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ORIGINAL ARTICLE

Outcomes of delayed endoscopic retrograde cholangiopancreatography in patients with acute biliary pancreatitis with cholangitis

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ABSTRACT

Objective: The recommended treatment for acute biliary pancreatitis(ABP) with cholangitis is urgent endoscopic retrograde cholangiopancreatography(ERCP). However, tight schedules in the endoscopy room mean that urgent ERCP may not always be performed. This study aimed to compare the outcomes of early (≤72 h) and delayed(>72 h) ERCP in patients with ABP with cholangitis.
Methods: Ninety-five patients diagnosed with ABP with cholangitis who underwent ERCP between May 2012 and April 2018 were retrospectively reviewed.
Results: Sixty-seven patients(70.5%) were classified in the early ERCP and 28(29.5%) in the delayed ERCP groups. There was no significant difference in pancreatitis severity between the groups. Total bilirubin was higher in the early compared with the late ERCP group (5.7 ± 5.2 versus 3.5 ± 2.3 mg/dL, p = 0.03). Fewer patients in the early group had end-stage renal disease (0 versus 3, p = 0.006) and relatively fewer patients in the early group took aspirin (15(22.4%) versus 12(42.9%), p = 0.04). There were no significant differences between the early and delayed ERCP groups in terms of mortality (2(3.0%) versus 0), disease-related complications(11 (16.4%) versus 5(17.9%), p = 0.86), or ERCP-related complications(5(7.5%) versus 3(10.7%), p = 0.60). The total length of stay(LoS) was shorter in the early group(6.3 ± 4.4 versus 9.8 ± 6.1 days, p = 0.002). The rate of complete stone removal was lower in the early compared with the delayed ERCP group(32/42(76.2%) versus 18/18(100%), p = 0.02).
Conclusion: Delayed ERCP can be performed in selected patients with ABP with cholangitis, with similar complication rates but longer LoS compared with early ERCP.
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Introduction

Acute biliary pancreatitis (ABP) is the most common cause of acute pancreatitis in Thailand.[1] It is caused by obstruction of the common channel of the pancreatic duct and distal common bile duct due to choledocholithiasis.[2] The choledocholithiasis pass spontaneously into the intestine,[3] but ABP coexisting with cholangitis can occur in patients with persistent biliary tract obstruction.[4] The recommended treatment for ABP with biliary tract obstruction without cholangitis is early endoscopic retrograde cholangiopancreatography (ERCP) within 72 h, while urgent ERCP within 24 h after admission is recommended in patients with ABP accompanied by cholangitis.[5] However, tight schedules in the endoscopy room mean that ERCP may not always be performed within 24 h. This study therefore aimed to compare the outcomes of early ERCP (≤72 h after admission) and delayed ERCP (>72 h after admission) in patients with ABP with cholangitis.

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Methods

Data collection

In this retrospective study, we recruited 132 patients diagnosed with ABP who underwent ERCP at our hospital from May 2012 to April 2018. Thirty-seven patients diagnosed with ABP without cholangitis were excluded. The remaining 95 patients who were diagnosed with ABP accompanied by cholangitis were classified into an early ERCP group (ERCP ≤72 h after admission) or delayed ERCP group (ERCP >72 h after admission) (Fig. 1). The study was approved by the Institutional Review Board of University. Electronic medical records and radiologic imaging data were reviewed for these 95 patients. The clinicopathological data and intraoperative and postoperative outcomes were collected and analyzed. ERCP was performed by six hepato-pancreato-biliary surgeons and five gastroenterologists.

