

Early verses delayed laparoscopic cholecystectomy among symptomatic cholelithiasis patients: two years' experience in King Fahad Hospital, Al-Madinah Al-Munawarah

Tajammal Abbas Shah, Masood Raza Khan

Abstract:

Objectives: A comparative, prospective study was conducted to compare the results of early and delayed laparoscopic cholecystectomy in tertiary care centre of Al-Madinah Al-Munawara region in terms of hospital stay, cost effectiveness, complications, conversion to open cholecystectomy, patient compliance, morbidity and mortality.

Materials and Methods: Study was conducted in Surgical Unit, King Fahad Hospital from February 2014 to January 2016. 100 patients were part of this study. Group A, 50 patients presented in surgical emergency with first attack of acute cholecystitis. Group B, 50 patients with more than one episodes of acute cholecystitis and admitted through out-patient department. Patients unfit for laparoscopic surgery, previous abdominal surgery, with acute pancreatitis, acute cholangitis, jaundice and stones in common bile duct were excluded from this study. **Results:** Among Group A, 50 patients underwent early laparoscopic cholecystectomy; mean hospital stay was 4.48 days, cost for single patient S.R. 5016, 3 patients (6%) were converted to open cholecystectomy, 5 patients (10%) had bile leak during procedure, 2 patient (4%) have additional ERCP with slipped stone in common bile duct and all patients recovered with no significant morbidity and mortality. Among group B, 50 patients; mean hospital stay was 6.72 days, cost for single patient S.R. 6024, 1 patient (2%) converted to open cholecystectomy, 2 patients (4%) with bile leakage, with no significant morbidity and mortality.

Conclusion: Early laparoscopic cholecystectomy has advantage of less hospital stay and cost benefits but greater conversion rate to open cholecystectomy and higher complication rate with no significant difference in morbidity and no mortality.

Key words: Early cholecystectomy, delayed cholecystectomy, acute cholelithiasis, conversion to open cholecystectomy, complications, patient compliance

Introduction:

Worldwide, laparoscopic cholecystectomy is the established "gold standard" treatment¹ for symptomatic cholelithiasis in terms of biliary colic, acute cholecystitis, chronic cholecystitis or certain other conditions. However, the timing of laparoscopic cholecystectomy for symptomatic cholelithiasis remains controversial.² Laparoscopic cholecystectomy is usually done; either by early or elective/delayed approach. Early laparoscopic cholecystectomy (ELC) is performed within 72 hours of onset of acute symptoms³ during same hospital admission, while in delayed laparoscopic cholecystectomy (DLC) patient is initially being treated conser-

vatively with antibiotics and cholecystectomy performed with interval of 6 to 12 weeks of onset of initial symptoms. Hospital infrastructure, patient's general conditions, available resources and surgeon's expertise greatly influence the decision of approach whether to perform early or delayed laparoscopic cholecystectomy.

Laparoscopic approach for cholecystectomy was introduced in year 1987⁴. Earlier, laparoscopic cholecystectomy was considered to be contraindication⁵ for acute cholecystitis; patients were managed conservatively by antibiotics and called after 6 weeks interval for laparoscopic cholecystectomy when inflammatory process completely settled down. Laparoscopic

Received:
4th February 2016

Accepted:
17th July 2016

Taibah University, Al-Madina Al Munawara, KSA
TA Shah

King Fahad Hospital Al-Madinah Al-Munawarah, KSA.
MR Khan

Correspondence:
Dr Tajammal Abbas Shah,
Assistant Professor, Taibah University, Al-Madinah, Al-Munawarah
mail: tashah7067@yahoo.com

