

Does restricting fluid volume impact post-ERCP pancreatitis in patient with heart disease?

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Abstract

Background: To investigate patient characteristics and the risk of post endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) in association with fluid volume and type during ERCP.

Methods: Two hundred and forty seven of 480 patients with naïve papilla undergoing therapeutic ERCP between April 2013 and March 2018 were enrolled for the study. The following patient characteristics were investigated: age, sex, body mass index, previous diseases (heart disease, renal failure, cerebrovascular disorders, coexisting malignancy and pulmonary disease), history of PEP, common bile duct diameter, diverticula and volume of fluid infused 24 hours after the procedure. All ERCP cases had naïve papilla and had undergone treatment.

Results: The incidence of PEP was 8.5%. Significant differences were observed in the volume of fluid infused between patients without and with a history of heart disease (1,380 vs. 1,755 mL). The mean volume of the infused fluid was significantly lower in the PEP than non-PEP group (1,483 vs. 1,688 mL, $P = 0.02$). Moreover, PEP incidence differed according to a fluid infusion cutoff of 1,000 mL (7 vs. 11 cases of PEP in those with $\leq 1,000$ mL and $> 1,000$ mL fluid volume, respectively, $P < 0.001$).

Conclusion: Restricted fluid volume was a newly identified risk factor for PEP, particularly in patients with heart and renal diseases as comorbidities.

Keywords: Endoscopic retrograde cholangiopancreatography, fluid volume, pancreatitis

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INTRODUCTION

Pancreatitis is the most common and severe adverse event after endoscopic retrograde cholangiopancreatography (ERCP), and is the most likely to be fatal. The incidence of post ERCP pancreatitis (PEP) reported in a meta-analysis varied from 3.5 to 9.7%.^[1,2] However, the likelihood of PEP varied depending on patient characteristics, including the

primary disease, and procedural risk factors. Younger age, a lack of extrahepatic bile duct dilatation and chronic PEP, as well as normal serum bilirubin levels, were risk factors in previous prospective multicenter studies.^[3-7] Other risk factors include clinically suspected sphincter of Oddi dysfunction, a history of PEP and female sex.^[8] In another retrospective report, obesity and excess subcutaneous

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adipose tissue were associated with the incidence and severity of PEP.^[9] Procedural risk factors include multiple cannulation attempts, pancreatic sphincterotomy, precut sphincterotomy, biliary balloon sphincter dilation or ampullectomy and multiple contrast injections into the pancreatic duct.^[4] A meta-analysis reported a PEP incidence of 14.7% in patients with these risk factors.^[2] Therefore, identifying high-risk groups for PEP is very important.

Some studies have aimed at preventing PEP after ERCP, including those with the use of protease inhibitors (gabexate mesilate, urinastatin and nafamostat mesylate) and nitroglycerin.^[10-14] However, high-dose protease inhibitor therapy has not demonstrated efficacy in severe cases, so it is not strongly recommended. Non-steroidal anti-inflammatory drugs (NSAIDs) and pancreatic duct stents are useful for preventing PEP.^[15-17] Large-volume infusion before and after ERCP has been reported to prevent PEP.^[18,19] However, NSAIDs and large-volume infusions are themselves risk factors in patients with renal or cardiac dysfunction. Few reports have described the characteristics of patients with renal and cardiac dysfunction. In addition, no clear guidelines have been provided on when preventive measures should be implemented. In particular, more detailed indications are required for patients with renal or cardiac dysfunction. It is important to be aware of the disease history of patients undergoing ERCP, and to choose a method of PEP prophylaxis according to the patient's condition.

This study aimed to investigate patient characteristics and the risk of PEP in association with fluid volume and type during ERCP.

METHODS

Study design

This study was conducted as a single-center retrospective analysis and was approved by the institutional ethics committee on September 11th, 2020.

