ORIGINAL ARTICLE

Early laparoscopic cholecystectomy following acute biliary pancreatitis expedites recovery

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ABSTRACT

BACKGROUND: In this retrospective study, we aimed to assess the reliability of early cholecystectomy, risk of recurrent biliary pancreatitis, and their effects on hospital length of stay and morbidity by comparing the results of early and late laparoscopic cholecystectomy in patients with acute biliary pancreatitis.

METHODS: A total of 131 patients, who were diagnosed with acute biliary pancreatitis at Okmeydanı Education and Research Hospital in January 2009–December 2012, were included in the study. Demographic specifications of patients, duration of their complaints, biochemistry and hemogram values at first arrival, Ranson criteria, number of attacks, screenings, operation type and period, number of days between the first attack and operation, hospital length of stay, and complications were recorded. Patients who underwent cholecystectomy within the first 2 weeks were considered early (group 1) and those who under the operation after 2 weeks were considered late (group 2).

RESULTS: There were 47 patients in group 1 and 84 patients in group 2. Open surgery was not performed on any patient, and there was no choledoch injury and mortality. The average hospital length of stay was 7.6±3.0 days in group 1 and 10.7±8.3 days in group 2, with a statistically significant difference between the groups (p=0.006). Two or more number of attacks occurred in 15 patients in group 2 (18%), with a statistically significant difference between the groups (p=0.000).

CONCLUSION: Laparoscopic cholecystectomy is safe as it does not increase operation time and morbidity in biliary pancreatitis with a Ranson score of ≤3 or cause difficulty in dissection. Late cholecystectomy causes recurrent attacks and increases the hospital length of stay and treatment costs. Using randomized controlled studies, the effectiveness and reliability of early cholecystectomy in mild and moderate biliary pancreatitis can be verified.

Keywords: Biliary pancreatitis; laparoscopic cholecystectomy; timing of cholecystectomy.

INTRODUCTION

Cholecystectomy is recommended following an acute biliary pancreatitis (ABP) episode to prevent the development of biliary-related complications. However, there is an ongoing debate with regards to the optimal timing of intervention.[1] Acute pancreatitis has an annual incidence of 5–80/100.000 with gallstones being the most common etiology.[2,3] Gallstone pancreatitis is an inflammatory process due to temporary obstruction of both biliary and pancreatic drainage routes, usually self-limiting in nature. Treatment consists of initial supportive care followed by laparoscopic cholecystectomy (LC). In a few ABP patients, severe pancreatitis develops with impending cholangitis, which necessitates endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy and stone extraction.

Biliary pancreatitis accounts for 40% of pancreatitis cases. Moderate pancreatitis is encountered in 80% of all cases and severe pancreatitis in 20%, which is associated with high morbidity and mortality.[4] There is a general consensus on performing an interval cholecystectomy when the inflammatory process subsides, following an episode of severe pancreatitis.[5] Recent guidelines recommend early cholecystectomy after moderate biliary pancreatitis episodes.[6–8] However, the definition of early cholecystectomy is not universal. Some authors recommend cholecystectomy after im-

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mediate convalescence from an ABP episode, whereas others recommend that surgery should be postponed for 2–4 weeks.[8–14] The variation between guidelines is due to an absence of randomized controlled trials. The idea behind early cholecystectomy rests on decreasing the risk of developing recurrent biliary-related complications (i.e., acute pancreatitis, acute cholecystitis, symptomatic bile duct stones, biliary colic). As a recurrent biliary pancreatitis episode may be life-threatening, early cholecystectomy may prove pivotal.[15] In general practice, surgeons postpone surgery until cessation of the inflammatory process, as evidenced by the absence of abdominal pain and normal liver function tests. However, this approach is not evidence-based and may unnecessarily prolong hospital stay.

We hypothesized that early LC would improve outcomes without additional morbidity and compared the outcomes following early (<2 weeks) and delayed (>2 weeks) LC performed after an ABP episode.

