Kobe J. Med. Sci., Vol. 63, No. 1, pp. E1-E8, 2017

History of Post-Endoscopic Retrograde Cholangiopancreatography Pancreatitis and Acute Pancreatitis as Risk Factors for Post-ERCP Pancreatitis

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Received 13 January 2017 / Accepted 31 January 2017

Key words: Post-endoscopic retrograde cholangiopancreatography pancreatitis, Previous acute pancreatitis, Procedure-related factors, Total procedure time, Risk factor

Background: Previous pancreatitis is a definite patient-related risk factor for pancreatitis after endoscopic retrograde cholangiopancreatography (post-ERCP pancreatitis: PEP). However, the effects of differences in the history of PEP and acute pancreatitis on the occurrence of PEP have not been fully investigated. We examined the relationship between previous PEP or previous acute pancreatitis and procedural factors associated with PEP. Methods: Clinical data on 1,334 consecutive patients undergoing ERCP between April 2006 and June 2010 were collected. A multivariate logistic regression analysis was conducted to assess the relationship between PEP and the cannulation time (<15 min vs. ≥15 min) or total procedure time (<30 min vs. ≥30 min) according to previous pancreatitis (previous PEP: pPEP or previous acute pancreatitis: pAP), with adjustments for clinical characteristics. Results: Longer cannulation times (≥15 min) correlated with the occurrence of PEP in the pPEP group (OR=2.97; 95% CI=1.10 to 8.43, *P*=0.03) and in patients without previous pancreatitis (non-preP group) (OR=2.43; 95% CI=1.41 to 4.14, *P*= 0.002), but not in the pAP group (OR=2.78; 95% CI=0.50 to 22.42, *P*= 0.25). In contrast, longer procedure times correlated with the occurrence of PEP in the pAP group (OR=3.93; 95% CI=1.11 to 16.5, *P*= 0.03), but not in the pPEP group (OR=2.79; 95% CI=0.92 to 9.18, *P*= 0.068) or non-preP group (OR=0.71; 95% CI=0.39 to 1.24, *P*= 0.23). Conclusions: A higher risk of PEP with previous PEP was associated with longer cannulation times, whereas a higher risk of PEP with previous acute pancreatitis was associated with longer procedure times.

INTRODUCTION

The most frequent complication of endoscopic retrograde cholangiopancreatography (ERCP) is pancreatitis (post-ERCP pancreatitis: PEP) (1-6) . According to the recent Guidelines of the European Society for Gastrointestinal Endoscopy (ESGE) and the American Society for Gastrointestinal Endoscopy (ASGE), previous pancreatitis (previous PEP and previous acute pancreatitis), suspected sphincter of Oddi dysfunction (SOD), female gender, and a young age are definite "patient-related risk factors" for PEP (3; 6). On the other hand, difficult cannulation, pancreatic injection, and pre-cut sphincterotomy are definite "procedure-related risk factors" for PEP(3; 6). A previous study reported that procedure-related risk factors for PEP identified in a multivariate analysis were pancreatic duct injection, the non-placement of an endoscopic pancreatic stent (EPS) after ERCP, a prolonged procedure time (≧30 min), pancreatic cytology by any method, pancreatic intra-ductal ultrasonography (IDUS), and difficult cannulation (≧15 min)(7). These procedure-related risk factors have been divided into two categories: the procedure itself (pancreatic duct injection, EPS, pancreatic cytology, and IDUS) and physician-related factors (difficult cannulation and a prolonged procedure time)(8-10). Each of these risk factors for PEP has been fully evaluated in previous studies(9; 11-13).

The selection of patients who need to undergo ERCP is important for avoiding PEP(11; 13-16); however, patients with risk factors for PEP are sometimes indicated for ERCP. Patient-related factors include suspected SOD, female gender, and a young age; however, previous pancreatitis indicates that a patient has already had acute pancreatitis and, thus, has the organic potential for pancreatitis. Patient backgrounds differ among previous

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acute pancreatitis and previous PEP. The effects of differences in the history of PEP and acute pancreatitis on the occurrence of PEP have not been fully investigated. Procedure-related factors, such as longer cannulation times or procedure times, may have a different influence on the occurrence of PEP between patients with previous PEP and those with previous acute pancreatitis.

Once a physician decides to perform ERCP and selects the appropriate procedure for a patient with previous pancreatitis, it is important to avoid PEP in patients with a risk of PEP. We previously reported that previous pancreatitis and difficult cannulation were significant risk factors for PEP(17). However, the procedure-related risk factors, particularly physician-related factors that may strongly influence the occurrence of PEP in patients with previous pancreatitis have not yet been identified. Therefore, we conducted the present study with a focus on the relationship between previous pancreatitis and procedure-related factors for the risk of PEP.