Patients

We retrospectively analyzed 247 of 480 patients with naïve papilla undergoing therapeutic ERCP at Juntendo Shizuoka Hospital, between April 2013 and March 2018. The exclusion criteria were a history of ERCP, age <20 years, Billroth II gastrectomy, Roux-en-Y reconstruction, and non consent to participate in this study. We also excluded patients with chronic pancreatitis, and those with pancreatic head cancer (who are considered less likely to develop PEP). The following patient characteristics were investigated: Age, sex, body mass index (BMI), previous diseases

(heart disease, renal failure, cerebrovascular disorders, coexisting malignancy and pulmonary disease), history of pancreatitis, common bile duct diameter, diverticula and volume of fluid infused 24 hours after the procedure. Blood parameters (white blood cell count, C-reactive protein, total bilirubin and albumin) and the presence of cholangitis were also analyzed. Procedural factors included the duration of the procedure, number of cannulations in the bile and pancreatic ducts, pancreatography, endoscopic sphincterotomy (EST), stone balloon removal, lithotripsy, use of pancreatic duct guidewire or stents and use of NSAID suppositories. All ERCP cases had naïve papilla and had undergone treatment; those who had only undergone procedures using contrast medium were excluded from the analysis. Procedural-related adverse events and incidents were recorded according to the definitions and grades formulated as per the 2010 American Society of Gastrointestinal Endoscopy workshop.^[20]

Definition of PEP

Serum amylase levels were measured before the examination and on the following morning after the procedure. PEP was defined by consensus as a “clinical syndrome consistent with pancreatitis with an amylase level at least three times the normal level, more than 24 hours after the procedure and requiring more than one night of hospitalization”.^[20] PEP severity was classified using Cotton's criteria as follows: Mild, hospitalization for less than three nights; moderate, hospitalization for 4-10 nights; or severe, hospitalization for >10 nights and/or the presence of a pseudocyst, pancreatic necrosis, need for percutaneous drainage or surgery or death.^[20]

ERCP procedures

Local anesthesia of the pharynx was administered with 8% lidocaine; patients were sedated with an intravenous injection of pentazocine (15 mg) and midazolam (2-10 mg) before intubation. These sedative drugs were monitored during the procedure. The procedures were performed using a JF-260V or TJF-260V electronic duodenoscope (Olympus Medical Systems, Tokyo, Japan). We used standard catheters, 0.035" guidewires, papillotomes, balloon catheters, mechanical lithotripsy and a basket or balloon to remove stones. In most cases, biliary access was achieved with a standard catheter and a 0.035" guidewire. A 0.025" soft guidewire or 0.025" pancreatic guidewire was used in difficult cannulation cases. We used nonionic iso-osmolar contrast medium and tried to avoid pancreatic duct injection. We placed a cannula in the bile duct and confirmed cannulation by contrast injection. Wire-guided cannulation or the double-guidewire method was used in difficult cases.^[21]

EST involved less than one-third of the diameter of the duodenal papilla. EST was combined with endoscopic papillary balloon dilatation (EPBD) using a 10-20 mm balloon for cases with large bile duct stones (>10 mm). The EPBD balloon size was selected based on the diameter of the common bile duct and size of the stones. Stone removal was attempted using a basket or balloon catheter. Endoscopic mechanical lithotripsy was performed to crush the stones if removal was difficult. A 5 Fr prophylactic pancreatic duct stent was used if the operator judged that it was necessary.

Statistical analysis

The statistical analysis was performed using BellCurve for Excel statistical software (Microsoft Inc., Redmond, WA, USA). Data are presented as mean and standard deviation or median with range. The data were analyzed using Fisher's exact probability test and the Mann-Whitney U test. A two-sided *P* value <0.05 was considered significant. We used Bonferroni correction in the factors which had tendency with PEP in univariate analysis. We used logistic regression analysis as multiple analysis.

RESULTS

We retrospectively analyzed 247 of 480 patients with naïve papilla who underwent therapeutic ERCP at Juntendo Shizuoka Hospital between April 2013 and March 2018. The baseline characteristics of these patients are summarized in Table 1. The most common indication for ERCP was choledocholithiasis/cholangitis (62%), followed by a malignant biliary obstruction (25%), benign stricture (11%) and "other" (2%). The median procedure time was 30 min. The treatments were as follows:

drainage (67%), lithotomy (28%) and other (5%). The incidence of PEP was 8.5%. Three patients developed severe PEP. While one developed severe PEP on day 1 and died on day 3, another case was complicated by walled-off necrosis; drainage was performed and he was discharged 5 months later. The third case improved with medication. Eighteen moderate-to-mild cases improved with medication alone. Hyperamylasemia was observed in 23 cases, and duodenal perforation was observed in 1 case. Risk factors for PEP were examined in a univariate analysis. Significant group differences were identified in the prevalence of a history of heart disease (9 vs. 47 cases, *P* = 0.03) and mean infusion volume (1,483 vs. 1,688 mL, *P* = 0.02). As previously reported, significant differences in procedure time (60 vs. 30 min, *P* < 0.001), over two times of cannulation (16 vs. 104 cases, *P* = 0.01), and pancreatography rate (17 vs. 99 cases, *P* = 0.001) were observed [Table 2].