MATERIALS AND METHODS

Approval was received for this study from the ethics committee of Okmeydanı Education and Research Hospital. Hospital electronic records were retrospectively extracted for patients with ABP who underwent LC between January 2009 and December 2012. Patients who required conventional bile duct exploration during LC were excluded. Severe and necrotizing pancreatitis cases were excluded. ABP was defined as right upper quadrant pain, a three-fold increase in serum amylase level, and the presence of stones in the gallbladder or biliary ducts. The management of each individual patient with regards to early (<2 weeks) or delayed (>2 weeks) LC was at the discretion of the attending surgeon.

The study cohort was divided into early (<2 weeks; group 1) and delayed (>2 weeks; group 2) LC. Univariate analysis was performed comparing demographics (age, sex), clinical characteristics (duration of symptoms, period from onset to surgery, episode count, Ranson score), surgical procedure [LC, intraoperative cholangiography, laparoscopic bile duct exploration (LBDE), duration of surgery], complications (retained bile duct stone, intra-abdominal bleeding, postoperative pancreatitis, pancreatic pseudocyst, cystic duct stump leakage), and hospital length of stay (HLOS) between the two treatment groups. Primary endpoint consisted of HLOS, and secondary endpoints were recurrent pancreatitis episodes and postoperative complications. C-reactive protein (CRP) level was used to monitor patient progress. When CRP level failed to decrease or when it reached >150 mg/dL, a contrast-enhanced abdominal computerized tomography (CT) scan was indicated to assess for necrotizing pancreatitis. ERCP was selectively performed in both pre and postoperative periods. When acute cholangitis was associated with ABP, ERCP was preoperatively performed. A total bilirubin level of >4 mg/dL at admission was evaluated with ultrasonography (US) and/or magnetic resonance cholangiopancreatography (MRCP). When a dilatation of the biliary tree was encountered, preoperative ERCP was performed.

Statistical Analysis

Chi-square or Fisher's exact tests were used to compare categorical variables. Continuous variables were examined for normality of distribution using the Shapiro–Wilk test. Student's t test was used for the analysis of normally distributed variables, and the non-parametric Mann–Whitney U test was used for the analysis of values with non-normal distribution. Statistical analyses were performed using IBM SPSS Statistics 22.0. Statistical significance was set at a p-value of <0.05.

RESULTS

Age, sex, duration of symptoms, and Ranson score were not different between the two groups. Duration from onset till surgery and the number of episodes were significantly shorter and less, respectively, in group 1 (Table 1).

Operation time and postoperative complication rates were

Table 1. Demographics and clinical characteristics

	Group 1 (n=47) Early LC	Group 2 (n=84) Late LC	p
Age, Mean±SD/Med (Min-Max)	54.3±17 / 56.0 (17-82)	51.9±15.4 / 51.5 (23-83)	0.419
Sex, n (%)			
Female	37 (79)	61 (73)	0.440
Male	10 (21)	23 (27)	
Symptom duration, Mean±SD–Med (Min-Max)	1.5±1.1 / 1 (1–7)	1.5±1.2 / 1 (1–7)	0.878
Duration from onset to surgery, Mean±SD/Med (Min-Max)	5.7±2.8 / 5 (1–14)	82.8±83.0 / 57.5 (14–496)	0.000
Episode count, Mean±SD/Med (Min-Max)	1.0±0.0 / 1 (1-1)	1.3±0.7 / 1 (1–6)	0.001
Ranson score, Mean±SD/Med (Min-Max)	1.9±1.2 / 2 (0–4)	1.8±1.1 / 2 (0–5)	0.505

LC: Laparoscopic cholecystectomy; SD: Standard deviation; Med: Median; Min: Minimum; Max: Maximum.