Definition

ABP was diagnosed by the presence of two of the three following criteria by American College of Gastroenterology guideline: (1) abdominal pain consistent with the disease, (2) serum amylase and/or lipase greater than three times the upper limit of normal, and/or (3) characteristic findings from abdominal imaging, as well as abnormal liver enzymes.[6] Other causes of acute pancreatitis were excluded by a history of absence of abdominal trauma and alcohol consumption. Cholangitis was diagnosed according to the 2018 Tokyo Guidelines, with some increase in cut-off values (temperature ≥38.5 °C and white blood cell count ≥12,000/mm^3),[7] or by the presence of purulent bile during ERCP. The severity of ABP was graded and defined according to the Atlanta definition 2012,[8] and the predicted severity of ABP was assessed according to the Bedside Index for Severity in Acute Pancreatitis (BISAP) scoring system.[9] ERCP complications were assessed based on the American Society for Gastrointestinal Endoscopy guidelines.[10]

Surgical procedure

The admission schedule was arranged by the emergency physicians when a patient presented in the emergency room. Patients received antibiotic treatment for cholangitis after blood sampling for hemoculture. The timing of ERCP after admission depended on the patients' condition, the doctor in charge, and the availability of the endoscopy room. The criteria for selecting early ERCP group in our institution included (1) cholangitis with organ failure (2) persistent high-grade fever after antibiotic administration for 24 h (3) Total bilirubin level >4 mg/dL. Delayed ERCP was preferred for the patients with other indications apart from those three conditions. Emergency ERCP was performed in patients who were clinically deteriorating due to biliary sepsis, while ERCP was scheduled during regular office hours in patients with clinically stable cholangitis. Patients underwent ERCP in a semi-prone position under general anesthesia with an endotracheal tube. After intubation with a side-view endoscope, the bile duct was cannulated using a standard wire-guided technique, bile was then aspirated for bile duct decompression and culture, and contrast material was injected. Endoscopic sphincterotomy was performed, except in cases with a high risk of bleeding. A biliary stent was placed in case of failed choledocholithiasis removal, inadequate biliary drainage, or swelling of the ampulla, and a pancreatic duct stent was placed in selected cases. ERCP was contraindicated in patients with an unstable medical condition who might not tolerate the general anesthesia or the procedure.

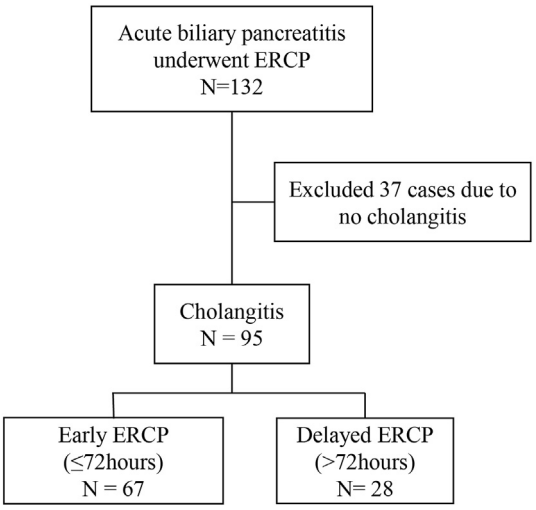

Fig. 1. Patient disposition.

Statistical methods

Statistical analysis was carried out using SPSS software version 20 (SPSS Inc., Chicago, IL, USA). Variables were compared using χ^2 tests and independent samples *t*-tests. Differences were considered significant at a p value of <0.05. Univariate and multivariate logistic regression analysis was calculated by stepwise technique.

Results

Patient characteristics

Among the 95 patients, 67 (70.5%) patients were classified into the early ERCP group and 28 (29.5%) patients into the delayed group. There were no differences in age, body mass index(BMI), American Society of Anesthesiologists score(ASA), lipase and amylase level between the two groups. No patients had malignant obstruction. There were also no differences in cholangitis diagnostic criteria or pancreatitis severity according to either the Atlanta classification or the BISAP score. The mean (±standard deviation) total bilirubin level was significantly higher in the early compared with the delayed ERCP group (5.7 ± 5.2 versus 3.5 ± 2.3 mg/dL, respectively, p = 0.03). There were also significantly fewer patients with end stage renal disease (ESRD) in the early ERCP group (0/67, 0%) compared with the delayed group (3/28, 10.7%) (p = 0.006), and relatively fewer patients took aspirin in the early ERCP group (15/67, 22.4%) compared with the delayed ERCP group (12/28, 42.9%) (p = 0.04). The mean duration in the emergency room before admission was 1.1 ± 1.3 days. The mean duration from admission to ERCP was significantly shorter in the early ERCP group (42.1 ± 18.4 h) compared with the delayed group (152.9 ± 92.4 h) (p < 0.001). There was no significant difference between the two groups in the presence of choledocholithiasis by radiological imaging (early: 30/67 (44.8%); delayed: 18/28 (64.3%), p = 0.08) or by ERCP (early: 42/67 (62.7%); delayed: 18/28 (64.3%), p = 0.83) (Table 1).