cholecystectomy in acutely inflamed gallbladder is more difficult because the gallbladder is distended, edematous and congested; with compromised blood supply and more likely superadded infection. The surrounding structures anatomy usually become distorted by adhesion of omentum to wall off the inflammatory process and the tissues are more fragile which may predispose to complications during procedure and more conversion rate to open cholecystectomy⁶. Laparoscopic cholecystectomy among patients initially managed conservatively results in fewer complications and less conversion rate to open cholecystectomy⁷ when compared with early and acutely inflamed cases because the inflammatory process gets settle down in delayed approach, although there are greater chances of repeated attacks of acute inflammation as well as prolonged hospital stay with more hospital admissions and higher cost. With the advent of more expertise in the field of laparoscopy the reluctant surgeons started early laparoscopic cholecystectomy although still only minorities of surgeons^{8,9,10} attempt this timing approach. In terms of exact timing of surgery, patient compliance, complications rate and cost effectiveness of these procedures to decrease morbidity and mortality is still controversial¹¹.

The aims of this study are to compare the results of early and delayed laparoscopic cholecystectomy in terms of hospital stay, cost effectiveness, complications rate, conversion to open cholecystectomy, patient compliance, and advantage or disadvantages of these procedures to decrease morbidity and mortality.

Materials and Methods:

This prospective, comparative study was conducted in King Fahad Hospital, Surgical Ward Al-Madinah Al-Munawara which is a more than 500 bedded tertiary care center. The duration of study was for two years from February 2014 to January 2016. The compared variables in this study were; hospital stay, cost effectiveness, complications during and after procedures, conversion to open cholecystectomy, patient compliance in terms of recovery period, morbidity and mortality in either of the two groups. The

patients were divided into two groups without difference of age and sex. In group A, the patients presented first time in emergency with signs and symptoms of acute cholecystitis within 72 hours of onset of symptoms. In group B, all other patients later than 72 hours duration of symptoms being first treated conservatively with antibiotics and called for interval or delayed cholecystectomy after 6 to 12 weeks were part of this study. Patients with repeated attacks or already diagnosed cases of symptomatic cholelithiasis were also included in this group. The number of patients in each group; Group A for early laparoscopic cholecystectomy and Group B for delayed laparoscopic cholecystectomy was 50. The Group A, patients presented in emergency all were investigated for complete blood count, blood glucose, liver function tests, alkaline phosphatase, serum amylase and renal function tests. Ultrasonography was done for all patients in emergency department. Diagnosis of acute cholecystitis was confirmed by taking detailed history of right hypochondrial pain radiating to right shoulder, nausea, vomiting and clinical examination with positive Murphy's sign, raised white blood cells and sonographic evaluation of distended, thicken edematous wall gallbladder, pericholecystic fluid and presence of gallstones. Informed consent was taken after well explaining the results of early surgery with special emphasis for conversion rate to open cholecystectomy and higher complication rate. Informed consent was also taken from group B patients after complete investigation and confirmation of diagnosis and indications for elective cholecystectomy. Patients excluded from this study were those; unfit for laparoscopic surgery, with previous abdominal surgery and which during first attack developed acute pancreatitis, acute cholangitis, jaundice and stones in common bile duct. All patients in both groups were operated in King Fahad Hospital Al-Madinah Al-Munawara. After surgery patients were shifted to in-patient surgical ward of this hospital. Patients were followed up for 4 month after surgery to see the morbidity and other complications. Data was analyzed by applying student t-test and z test score for calculating two population proportions.

Discussion:

This comparative, prospective study was conducted in King Fahad Hospital Al-Madinah Al-Munawara for the period of two years. After the laparoscopic cholecystectomy established as a “gold standard” for cholelithiasis, debate for timing of early or delayed laparoscopic cholecystectomy emerged as a controversial issue¹². The evolving expertise in laparoscopic surgery further directed the surgeons to solve this subjective approach of timing that was initially regarded as contraindication¹³ for early intervention in acutely inflamed gallbladder. Across the world, a lot of work has been established to recommend early laparoscopic cholecystectomy¹⁴ which yield early outcome from disease process with insignificant disadvantages of this early timing approach. In this study patients were divided into two groups.