Table 2. Surgical procedure, complications, and outcomes

	Early LC	Late LC	p
Operation type, n (%)			
LC	43 (91)	77 (92)	
LC + IOC	0 (0)	2 (2)	
LC + LBDE	4 (9)	5 (6)	
Duration of surgery, Mean±SD min./Med (Min-Max)	77.4±34.8 / 70 (30–195)	76.7±33.4 / 72.5 (25–180)	0.971
Postoperative complications, n (%)			
Absent	46 (98)	79 (94)	
Present	1 (2)	5 (6)	0.315
Retained bile duct stone	1 (2)	0 (0)	
Intra-abdominal bleeding	0 (0)	1 (1)	
Postoperative pancreatitis	0 (0)	1 (1)	
Pancreatic pseudocyst	0 (0)	1 (1)	
Cystic duct stump leak	0 (0)	2 (2)	
HLOS, Mean±SD days/Med (Min-Max)	7.6±3.0 / 7.0 (2–17)	10.7±8.3 / 9.0 (2–72)	0.006
Recurrent pancreatitis episodes, n (%)	0 (0)	15 (18)	0.000

LC: Laparoscopic cholecystectomy; IOC: Intraoperative cholangiography; LBDE: Laparoscopic bile duct exploration; HLOS: Hospital length of stay; SD: Standard deviation; Med: Median; Min: Minimum; Max: Maximum.

Table 3. MRCP and ERCP findings

	Early LC	Late LC	Total
Preoperative MRCP	11	19	30
Bile duct pathology			
Absent	10	17	27
Present	1	2	3
Common bile duct stone	1	1	2
Biliary tree dilatation	0	1	1
Preoperative ERCP	6	8	14
Acute cholangitis			
Absent	6	3	9
Present	0	5	5
Stone extracted	0	5 (acute cholangitis)	5
Postoperative ERCP	1	3	4
LC+LBDE retained stone	1	0	1
Recurrent pancreatitis	0	1	1
Cystic stump leak	0	2 (stent)	2

MRCP: Magnetic resonance cholangiopancreatography; ERCP: Endoscopic retrograde cholangiopancreatography; LC: Laparoscopic cholecystectomy; LBDE: Laparoscopic bile duct exploration.

not different between the groups. HLOS was significantly shorter in group 1. The incidence of recurrent pancreatitis episodes and emergency room (ER) visits were significantly high in group 2. Postoperative complications were not significantly different between the groups (Table 2).

An abdominal CT scan was indicated in 16 patients, none of whom showed signs compatible with necrotizing pancreatitis. Preoperative ERCP was preoperatively performed in five patients due to associated acute cholangitis, and gallstones were extracted from common bile duct in all cases. US or MRCP findings were suggestive of bile duct stones in six patients in group 1 and in three patients in group 2 (Table 3).

There was no conversion to conventional cholecystectomy, no biliary tree injury, and no mortality. Two common bile duct stones were identified and extracted with ERCP before discharge in one patient from group 1 who underwent LC and LBDE. One patient from group 2 who underwent LC and LBDE required emergency laparotomy on postoperative day 1 due to intraabdominal hemorrhage, and hemostasis was performed on common bile duct arteries at 3 and 9 o'clock positions. One patient in group 2 developed a pancreatic pseudocyst after ABP, which was initially treated with percutaneous cyst drainage and then with LC after 210 days of the ABP episode. One patient in group 2 had a recurrent ABP after 15 days of LC, which was treated with ERCP. Two patients in group 2 developed bile leakage: in one patient, the leakage was identified as originating from a cystic duct stump and treated with a bile duct stent, whereas in the other patient, a diagnostic laparoscopy with biloma drainage was performed followed by ERCP and bile duct stenting on postoperative day 13.

DISCUSSION

LC performed within 2 weeks of ABP onset was shown to

decrease HLOS compared with LC performed after 2 weeks. Similar results were reported in a recent systematic review.[16] Recurrent pancreatitis was observed in 18% of group 2. In a recent systematic review, the ER readmission rate due to recurrent biliary pancreatitis was reported as 8%. When readmissions due to acute cholecystitis and biliary colic were taken into account, an 18% readmission rate after late cholecystectomy was reported.[16] Readmissions to ER due to acute cholecystitis or biliary colic were out of the scope of the present study and thus were not recorded. The recurrent biliary pancreatitis rate of 18% in the present study may seem relatively high compared with that of previous data. This may partially be explained by fact that Turkish cuisine and eating habit usually contains high levels of saturated fat. Recurrent biliary pancreatitis is encountered in 4%–50% of cases and may become fatal.[15,17,18] According to our study, only one patient in group 2 developed recurrent biliary pancreatitis with impending necrotizing pancreatitis and pseudocyst formation.