Endoscopic techniques

There were no differences in terms of ERCP techniques. The majority of patients underwent bile duct cannulation by guidewire assisted technique (early: 60/67, 89.6%); delayed: 26/28, 92.9%) (p = 0.60). The endoscopic sphincterotomy technique (EST) was

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Table 1
Patient characteristics.

	Early ERCP ≤72 h (N = 67)	Delayed ERCP >72 h (N = 28)	p-value
Sex, N(%)			0.44
Male	32(47.8%)	11(39.3%)	
Female	35(52.2%)	17(60.7%)	
Age (years), mean ± SD	67.7 ± 16.3	66.3 ± 16.2	0.70
Body mass index (kg/m^2), mean ± SD	25.9 ± 5.1	23.9 ± 3.4	0.05
Total bilirubin (mg/dL), mean ± SD	5.7 ± 5.2	3.5 ± 2.3	0.03
Albumin (g/L), mean ± SD	33.1 ± 5.8	33.7 ± 4.6	0.67
Lipase (U/L), mean ± SD	11709.7 ± 8275.8	11618.6 ± 9125.4	0.98
Amylase (U/L), mean ± SD	1291.6 ± 1282.6	1560.6 ± 1883.3	0.59
WBC, mean ± SD	15630.6 ± 11997	14465.5 ± 5612	0.62
ASA, N(%)			0.23
Class I	1(1.5%)	0	
Class II	18(26.9%)	10(35.7%)	
Class III	33(49.3%)	8(28.6%)	
Class IV	15(22.4%)	10(35.7%)	
Underlying disease, N(%)			
Myocardial infarction/atrial fibrillation	*10(14.9%)*	*6(21.4%)*	*0.44*
End-stage renal disease	*0*	*3(10.7%)*	*0.006*
Diabetes mellitus	*21(31.3%)*	*8(28.6%)*	*0.78*
Other	*15(22.4%)*	*5(17.9%)*	*0.62*
Anti-platelet or anti-coagulant, N(%)			
Aspirin	15(22.4%)	12(42.9%)	0.04
Warfarin	2(3.0%)	2(7.1%)	0.35
Other	3(4.5%)	1(3.6%)	0.84
Pancreatitis severity, N(%)			0.80
Mild	51(76.1%)	23(82.1%)	
Moderately severe	9(13.4%)	3(10.7%)	
Severe	7(10.4%)	2(7.1%)	
BISAP score, N(%)			0.24
<3	55(82.1%)	20(71.4%)	
≥3	12(17.9%)	8(28.6%)	
Duration from presenting symptom to hospital (day), mean ± SD	2.0 ± 2.0	2.5 ± 3.8	0.42
Duration from admission to ERCP (h), mean ± SD	42.1 ± 18.4	152.9 ± 92.4	<0.001
Cholangitis criteria, N(%)			0.23
Definite cholangitis	53(79.1%)	25(89.3%)	
Suspected cholangitis	14(20.9%)	3(10.7%)	
Pre-ERCP imaging, N(%)			0.36
Ultrasound	35(53.8%)	9(34.6%)	
Computed tomography	25(38.5%)	13(50.0%)	
MRCP	4(6.2%)	3(11.5%)	
Endoscopic ultrasound	1(1.5%)	1(3.8%)	
Presence of choledocholithiasis by imaging, N(%)	30(44.8%)	18(64.3%)	0.08

ERCP, endoscopic retrograde cholangiopancreatography; *ASA*, American Society of Anesthesiologists; *BISAP*, bedside index of severity in acute pancreatitis; *MRCP*, magnetic resonance cholangiopancreatography; *SD*, standard deviation; *WBC*, white cell count.

commonly used in both group (early: 56/67, 83.6%); delayed: 24/28, 85.7%) (p = 0.93). The mean duration of bile duct cannulation revealed no differences (early: 9.4 ± 0.8 versus 9.0 ± 0.6 min, p = 0.84), and the mean duration of ERCP was not different (early: 47.1 ± 22.1 versus 42.5 ± 11.2 min, p = 0.30) (Table 2).

