group to be ten days.¹⁸ The total hospital stay was shorter by 5 days in the early group when compared to the delayed group. This may result from the more treatment and therapies following intraoperative and post operative complications.

In present study no patient in both the groups were converted into open cholecystectomy surgery.

In present study, 96.7% of cases in early cholecystectomy group had no complication, 3.3% of cases had post-site infection. In delayed cholecystectomy group, 80% of cases had no complications, 13.4% had fever, 3.3% each had post-site infection and sub-hepatic abscess. There was no statistical significance between complications post-operatively among the study group (P > 0.05). Linden et al [1970] described post operative wound infection is the most common postoperative complication which is more common in patients undergoing early cholecystectomy.¹⁹ In a study done by zahid M Rather et al²⁰ showed that among 70 patients, early cholesteotomy had statistically significant shorter days of hospital stay (1.5 days when compared to late surgery (7.95 days).

CONCLUSION:

ELC provides better morbidity results, as well as a clear trend toward lower mortality and fewer injuries to the main bile duct.

- The complications rates in ELC group is much lower than the DLC group.
- Hospital stay in ELC is less compared to DLC which inturn direct effect on costs savings and manpower.
- We would recommend DLC only in cases where acute pancreatitis, choledocholithiasis, or cholangitis cannot be ruled out and those with unacceptable anesthetic risk at the time of diagnosis.

Recommendations:

1. The current study suggests that early LC after ERCP for the management of cholecysto-choledocholithiasis is a safe, effective, and time saving technique with a low rate of postoperative complications.
2. Based on our study results, we thought that if patients could be taken to surgery sooner after ERCP, morbidity could be significantly reduced.

REFERENCES:

1. Corradini SG, Elisei W, Giovannelli L, et al. Impaired human gallbladder lipid absorption in cholesterol gallstone disease and its effect on cholesterol solubility in bile. *Gastroenterology* 2000;118(5):912-20.
2. Sahu D, Mathew MJ, Reddy PK. Outcome in patients undergoing laparoscopic cholecystectomy following ERCP: Does timing of surgery really matter? *Journal of Minimally Invasive Surgical Sciences* 2015;4(1):e25226.
3. Ko CW, Lee SP. Epidemiology and natural history of common bile duct stones and prediction of disease. *Gastrointest Endosc* 2002;56(Suppl 6):S165-9.
4. Sugiyama M, Atomi Y. Endoscopic ultrasonography for diagnosing choledocholithiasis: a prospective comparative study with ultrasonography and computed tomography.

- Gastrointest Endosc 1997;45(2):143-6.
5. Mallery JS, Baron TH, Dominitz JA et al. Complications of ERCP. *Gastrointest Endosc* 2003;57(6):633-8.
 6. Carr-Locke DL. The therapeutic role of ERCP in the management of suspected common bile duct stones. *Gastrointest Endosc* 2002;56(Suppl 6):S170-S4.
 7. Binmoeller KF, Schafer TW. Endoscopic management of bile duct stones. *J Clin Gastroenterol* 2001;32(2):106-18.
 8. Cotton PB, Lehman G, Vennes J, et al. Endoscopic sphincterotomy complications and their management: an attempt at consensus. *Gastrointest Endosc* 1991;37(3):383-93.
 9. Wojtun S, Gill J, Gietka W, et al. Endoscopic sphincterotomy for choledocholithiasis: a prospective single-centre study on the short-term and the long-term treatment results in 483 patients. *Endoscopy* 1997;29(4):258-65.
 10. Schirmer BD, Edge SB, Dix J, Hyser MJ, Hanks JB, Jones RS. Laparoscopic cholecystectomy. Treatment of choice for symptomatic cholelithiasis. *Ann Surg*. 1991;213:665-76. doi: 10.1097/0000658-199106000-00018.
 11. Reinders JS, Goud A, Timmer R, et al. Early laparoscopic cholecystectomy improves outcomes after endoscopic sphincterotomy for choledochocystolithiasis. *Gastroenterology*. 2010;138:2315-20. doi: 10.1053/j.gastro.2010.02.052.
 12. Boerma D, Rauws EA, Keulemans YC, et al. Wait-and-see policy or laparoscopic cholecystectomy after endoscopic sphincterotomy for bile-duct stones: A randomized trial. *The Lancet* 2002 Sep 7;360(9335):761-65.
 13. Williams EJ, Green J, Beckingham I, et al. Guidelines on the management of Common Bile Duct Stones (CBDs). *Gut* 2008 Jul 1;57(7):1004-21.
 14. Alper bilal ozkardes, Mehmet tokac et al. Early Versus Delayed Laparoscopic Cholecystectomy for Acute Cholecystitis: A Prospective, Randomized Study. *Int surg*. 2014 99(1):56-61.
 15. Rouf gul, rayess ahmed dar et al. comparison of early and delayed laparoscopic cholecystectomy for acute cholecystitis: experience from a single center. *N Am J Med Sci*. 2013; 5(7):414-418.
 16. Rohit Prasad yadav, S adhikary et al. A comparative study of early vs delayed laparoscopic cholecystectomy in acute cholecystitis. *Kathmandu university med j*. 2009; 7(25): 16-20.
 17. Payne RA, 1969, *brit j surg* 56/3.
 18. Ahmed ijaz, 1992, *JPM amay* 42:112-115.
 19. Liden WVD. 1981, *brit j surg* 68:753-57.
 20. Zahid mohd rather, nighat ara majid et al. outcome of early laparoscopic cholecystectomy vs delayed laparoscopic cholecystectomy for patients with acute cholecystitis. *Int Surg J*. 2020; 7(4):1212-1217.