All patients were operated in King Fahad Hospital under general anesthesia after pre-operative review by team of anesthesia. 3rd generation cephalosporin 1 Gram was given half hour before induction and single short postoperatively in almost all delayed or elective cases except in those who have inadvertently difficult and distended gallbladder and were aspirated during procedure. Injectable antibiotics for acutely inflamed cases were started soon after final diagnosis and continued till the discharge date. Patients were given injectable pain killer during periods of nothing per oral but replaced with oral medication after oral free. CO₂ was used for intraperitoneal insufflation. Three ports, supra-umbilical, epigastric and right lumbar region were utilized in majority of cases but the patients of acute cholecystitis underwent early cholecystectomy sometimes required fourth port in right iliac fossa. In certain acute cases, gallbladder was drained by needle aspiration before proceeding for further dissection. Liver bed hemostasis done carefully and sub-hepatic drain was placed in all patients of both groups and removed after the drain is less than 50 ml. All patients were discharged after morning rounds and hospital stay was counted as registered in hospital record. Patients were followed up for 4 month for post-operative complications. Patients were called on

7th post-operative day for follow up along with stitch removal and next follow up visit after one month of procedure and second follow up visit after two month of surgery and after that patient were advised to consult, if they have any morbid signs and symptoms.

Hospital stay:

In Group A, patients presenting with first attack in emergency unit of this hospital within 72 hours of start of symptoms and operated for early laparoscopic cholecystectomy. 28 patients were operated within 12 to 24 hours of admission after completing all initial workup and confirmed diagnosis of acute cholecystitis. The hospital stay for these patients was for 4 days. 14 patients were operated within 25 to 50 hours of admission among this Group A, patients; their stay in hospital was for 5 days. 6 patients in this group were operated within 72 hours of admission, stayed in hospital for 6 days. Two other patients operated within 25- 50 hours of admission with hospital stay of 8 and 9 days. The minimum hospital admission stay was 4 days while some patients were admitted for 9 days. The mean hospital stay for all 50 patients on an average was for 4.48 days as given in following Table 1.

In Group B; 35 patients have two times admissions with 6 days hospital stay. 11 patients have 3 times admissions with 8 days hospital stay. 2 patients in this group have 3 admissions and hospital stay was 9 days while another 2 patients have 3 admissions for 10 days. The minimum hospital admission stay in these Group B patients was 6 days while some patients were admitted for up to 10 days on different occasions, with an average mean hospital stay for these Group B patients was 6.72 days as given in Table 2.

If we compare international studies the average hospital stay in early and delayed laparoscopic cholecystectomy is 5.2 ± 1.40 versus 7.8 ± 1.65 days¹⁵ and 4.5 versus 10 days¹⁶ which well corresponds to this our present study.

Cost of admission and procedure:

Although the King Fahad Hospital is government hospital and treatment for Saudi and en-

Table 1: Shows number of patients, procedure timing after admission, hospital stay and mean hospital stay for all those underwent early laparoscopic cholecystectomy

No. of patients	Procedure timing after admission in ER (hours)	Hospital stay (days)	Total hospital stay(days)
28	12 - 24	4	96
14	25 - 50	5	75
6	51 - 72	6	36
1	25-50	8	8
1	25-50	9	9
Total	50 patients stay (days)		224
Mean hospital stay in days for (ELC):		219/50= 4.48 days	

Table II: Shows No. of patients, number of admissions, hospital stay and mean hospital stay for all those underwent delayed laparoscopic cholecystectomy

No. of patients	Number of admissions	Hospital stay (days)	Total hospital stay(days)
35	2	6	210
11	3	8	88
2	3	9	18
2	3	10	20
Total	50 patients stay (days)		336
Mean hospital stay in days for (DLC):		336/50= 6.72 days	

Table III: Shows total difference of cost in Group A and Group B

Groups	Admission cost /day in S.R	Proce- dure cost in S.R	Mean hos- pital stay (days)	Cost for single in S.R	Number of total patients	Cost for all in S.R
Group A	450	3,000	4.48	5016	50	250,800
Group B	450	3,000	6.72	6024	50	301,200
Difference of cost (more cost than Group A) among 50 patients in (DLC) is: S.R.						50,400