Operative outcomes

There were two deaths (3.0%) in the early ERCP group, due to myocardial infarction and pneumonia, respectively, but no deaths in the delayed ERCP group. There was one (1.1%) case of failed biliary cannulation, but this was achieved successfully within 2 days after the initial unsuccessful attempt. There were no significant differences in disease-related or ERCP-related complications between the early and delayed ERCP groups (11/67 (16.4%) versus 5/28 (17.9%), p = 0.86 and 5/67 (7.5%) versus 3/28 (10.7%), p = 0.60, respectively). The total length of hospital stay (LoS) was shorter in the early ERCP group (6.3 ± 4.4 days) compared with the delayed group (9.8 ± 6.1 days) (p = 0.002), but there was no significant difference in LoS after ERCP. There were also no significant differences in positive bile culture rate, positive hemoculture rate, and duration of ERCP. The sizes of the stones were similar in the early (9.0 ± 5.2 mm) and delayed ERCP groups (7.4 ± 5.2 mm) (p = 0.37). However, the rate of complete stone removal was significantly higher in the delayed ERCP group (early: 32/42 (76.2%), delayed: 18/18 (100%), p = 0.02) (Table 3).

The pre-operative factors associated with delayed ERCP group including BMI, total bilirubin and antiplatelet or anticoagulant were analyzed by univariate and multivariate logistic regression. The low total bilirubin level ≤4 mg/dL and patients taking antiplatelet or anticoagulant were independent factors for delayed ERCP. The adjusted odd ratio (95%CI) of total bilirubin was 0.37(0.14, 0.97), p 0.04 and the adjusted odd ratio (95%CI) of patients taking antiplatelet or anticoagulant was 2.54(1.01, 7.29), p 0.03 (Table 4).

Patients who underwent ERCP after ≤24 h had a higher rate of positive bile cultures compared with patients who underwent ERCP within >24 h (64% versus 48%, respectively, p = 0.02). There was no significant difference in the rate of positive hemocultures between

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Table 2
Endoscopic techniques.

	Early ERCP ≤72 h (N = 67)	Delayed ERCP >72 h (N = 28)	p-value
Cannulation techniques, N(%)			0.60
Guidewire assisted	60 (89.6%)	26 (92.9%)	
Precutting sphincterotomy assisted	7 (10.4%)	2 (7.1%)	
Papillary manipulation techniques, N(%)			0.93
EST	56 (83.6%)	24 (85.7%)	
EST + EPBD	9 (13.4%)	4 (14.3%)	
EPBD	2 (3%)	0	
PD cannulation, N(%)	20 (29.9%)	5 (17.9%)	0.21
PD stent insertion, N(%)	7 (10.4%)	1 (3.6%)	0.26
Pancreatogram, N(%)	3 (4.5%)	0	0.25
Duration of cannulation (min), mean ± SD	9.4 ± 0.8	9.0 ± 0.6	0.84
Duration of ERCP (min), mean ± SD	47.1 ± 22.1	42.5 ± 11.2	0.30

EST, endoscopic sphincterotomy; *EPBD*, endoscopic papillary balloon dilatation; *PD*, pancreatic duct; *SD*, standard deviation; *WBC*, white cell count.

Table 3
Treatment outcomes.