History of heart disease

The underlying conditions of the 56 cases were myocardial infarction (5 vs. 14 cases), atrial fibrillation (1 vs. 13 cases), chronic heart failure (2 vs. 7 cases), angina pectoris (0 vs. 5 cases), coronary atherosclerosis (0 vs. 4 cases), arrhythmias (0 vs. 2 cases) and others (1 vs. 2 cases) [Table 3]. No significant differences were observed between the PEP and non-PEP groups in the prevalence of any disease. Significant differences were observed in the volume of fluid infusion between patients without and with a history of heart disease (1,380 vs. 1,755 mL, *P* < 0.001, respectively) [Figure 1]. Although brain natriuretic peptide (BNP) data were blank in 98 cases, significant differences were also observed between

Table 1: Baseline characteristics

	Value (n=247)
Age, yrs (range)	76 (28-95)
Sex, female	105 (43)
Indication for ERCP	
Choledocholithiasis/cholangitis	153 (62)
Malignant biliary stricture	61 (25)
Others	33 (13)
Successful rate of cannulation	236 (96)
Procedure time, min (range)	30 (10-120)
Treatment details	
Drainage	165 (67)
Stone removal	69 (28)
Others	13 (5)
Adverse events	
Pancreatitis	21 (8.5)
Mild	16 (6.5)
Moderate	2 (0.8)
Severe	3 (1.2)
Hyperamylasemia	23 (9)
Bleeding	0 (0)
Perforation	1 (0.4)

Data presented as *n* (%), or median (range)

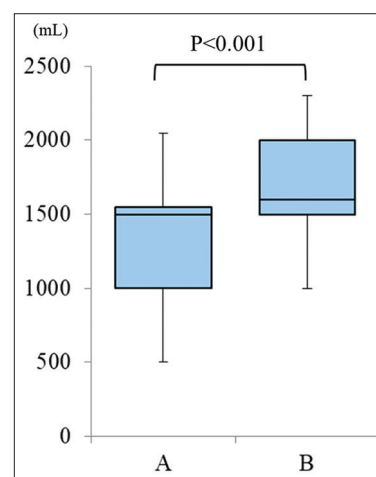


Figure 1: Box plot showing the relationship between heart disease status and infusion volume. (A) Heart disease present. (B) Heart disease not present

Table 2: Relationship between PEP and non-PEP

Patients factors	PEP (n=21)	NonPEP (n=226)	P
Age, yrs	77	76	0.8
Sex, female	10 (48)	95 (42)	0.7
BMI, (kg/m ²)	22.3	21.9	0.3
Past history			
Heart disease	9 (43)	47 (21)	0.03
Renal failure	5 (24)	22 (10)	0.06
Cerebrovascular disorder	1 (5)	22 (10)	0.7
Coexisting malignancy	5 (24)	45 (20)	0.8
History of pancreatitis	1 (5)	10 (4)	1.0
Pulmonary disease	1 (5)	7 (3)	0.5
Diameter of CBD (mm)	12	11	0.6
Diverticulum	7 (33)	78 (35)	1.0
Infusion volume			
total volume, 24 h (mL)	1483±493	1688±347	0.02
≤1000ml/24h*	7 (33)	11 (4.9)	<0.001
Disease factors			
Indication for ERCP			
Cholelithiasis	13 (62)	140 (62)	1.0
Malignant biliary stricture	5 (24)	56 (25)	1.0
Others	3 (14)	30 (13)	1.0
Laboratory findings			
WBC (μL)	6500	7400	0.3
CRP (mg/dL)	2.4	1.6	0.6
T-bil (mg/dL)	1.2	1.9	0.5
Symptoms of cholangitis	16 (76)	173 (77)	1.0
Procedural factors			
Procedural time (min)	60	30	<0.001
Over 2 times of cannulation	16 (76)	104 (46)	0.01
Pancreatography	17 (81)	99 (44)	0.001
EST	8 (38)	60 (27)	0.3
Balloon	3 (14)	27 (12)	0.7
Mechanical lithotripsy	6 (29)	42 (19)	0.3
Double-guidewire method	7 (33)	36 (16)	0.07
Pancreatic stent	1 (5)	16 (7)	1.0
Suppositories of NSAIDs	2 (10)	22 (10)	1.0