Table IV: Shows difference of hospital stay days and cost in S.R. with p-values between two groups

Group	Early cholecystec- tomy (n=50)	Delayed cholecystec- tomy	p- value
Hospital stay in days	4.48	6.72	0.211
Cost of procedure in S.R.	250,800	301,200	0.500

p- values <0.05 are insignificant

titled patients is free but after consultation with administration and finance department in terms of average cost, the average expenditure for a un-entitled patient in surgical unit of this hospital for single day is 450 S.R and the procedure prices for laparoscopic cholecystectomy are 3000 S.R. for any groups. If we calculate this expenditure for the two groups in Saudi Riyals among

Group A; By multiplying it with average or mean hospital stay the cost for one individual patient amounts S.R. = 5016 and total cost for all 50 patients is S.R. = 250,800. Similarly in Group B, by multiplying admission cost /day with mean hospital stay and addition of procedure cost it amounts S.R. = 6024 for one patient and S.R. = 301,200 for total 50 patients. The average difference of cost among two groups remains S.R. = 50,400 which is a reasonable amount and can be utilized for other purposes as shown in table 3.

If we see the international published literature early laparoscopic cholecystectomy is cost effective^{15,16,17} than delayed laparoscopic cholecystectomy. From this data we can calculate difference of hospital stay and cost in S.R. with p- values as is given in table 4 demonstrate

Complication rate:

If we compare the complication rate for these two groups, the complications that can be encountered during procedure and post-operative-ly are; bile leakages, significant bleeding during procedure, visceral injury, bile duct injury, post-operative bleeding, fever, jaundice, wound infection, stricture common bile duct and mortality if any during or after procedure.

Table 4 shows different complication among these two groups. The complications encountered during or after procedure are as such. Among Group A, 5 patients (10%) have bile leakage during procedure but 2 of the them developed bile collection in drain post-operatively. 5 patients (10%) have significant bleeding that necessitated insertion of 4th port for hemostasis while 3 patients (6%) have significant post-operative bleeding. Significant bleeding means about 150-200ml bloody discharge collected in drain. 2 patients (4%) underwent additional procedures.

1. One patient have choledocho-duodenal fistula found after adhenolysis during laparoscopic cholecystectomy. This patient was operated on 2nd day of admission, repaired by open conversion and patient recovered well and discharged on 7th post-operative

Table IV: Shows different complications in Group A, and Group B

Complication	Group A (n=50)	Group B (n=50)	P- VALUES
Bile leakage	5 (10%)	2 (4%)	0.238
Significant bleeding during procedure	5 (10%)	1 (2%)	0.092
Bile duct injury	1 (2%)	Nil	0.312
Post-operative bleeding	3 (6%)	1 (2%)	0.307
Additional procedure	2 (4%)	Nil	0.152
Post-operative fever	5 (10%)	1 (2%)	0.092
Jaundice	2 (4%)	Nil	0.152
Wound infection	3 (6%)	1 (2%)	0.307
Stricture common bile duct	Nil	Nil	0.000
Morbidity	17	14	0.515
a. Dyspeptic symptoms	7 (14%)	5 (10%)	0.535
b. Pain	8 (16%)	7 (14%)	0.779
c. Stitch granuloma	2 (4%)	Nil	0.152
d. Hypertrophic scars	3 (6%)	2 (4%)	0.645
Mortality	Nil	Nil	0.000

p- values <0.05 are insignificant

day with total 9 days of admission. Figure 1 illustrated with arrows to show choledochoduodenal fistula.

2. One patient have slipped stone and ERCP done on 4th post-operative day as patient developed mild icterus clinically with post-operative conjugated bilirubin of 3.2 mg/dl and ultrasonography visualized 10.5 mm CBD and stone at distal end of CBD. Patient recovered well post-operatively and discharged with 8 days of admission.