	Early ERCP ≤72 h (N = 67)	Delayed ERCP >72 h (N = 28)	p-value
Mortality, N(%)	2(3.0%)	0	0.35
Disease-related complications, N(%)	11(16.4%)	5(17.9%)	0.86
ERCP-related complications, N(%)	5(7.5%)	3(10.7%)	0.60
Bleeding	2(3.0%)	0	
Perforation	0	0	
Pancreatitis	0	1(3.6%)	
Cholangitis	1(1.5%)	0	
Cholecystitis	2(3.0%)	2(7.1%)	
Total length of hospital stay (day), mean ± SD	6.3 ± 4.4	9.8 ± 6.1	0.002
Length of hospital stay after ERCP (day), mean ± SD	4.5 ± 4.2	5.2 ± 6.4	0.49
Emergency ERCP, N(%)	25(37.3%)	9(32.1%)	0.63
Endoscopist, N(%)			0.32
Surgeon	54(80.6%)	20(71.4%)	
Gastroenterologist	13(19.4%)	8(28.6%)	
Positive bile culture, N(%)	29(43.3%)	9(32.1%)	0.31
Positive hemoculture, N(%)	15(22.4%)	7(25%)	0.78
Size of stone (mm), mean ± SD	9.0 ± 5.2	7.4 ± 5.2	0.37
Number of stones, mean ± SD	2.8 ± 3.5	3.8 ± 5.6	0.49
Presenting choledocholithiasis by ERCP, N(%)	42(62.7%)	18(64.3%)	0.88
Complete stone removal, N(%)	32/42(76.2%)	18/18(100%)	0.02

ERCP, endoscopic retrograde cholangiopancreatography; *SD*, standard deviation.

Table 4
Pre-operative factors asscociated with delayed ERCP from univariate and multivariate logistic regression.

	OR(95%CI)	p-value	Adjusted OR(95%CI)	p-value
Total bilirubin (mg/dL)				
> 4	0.32(0.13, 0.84)	0.02	0.37(0.14, 0.97)	0.04
≤ 4	1		1	
Anti-platelet or anti-coagulant, N(%)				
Yes	2.91(1.16, 7.26)	0.02	2.54(1.01, 7.29)	0.03
No	1	–	1	–

the groups (Fig. 2). The detail of bile and hemocultures were shown in Table 5.

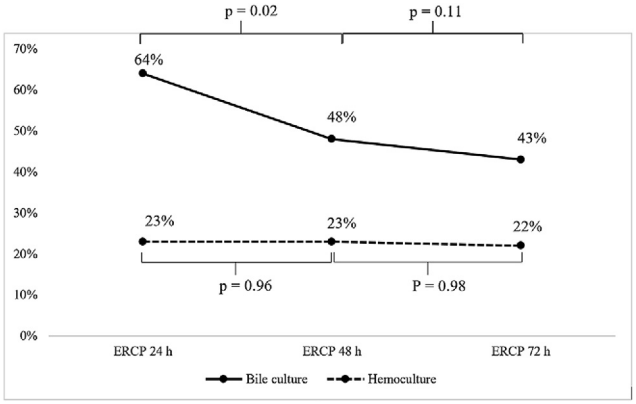

Fig. 2. Positive cultures related to ERCP timing.

Discussion

ABP is caused by acute obstruction of the distal common bile duct due to choledocholithiasis. However, the choledocholithiasis pass spontaneously into the intestine in 70%–80% of cases, with resolution of the bile duct and pancreatic duct obstruction.[3] Bile duct obstruction may cause concomitant cholangitis with ABP. Previous randomized controlled trials found no differences in terms of local or systemic complications of ABP between patients treated with routinely early ERCP and conservative treatment.[11–13] However, Fölsh et al. found an unexplained higher incidence of respiratory failure among patients who underwent early ERCP.[14] Nevertheless, early ERCP might be beneficial in patients with

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Table 5
Bile and hemoculture data.