Data presented as n (%). Values represented as medians unless otherwise stated, *mean ± SD. BMI, body mass index; CBD, common bile duct; CRP, C-reactive protein; ERCP, endoscopic retrograde cholangiopancreatography; EST, endoscopic sphincterotomy; NSAIDs, non-steroidal anti-inflammatory drugs; PEP, post-ERCP pancreatitis; T-bil, total bilirubin; WBC, white blood cell

patients with and without a history of heart disease (121.5 vs. 52 pg/dL, $P < 0.001$, respectively). The significantly higher BNP levels in patients with heart disease suggests that physicians may have limited the fluid infusion volume in these patients during ERCP.

Fluid infusion volume

The mean volume of infused fluid was significantly lower in the PEP than in non-PEP group (1,483 vs. 1,688 mL,

Table 3: History of heart disease

	n=56
Myocardial infarction	19
Atrial fibrillation	14
Chronic heart failure	9
Angina pectoris	5
Coronary atherosclerosis	4
Arrhythmias	2
Others	3

$P = 0.02$). Moreover, PEP incidence differed according to a fluid infusion cut-off of 1,000 mL/24 hours from ROC curve analysis (7 vs. 11 cases of PEP in those with ≤ 1,000 mL and >1,000 mL fluid volume, respectively, $P < 0.01$, odds ratio 9.7). Factors showing significant group differences were subjected to logistic regression analysis: significant predictors of PEP were ≤ 1,000 mL of fluid infused during the first 24 hours after ERCP (odds ratio [OR] 7.41, 95% confidence interval [CI]: 1.52-36.1, $P = 0.01$), pancreatography ($P < 0.01$, OR 7.16, 95% CI 1.87–27.3) [Table 4]. Baseline characteristics were compared between the ≤1,000 and > 1,000 mL fluid volume groups [Table 5]. Cardiac and renal diseases were more common in the ≤1,000 mL fluid infusion group. The BNP level was significantly higher in the ≤1,000 mL fluid infusion group (188 vs. 61 pg/dL, $P < 0.001$).

DISCUSSION

PEP occurs due to the impaired flow of pancreatic fluid following intraductal injection of contrast media, or due to edema and spasm of the sphincter of the papilla induced by cannulation. Poor drainage of the pancreatic fluid leads to increased intraductal pressure and impaired blood flow, while trypsin is activated by ductal epithelial and acinar disorders. PEP is caused by the generation of various chemical factors.^[22-24] It is important to prevent an increase in intraductal pressure during procedures. In addition, aggressive preventive measures are necessary for high-risk patients in whom infusion cannot be attempted before treatment. As shown in Table 2, no significant differences between the PEP and non-PEP groups were found in sex, age or BMI. It has been reported that pancreatography is a risk factor for the development of PEP after ERCP.^[25]

Table 4: Univariate and multivariate analyses of risk factors for post-ERCP pancreatitis

Variable	Univariate analysis			Multivariate analysis		
	PEP (n=21)	NonPEP (n=226)	P	Odds	95%CI	P
Heart disease	9	47	0.03	2.12	0.57-7.89	0.30
Infusion volume ≤ 1000ml/24h	7	11	<0.01	7.42	1.52-36.1	0.01
Renal failure	5	22	0.06	1.61	0.39-6.60	0.51
Double-guidewire method	7	36	0.07	1.60	0.51-5.08	0.42
Pancreatography	17	99	<0.01	7.16	1.88-27.3	<0.01

CI, confidence interval; PEP, post-ERCP pancreatitis

Table 5: Baseline characteristics of patients between <1000 and over 1000 mL of fluid volume for 24 h after ERCP

	24 h infusion volume		P
	≤ 1000 ml (n=18)	>1000 ml (n=229)	
Age, yrs	78.5	76	0.1
Sex, female	7 (39)	98 (43)	0.8
BMI, (kg/m ²)	21.7	22	0.4
Past history			
Heart disease	15 (83)	41 (18)	<0.001
Renal failure	10 (56)	17 (7)	<0.001
Cerebrovascular disorder	2 (11)	21 (9)	0.7
Coexisting malignancy	3 (17)	47 (21)	1
History of pancreatitis	2 (11)	9 (4)	0.7
Pulmonary disease	1 (6)	7 (3)	1
BNP, (pg/dL)	188	61	<0.001
Types of infusion*			
Ringer's solution	111	744	<0.001
Hypo-osmotic electrolyte solution	533	897	<0.001
PEP	7 (39)	14 (6)	<0.001