There has been a historical dogma among surgeons to believe that edema caused by pancreatitis would pose dissection difficulties and may increase complication and cause conversion to open surgery rates. In contrast, Sinha[19] proposed that dissection difficulties are encountered more in late cholecystectomies than in early cholecystectomies.

The initial assessment of acute pancreatitis should be performed well and with care. Regardless of the patient's clinical status, cholecystectomy within the initial 48–72 h is not recommended.[20] Fifteen percent of moderate pancreatitis patients will eventually develop severe pancreatitis.[21,22] Cholecystectomy in the presence of severe pancreatitis may predispose the patient to unbalanced risks.[5] In the present study, the patient cohort consisted of mild or moderate pancreatitis cases. Severe and necrotizing pancreatitis cases were excluded. When postoperative complications were compared between both groups, no significant differences were observed.

Total bilirubin was reported as the best predictor of common bile duct stones in biliary pancreatitis.[23] Within 2 days of the initial hospital admission, a total bilirubin level of >4 mg/dl was shown to be the best positive predictive value; therefore, preoperative ERCP is unnecessary for patients with more less this bilirubin level.[24] These levels were also reported to substantially increase the likelihood of developing acute cholangitis.[25] In the present study, ERCP was selectively performed in both pre and postoperative periods. According to our study, acute cholangitis was associated with ABP in five patients from group 2. Preoperative ERCP was performed, and in all cases, bile stones were extracted from the common bile duct. A total bilirubin level of >4 mg/dL was evaluated with US and/or MRCP. When dilatation of the biliary tree was encountered, preoperative ERCP was performed. Postoperative ERCP was performed in one patient from group 1 and in three patients from group 2 due to postoperative complications (Table 3).

The present study is limited mainly by its retrospective nature and small patient population. No prospective randomized study has reported on the timing of cholecystectomy, other than the trial by Aboulian et al.,[25] until the PONCHO trial of the Dutch Pancreatitis Study Group published in 2015. This trial was terminated after an interim analysis of 25 patients, who showed no differences in secondary endpoints. The early cholecystectomy group in this study consisted of operation performed within 48 h of admission. The PONCHO trial is designed to answer the question of whether early cholecystectomy leads to a reduction of re-acceptances for biliary events in patients with a first episode of mild biliary pancreatitis.[26] The first 72-h time interval after randomization is selected for the early cholecystectomy group. For the interval LC group, 25–30 days after randomization are chosen. The PONCHO trial is a superior trial, hypothesizing a reduction in readmission for biliary events in patients with a first episode of mild biliary pancreatitis. The primary endpoint was a composite of gallstone-related complications or mortality occurring within 6 months of randomization before or after cholecystectomy.[27] Readmission rate due to gallstone-related complications or mortality in the interval cholecystectomy group was reported as 17%. According to our study, readmission rate due to recurrent pancreatitis episodes in group 2 was 18%. There was no readmission due to gallstone-related events other than recurrent pancreatitis episodes or mortality in our study. The readmission rate in the late cholecystectomy group in our study also has similar results in the PONCHO trial of the Dutch Pancreatitis Study Group. Readmission rate in the same-admission cholecystectomy group of the PONCHO trial was 5%, while it was 0% in our study. The reason for this may be that the number of cases in our group 1 is 47, whereas that in the PONCHO trial was 128. The other reason may be that the surgeons are biased in the selection of patients in our study.

HLOS after randomization did not differ between groups in the PONCHO trial.[27] However, it was significantly longer in group 2 of our study. The reason for this may be that episode count and duration from onset to surgery is significantly higher in this group (Table 1). Long HLOS means increase in treatment costs.