	Bile culture (N)	Hemoculture (N)
Escherichia coli	17	14
Enterococcus spp.	16	2
Klebsiella pneumoniae	7	3
Staphylococcus spp.	3	1
Streptococcus spp.	0	1
Acinetobactor spp.	2	0
Pseudomonas spp.	1	0
Corynebacterium spp.	0	1

severe ABP.[15,16] Fan et al. found a lower incidence of biliary sepsis in patients treated with early ERCP.[11] Owing to this evidence, ERCP has not been used routinely for the treatment of ABP, but has tended to be reserved for patients with choledocholithiasis or cholangitis to prevent acute biliary sepsis or to treat patients with coexisting cholangitis.[5]

The timing of ERCP varies, with early ERCP (within 72 h) recommended for patients with ABP with choledocholithiasis, while urgent ERCP (within 24 h) is recommended for ABP with cholangitis.[6] However, evidence to support the timing of ERCP in patients with ABP and cholangitis is lacking, due to the small number of patients in this subgroup, the definition of timing of ERCP (after symptom onset, after hospital arrival, or after admission), and the different definitions of cholangitis.[12,15] From literature reviewed, there were studies which compared outcomes between early ERCP and non-ERCP group,[11–16] and only one study was found comparing the outcome of early ERCP and delayed ERCP but in ABP without cholangitis.[17] Therefore, this is the first study which focused on comparison outcomes between early and delayed ERCP in ABP with cholangitis.

In this study, we used the Tokyo Guidelines criteria for diagnosing cholangitis, because of their high accuracy and worldwide acceptance. However, the pathophysiology of pancreatitis may stimulate the systemic inflammatory response syndrome, fever, and an increased white blood cell count, without any infection,[18] and we therefore adjusted some of the cut-off parameters to increase the specificity of the diagnosis.

The rational of using ERCP to treat ABP with cholangitis is that it alleviates bile duct obstruction and reduces pancreatic duct pressure, thus improving biliary infection and pancreatitis. The spontaneous migration rate of choledocholithiasis is higher in patients with ABP with cholangitis compared with patients with cholangitis alone,[19] and many patients with cholangitis can improve clinically after treatment with broad-spectrum intravenous antibiotics, without the immediate need for biliary drainage.[20,21] Previous studies found no differences in mortality and morbidity rates between patients with non-severe cholangitis treated with urgent ERCP compared with elective ERCP,[21] and the 2018 Tokyo Guidelines recommend that urgent ERCP should be reserved for patients with severe cholangitis.[20] In terms of bile and hemocultures, positive bile cultures were detected in 59%–93% and positive hemocultures in 21%–71% of patients with cholangitis.[23,24] In the current study, the positive bile culture rate was significantly reduced after treatment with intravenous antibiotics for >24 h, in our opinion, indicating that biliary infection could be controlled by broad-spectrum antibiotics. We therefore suggest that the timing of ERCP could be delayed in patients with ABP with cholangitis who respond clinically to antibiotics.

In terms of pre-operative factors of delayed ERCP, the British Society of Gastroenterology and European Society of Gastrointestinal Endoscopy guidelines suggest that ERCP can be performed in patients taking aspirin, without being delayed and without the need for platelet transfusion.[25] However, in the current study, ERCP was more likely to be delayed in patients who took aspirin which might be from the endoscopist's hesitation and concerns regarding the bleeding. Moreover, patients with ESRD had a higher rate of delayed ERCP due to difficulties in preparing and stabilizing them for ERCP under general anesthesia. The total bilirubin level >4 mg/dL is a very strong predictor of choledocholithiasis.[26] Thus, the bilirubin level was used as one criteria to perform early or delayed ERCP in our institutional protocol. The rate of complete gallstone removal was higher in patients undergoing delayed ERCP, despite the fact that the sizes of the stones were similar in both groups. This suggests that ampulla and distal common bile duct swelling may be more frequent in patients with early ERCP, as indicated in a previous study.[11,15] The total LoS was shorter in the early ERCP group, but there was no difference in LoS after ERCP between the early and delayed groups, because patients in the delayed ERCP group had to wait for the availability of an endoscopy room. Early ERCP can thus help to reduce treatment-related hospital costs.

This study was limited by its retrospective nature and small samples sizes, potentially leading to selection bias and information bias. It was therefore not possible to demonstrate a beneficial effect of early ERCP.

Conclusion

Delayed ERCP can be performed in selected patients with ABP with cholangitis, with no difference in terms of complications but with a longer LoS compared with early ERCP.

Declaration of competing interest

Nothing to declare.

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