These same above 2 patients (4%) developed post-operative jaundice as well and recovered well. In this group A, 5 patients (10%) developed fever more than 38°C but less than 39.5°C and responded with post-operative antibiotics. 3 patients (6%) in this group have mild wound infection, two at umbilical port incision and one in epigastric port incision. All 3 wounds were opened and recovered well within 15 days, healing by secondary intention. In terms of morbidity 7 patients (14%) complained of dyspeptic symptoms, 8 patients (16%) have mild pain around the port sites, two patients (4%) have stitch granuloma and 3 patients (6%) developed hypertrophic scars.

Among Group B, bile leakage was observed among 3 patients (6%). Among these 3 patients two patient have difficult dissection due to fibrosis and thick wall of gallbladder that led to perforation per-operatively. One patient among these 3 patients per-operatively has distended gallbladder. Gallbladder was aspirated but there was bile leakage and even after aspiration the laparoscopic visual image was not clear and he developed not only bile leakage and bleeding but it necessitated conversion to open cholecystectomy. This same patient has post-operative bleeding that was observed to be 180 ml in total. One patient developed post-operative fever of 38°C and recovered with antibiotics while only one patient which was converted to open cholecystectomy have wound infection in two stitches on lateral corner of wound and healed well by secondary intention. None of the patient in this group has any additional procedure, bile duct injury, jaundice, stricture common bile duct and mortality during follow up period. Although stricture common bile duct may appear late but till the end of study no patient has been reported with such complaints. As far as morbidity is concerned, 5 patients (10%) complained of dyspeptic symptoms, 7 patients (14%) have mild pain around the port sites, one patient (2%) have stitch granuloma and 2 patients (4%) developed hypertrophic scars as given in table 4.

If we compare international studies for different complications encountered during procedure or post-operatively in these two groups; there are controversial results for early and delayed laparoscopic cholecystectomy complications rate although correspond with this present study. Some studies reported more while others have less and different rates of these complications such as; bile leakage, conversion rate, intraoperative bleeding, wound infection, CBD injury, additional procedures, and morbidity. The main point to be mentioned here is that there is no significant difference¹⁸ in intra-operative or post-operative complications during early or delayed laparoscopic cholecystectomy in majority of studies and almost all studies there is no mortality^{7,12,19,20}.

Conversion to open cholecystectomy:

Among Group A, all patients started with laparoscopic cholecystectomy but 3 patients (6%) were converted to open cholecystectomy.

1. One patient has a very short cystic duct with gangrenous gallbladder and it was not possible to apply clamps as there are greater chances of slippage of clamps postoperatively and in long term chances of common bile duct stricture. Figure 2 represents gangrenous gallbladder and short cystic duct.
2. Another one patient has marked inflammation and omental adhesion and he developed bleeding during separation of adhesive omentum as the anatomy was unclear and bleeding was significant so he was converted to open cholecystectomy.
3. In third patient, after identification of structures choledochoduodenal fistula was noticed, it was also converted to open cholecystectomy with repair of fistula.

Among Group B; 1 patient (2%) was converted to open cholecystectomy. This patient has inadvertently distended gallbladder without signs and symptoms of acute inflammation. On aspiration there was mucocele and laparoscopic visual image was not clear and he developed bile leakage and bleeding, the source of bleeding was not obvious and procedure was converted to open cholecystectomy. These results are shown in Figure 3

If we compare this conversion rate with international work done in various studies it ranges from 24%: 8%⁷ and 4%¹¹ in different studies during early and delayed laparoscopic cholecystectomy respectively while in this present study the conversion rate in early laparoscopic cholecystectomy is 6% and in delayed laparoscopic cholecystectomy it is 2%.