LC is not preferred in elderly patients due to comorbidity at the first admission. However, the best evidence till date has shown stable tendency in favor of laparoscopic procedures in terms of mortality, morbidity, and cardiac and respiratory complications in selected cases.[28] LC is safe in elderly patients, with low morbidity and mortality rates, and perioperative outcomes in elderly patients depend on the severity of gall bladder disease rather than chronologic age.[29] Early LC can be indicated for elderly patients with mild ABP and acceptable morbidity and mortality risks. LC reduces the risk of complications caused by recurrent pancreatitis in elderly patients. Therefore, surgery should be performed at the first admission.[30]

Cholecystectomy should be performed during index admission in patients with mild acute pancreatitis and should be delayed until clinical resolution in patients with severe acute pancreatitis.[31] Currently, clinical decision making relies on the available retrospective data until novel prospective randomized studies become available.

Conclusion

The present study demonstrated that in mild or moderate ABP, LC within 2 weeks of admission of the initial episode decreases HLOS and prevents the development of recurrent pancreatitis. Further large-scale prospective randomized trials are required to document the safety and efficacy of this approach.

Informed Consent

This was a retrospective clinical trial, and written informed consent was not obtained from patients who participated in this study.

Conflict of interest: None declared.

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ORİJİNAL ÇALIŞMA - *ÖZET*

Akut biliyer pankreatiti izleyen erken laparoskopik kolesistektomi iyileşme sürecini kısaltır

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AMAÇ: Bu geriye dönük çalışmamızda akut biliyer pankreatitli hastalarda erken ve geç laparoskopik kolesistektomi sonuçlarımızı karşılaştırarak, erken kolesistektominin güvenilirliğini, tekrarlayan biliyer pankreatit riskini, yatış günü ve morbidite üzerindeki etkilerini araştırmayı amaçladık.
GEREÇ VE YÖNTEM: Okmeydanı Eğitim ve Araştırma Hastanesinde Ocak 2009 – Aralık 2012 arasında akut biliyer pankreatitli 131 hasta çalışmaya alındı. Hastaların demografik özellikleri, şikayetlerinin süresi, ilk gelişteki biyokimya ve hemogram değerleri, Ranson skoru, atak sayısı, görüntülemeler, ameliyat türü ve süresi, ilk ataktan ameliyata kadar geçen gün sayısı, yatış günü ve komplikasyonlar kaydedildi. Ameliyatlarını ilk iki haftada olanlar erken (Grup 1), iki haftadan sonrakiler geç (Grup 2) olarak değerlendirildi.
BULGULAR: Grup 1'deki 47, Grup 2'deki 84 hastaya laparoskopik kolesistektomi yapıldı. Hiçbir olguda açık ameliyata geçilmedi, koledok yaralanması olmadı ve mortalite gelişmedi. Yatış günü ortalaması, Grup 1'de 7.6±3.0 gün, Grup 2'de 10.7±8.3 gün idi ve gruplar arasında istatistiksel anlamlı fark bulundu (p=0.006). İki ve üzerinde atak sayısı Grup 2'deki hastaların 15'inde (%18) saptandı ve istatistiksel anlamlı fark bulundu (p=0.000).
TARTIŞMA: Ranson ≤3 biliyer pankreatitlerde erken laparoskopik kolesistektomi, operasyon süresi ve morbiditeyi artırmadığından ve diseksiyon güçlüğü yaratmadığından güvenle uygulanabilir. Geç kolesistektomiler tekrarlayan ataklar, yatış günü ve tedavi maliyetlerinde artışa neden olmaktadır. Randomize kontrollü çalışmalarla hafif ve orta biliyer pankreatitlerde erken kolesistektominin etkinliği ve güvenilirliği doğrulanmalıdır.
Anahtar sözcükler: Biliyer pankreatit; kolesistektominin zamanlaması; laparoskopik kolesistektomi.

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