Data presented as n (%). Values represented as medians unless otherwise stated, *mean. BNP, brain natriuretic peptide; BMI, body mass index; PEP, post-ERCP pancreatitis

In our study, procedure time and pancreatography were significant predictors of PEP in the multivariate analysis. A fluid infusion volume ≤1,000 mL during ERCP was a newly identified risk factor for PEP. Both Ringer's solution and hypo-osmotic electrolyte solution were restricted in some of our cases [Table 4]. The proportion of Ringer's solution in our ≤1,000 mL infusion group was 11.3%, which was lower than that in the >1,000 mL infusion group (41.3%) [Figure 2]. Thus, in patients with underlying diseases not receiving sufficient fluids, Ringer's solution tends to be restricted.

Lactated Ringer's solution is reportedly more likely to prevent PEP than normal saline. Higher doses of lactated Ringer's solution (3 mL/kg/h during ERCP with a 20 mL/kg bolus thereafter) have been reported to be more effective than the typical dose (1.5 mL/kg/h).^[19] The guidelines of the American Pancreatic Society specify 5-10 mL/kg/h as the initial infusion. Lactated Ringer's solution may be better than normal saline due to the promotion of bicarbonate during metabolism, which can ameliorate metabolic

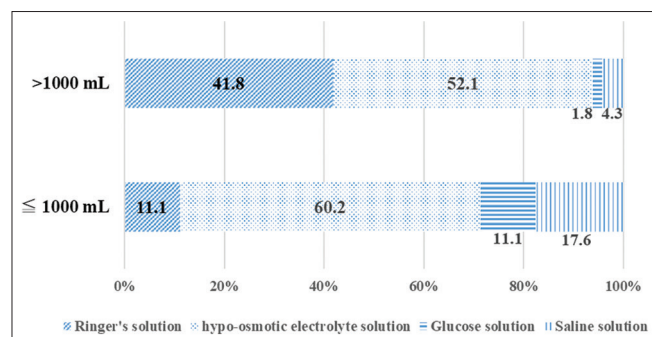


Figure 2: Proportions of Ringer's solution, hypo-osmotic electrolyte solution, glucose solution and saline solution in patients administered ≤1,000 and >1,000 mL of fluid during the first 24 hours after ERCP

acidosis and suppress the development of systemic inflammatory response syndrome. On the other hand, metabolic acidosis has been associated with normal saline use due to the high dose of chlorine.^[26] ERCP is carried out with patients in a dehydrated state, i.e., performed during fasting. Thus, saline may promote metabolic acidosis and exacerbate PEP. In addition, intravascular dehydration may occur with maintenance fluid, which can also exacerbate PEP after ERCP. Thus, the mechanism of exacerbation may differ between saline and other hydrating agents. The quantity and type of fluid therapy seem to be important factors with respect to outcomes. In this study, fluid therapy was limited in the PEP patients with cardiac and renal diseases as comorbidities, who were also dehydrated. In addition, decreased fluid administered during the procedure exacerbated dehydration, and caused PEP due to acidosis, in association with peripheral circulatory failure. The infusion volume was correlated with the proportion of Ringer's solution. A low infusion volume, particularly with respect to Ringer's solution, was a risk factor for metabolic acidosis.

Patients with cardiac or renal disease require thorough evaluation with respect to cardiac function before ERCP, and assessment of the need for fluid restriction by a cardiologist. For PEP prophylaxis, it is important that the fluid quantity not be restricted, particularly Ringer's solution. In addition, insertion of a pancreatic duct stent should be considered in patients who require fluid volume restriction, and NSAIDs should be considered when renal function is acceptable.

Limitations

This study included a small number of subjects and used a retrospective single-center design. NSAID suppositories and pancreatic duct stenting are now considered important

for preventing PEP^[16,17]; however, these were applied in only a small number of patients in this study. Prophylactic pancreatic duct stenting and the use of 25 mg or 50 mg NSAIDs was done at the discretion of the attending physician. The lack of a standard protocol to take an informed decision is certainly a limitation in our study.

In summary, restricted fluid volume was a newly identified risk factor for PEP, particularly in patients with heart and renal diseases as comorbidities.

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Conflicts of interest

There are no conflicts of interest.

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