Patient compliance:

In terms of patient compliance if we compare both study results, patients in Group A, has single admission, less hospital stay, low cost, with-

out any significant morbidity and no mortality but slightly higher complication and conversion rate. In Group B, patients experienced more than one admission, more hospital stay, high cost but lesser complication rate without any significant morbidity or mortality. Overall Group A, patients have better compliance than Group B. If we compare this with international data it is well stated in almost all studies that patients are well compliant, comfortable and more advantage of early return to work, less hospital stay and lower cost^{7,11,20} in early laparoscopic cholecystectomy.

Results:

In this prospective, comparative study conducted in King Fahad Hospital Al-Madina Al-Munawarah, among 50 patients in Group A, the mean hospital stay was 4.48 days with average cost for single patient of S.R. 5016 and 50 patients S.R. 250,800 while in Group B, the mean hospital stay was 6.72 days and average cost for single patient was S.R. 6024 while 50 patient costs S.R. 301,200 with a difference of extra amount of S.R. 50,400 for this group. As far as complications are concerned in Group A, 5 patients (10%) have bile leakage, 5 patients (10%) and 3 patients (6%) have significant bleeding during procedure and post-operative respectively. Two patients underwent additional procedures while 3 patients (6%) were converted to open cholecystectomy. 5 patients in this group developed post-operative fever, 2 patients (4%) jaundice, 3 patients (6%) wound infection. Moreover 7 patients (14%) in this group complained for dyspeptic symptoms, 8 patients (16%) have mild pain around stitches, 2 patients (4%) developed stitch granuloma, and 3 patients reported with hypertrophic scars without any mortality in this group. Among the Group B, 2 patients (4%) have bile leakage, 1 patient (2%) during procedure and 1 patient (2%) post-operative have significant bleeding. No patient underwent additional procedures while 1 patient (2%) was converted to open cholecystectomy. 1 patient (2%) in this group developed post-operative fever, none of them jaundice and 1 patient (2%) wound infection. Moreover 5 patients (10%) in this group com-

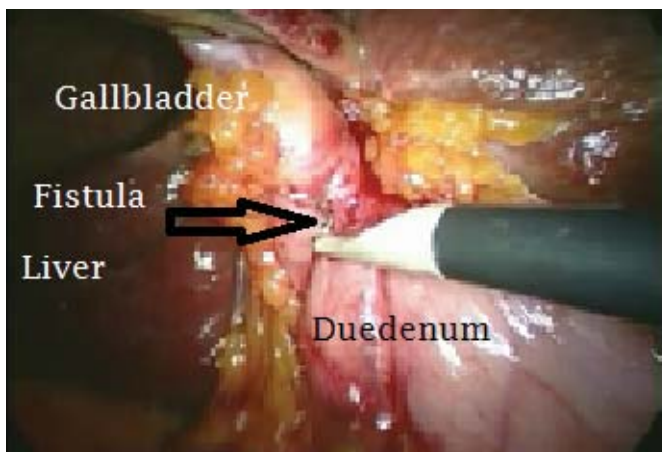


Figure 1: Arrow indicating Choledochoduodenal Fistula

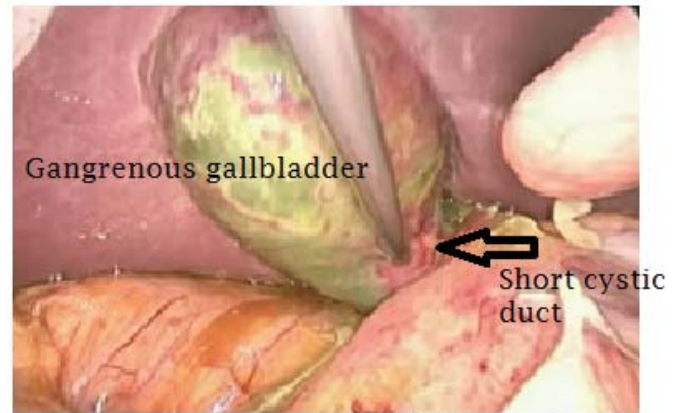
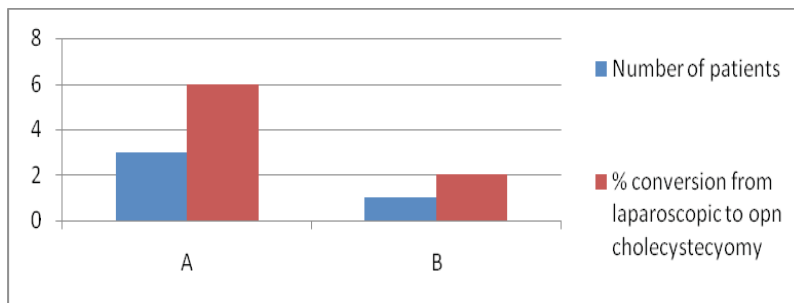


Figure 2: Gangrenous gallbladder and arrow indicating short cystic duct



plained for dyspeptic symptoms, 7 patients (14%) have mild pain around stitches, none of them developed stitch granuloma but 2 patients reported with hypertrophic scars without any mortality in this group.

Conclusion:

This prospective, comparative study concluded that the patients undergoing early laparoscopic cholecystectomy are more compliant, have less hospital stay, cost effective although higher conversion rate than delayed cholecystectomy but acceptable and fewer more complications than delayed laparoscopic cholecystectomy. Early laparoscopic cholecystectomy is strongly recommended in symptomatic cholelithiasis patients when compared with delayed cholecystectomy in which patient has multiple admissions, hospital visits, more hospital stay, higher cost with insignificant difference of complications and morbidity or mortality.

Conflict of Interest: None

Funding Sources: None

Role and contribution of authors:

Dr Tajammal Abbas Shah, FCPS Surgery, Assistant Professor, Faculty of Medicine, Taibah University, Al-Madina Al Munawara, KSA, did the initial writeup, collected the data references and wrote the discussion, results and conclusions.

Dr Masood Raza Khan, FCPS Surgery, Consultant Surgeon King Fahad Hospital Al-Madinah Al-Munawarah, KSA, critically reviewed the article and gave the final touchup.

References:

1. Soper NJ, Stockmann PT, Dunnegan DL, Ashley SW: Laparoscopic cholecystectomy. The new 'gold standard'?. Arch Surg. 1992; 127: 917-923.
2. Zafar SN, Obirize A, Adesibikan B, Cornwell EE 3rd, Fullum TM, Tran DD Optimal time for early laparoscopic cholecystectomy for acute cholecystitis. JAMA Surg. 2015 Feb; 150(2):129-36.
3. Masayuki Ohta, MD, Yukio Iwashita, MD, Kazuhiro Yada, MD, Tadashi Ogawa, MD, Seiichiro Kai, MD, Tetsuya Ishio, MD, Kohei Shibata, MD, Toshifumi Matsumoto, MD, Toshio Bandoh, MD, and Seigo Kitano, MD. Operative Timing of Laparoscopic Cholecystectomy for Acute Cholecystitis in a Japanese Institute JSLS. 2012 Jan-Mar; 16(1): 65-70.
4. Mouret P. How I developed laparoscopic cholecystectomy. Ann Acad Med. 1996; 25:744-7.
5. Gul R, Dar RA, Sheikh RA, Salroo NA, Matoo AR, Wani SH. Comparison of Early and Delayed Laparoscopic Cholecystectomy for Acute Cholecystitis: Experience from A Single Center. North American Journal of Medical Sciences. 2013; 5(7):414-418.
6. Alessia G Ferrarese, Mario Solej, Stefano Enrico, Alessandro Falcone, Silvia Catalano, Giada Pozzi, Silvia Marola, Valter Martino. Elective and emergency laparoscopic cholecystectomy in the elderly: our experience. BMC Surgery, 2013, Volume 13, Number 2, Page 1
7. Rati Agrawal, K. C. Sood, and Bhupender Agarwal. Evaluation

- of Early versus Delayed Laparoscopic Cholecystectomy in Acute Cholecystitis Surg Res Pract. 2015; 2015: 349801.
8. Sakowska MM, McKay J, Lake S, Deacon A. Index cholecystectomy: a continuing challenge for a provincial hospital. *N Z Med J*. 2013;126(1369).
 9. Sandzen B, Haapamaki MM, Nilsson E, Stenlund HC, Oman M. Surgery for acute gallbladder disease in Sweden 1989–2006 - a register study. *Scand J Gastroenterol*. 2013;48(4):480–486.
 10. Panagiotopoulou IG, Carter N, Lewis MC, Rao S. Early laparoscopic cholecystectomy in a district general hospital: is it safe and feasible? *Int J Evid Based Healthc*. 2012 Jun; 10(2):112-6
 11. Min-Wei Zhou, Xiao-Dong Gu, Jian-Bin Xiang, and Zong-You Chen, "Comparison of Clinical Safety and Outcomes of Early versus Delayed Laparoscopic Cholecystectomy for Acute Cholecystitis: A Meta-Analysis," *The Scientific World Journal*, vol. 2014, Article ID 274516, 8 pages.
 12. Alper Bilal Özkardeş, Mehmet Tokaç, ErsinGürkanDumlu, Birkan Bozkurt, Ahmet BurakÇiftçi, FahriYetişir, and MehmetKılıç. Early Versus Delayed Laparoscopic Cholecystectomy for Acute Cholecystitis: A Prospective, Randomized Study *Int Surg*. 2014 Jan-Feb; 99(1): 56–61.
 13. Kum CK, Goh PM, Isaac JR, Tekant Y, Ngoi SS. Laparoscopic cholecystectomy for acute cholecystitis. *Br J Surg*. 1994 Nov; 81(11):1651-4.
 14. Wu XD, Tian X, Liu MM, Wu L, Zhao S, Zhao L. Meta-analysis comparing early versus delayed laparoscopic cholecystectomy for acute cholecystitis. *Br J Surg*. 2015 Oct; 102(11):1302-13.
 15. Özkardeş AB, Tokaç M, Dumlu EG, et al. Early Versus Delayed Laparoscopic Cholecystectomy for Acute Cholecystitis: A Prospective, Randomized Study. *International Surgery*. 2014;99(1):56-61.
 16. Macafee DA, Humes DJ, Bouliotis G, Beckingham IJ, Whynes DK, Lobo DN. Prospective randomized trial using cost-utility analysis of early versus delayed laparoscopic cholecystectomy for acute gallbladder disease. *Br J Surg*. 2009 Sep; 96(9):1031-40.
 17. Chandler CF, Lane JS, Ferguson P, Thompson JE, Ashley SW. Prospective evaluation of early versus delayed laparoscopic cholecystectomy for treatment of acute cholecystitis. *Am Surg*. 2000 Sep; 66(9):896-900.
 18. Skouras C, Jarral O, Deshpande R, Zografos G, Habib N, Zacharakis E. Is early laparoscopic cholecystectomy for acute cholecystitis preferable to delayed surgery?: Best evidence topic (BET). *Int J Surg*. 2012; 10(5):250-8.
 19. Gutt CN, Encke J, Köninger J, Harnoss JC, Weigand K, Kipfmüller K, Schunter O, Götze T, Golling MT, Menges M, Klar E, Feilhauer K, Zoller WG, Ridwelski K, Ackmann S, Baron A, Schön MR, Seitz HK, Daniel D, Stremmel W, Büchler MW Acute cholecystitis: early versus delayed cholecystectomy, a multicenter randomized trial (ACDC study, NCT00447304). *Ann Surg*. 2013 Sep;258(3):385-93.
 20. Gurusamy K, Koti R, Fusai G, Davidson BR. Early versus delayed laparoscopic cholecystectomy for uncomplicated biliary colic. *Cochrane Database of Systematic Reviews*. *Annals of Surgery* 2013, Issue 6. Art. No.: CD007196.