MATERIAL AND METHODS

Study Design

In this retrospective study, clinical data from 1,334 consecutive patients treated at Kobe University Hospital between April 2006 and June 2010 were prospectively collected. We investigated clinical characteristics, including risk factors for PEP, and ERCP-related procedures. In the present study, risk factors for PEP were defined as follows based on the European Society of Gastrointestinal Endoscopy (ESGE) and American Society for Gastrointestinal Endoscopy (ASGE) Guidelines: female gender, a young age, previous pancreatitis, difficult cannulation (< 15 min vs. ≥ 15 min), total procedure time (< 30 min vs. ≥ 30 min), pancreatic duct injection, pancreatic intraductal ultrasonography (IDUS), pancreatic juice cytology, pancreatic duct brush cytology, pre-cut sphincterotomy, and suspected SOD. We also divided previous pancreatitis into previous PEP (pPEP group) and previous acute pancreatitis (pAP group) which was not caused by ERCP. The definition of PEP was standardized by a consensus conference in 1991, and conference criteria have now been widely accepted. Accordingly, PEP was defined as the occurrence of pancreatic pain and hyperamylasemia within 24 hours of the procedure. Pancreatic pain was defined as persistent pain in the epigastric or periumbilical region, while hyperamylasemia was defined as an increase in serum amylase to more than 3-fold the upper limit of normal defined by our institution (37-102 U/l). Previous pancreatitis was diagnosed according to the previous report(18). The diagnosis of acute pancreatitis was determined on the basis of acute onset of abdominal pain, elevated serum pancreatic enzymes and findings of pancreatitis detected by diagnostic imaging such as CT. Patients were excluded from this study if the papilla was unphysiological for any of the following reasons: (1) previous endoscopic sphincterotomy (EST) or papillary balloon dilation, (2) pancreas divisum, (3) papilla of Vater tumor, (4) endoscopic nasopancreatic drainage (ENPD)/pancreatic stenting (without spontaneous dislodgement), or (5) prior pancreaticoduodenectomy. This study was conducted in accordance with the Declaration of Helsinki and its amendments (UMIN-CTR ID: UMIN000019138). The study protocol was approved by the Kobe University School of Medicine Ethics Committee (No.1863). All the authors had access to the study data and reviewed and approved the final manuscript.

ERCP

ERCP was performed by four operators, each of whom had experience of more than 1000 ERCP procedures (E. Funatsu, H. Shiomi, Y. Arisaka, and H. Kutsumi). Therapeutic procedures accounted for approximately 65% of the total. Iopamidol was used for ERCP as a contrast medium. After the procedure, the patient fasted until the next morning and received an intravenous infusion. All patients received an infusion of a protease inhibitor (nafamostat mesilate, 20 mg/day) and antibiotics for 2 days. Serum amylase levels were measured at baseline, 4 hours after the procedure, and 18-24 hours after the procedure. Endoscopic pancreatic stenting was performed for the prophylaxis of PEP, when the pancreatic duct injection was administered and medium contact remained in the pancreatic duct at the end of the examination, and the operator judged that the protrusion of papilla had become swollen.

Statistical analysis

All statistical analyses were conducted using JMP software (version 11, SAS Institute, Cary, NC) and all *P* values were two-sided. In order to identify candidate procedure-related risk factors, we conducted a multivariate logistic regression analysis to assess risk factors for PEP in all patients, the pPEP group, pAP group, and patients without previous pancreatitis (non-preP group). We then conducted a binary logistic regression model to assess the relationship between the previous pancreatitis status and cannulation time or total procedure time in relation to the occurrence of PEP. The binary categorical variable (absence or presence) of the occurrence of PEP was used as the outcome variable. We performed a multivariate binary logistic regression analysis to adjust for potential confounders. The multivariate model initially included age (continuous), sex,

suspected SOD, cannulation time, total procedure time, pancreatic duct injection, EST, precut sphincterotomy, pancreatic duct IDUS, bile duct IDUS, pancreatic duct aspiration cytology, bile duct aspiration cytology, pancreatic duct brush cytology, bile duct brush cytology, and endoscopic pancreatic stenting (EPS) with spontaneous dislodgement. Backward stepwise elimination with a threshold of $P = 0.05$ was performed to select variables for the final models. In order to assess relationships between categorical variables, the chi-squared test (or Fisher's exact test where appropriate) was performed. A *t*-test or analysis of variance (ANOVA) assuming equal variances was performed to compare mean ages.

RESULTS

Logistic regression analysis of risk factors for PEP

The characteristics of all patients are shown in Table I. 81 patients had previous PEP, and 52 patients had previous acute pancreatitis. No patients had a history of both PEP and acute pancreatitis. We conducted a multivariate logistic regression analysis to identify risk factors for PEP in all 1,334 patients. Independent risk factors for PEP were identified as previous PEP (odds ratio [OR]=12.0; 95% confidence interval [CI]=7.10 to 20.5, $P< 0.0001$), previous acute pancreatitis (OR=5.2; 95% CI=2.54 to 10.2, $P<0.0001$), SOD (OR=8.7; 95% CI=3.17 to 22.5, $P<0.0001$), a cannulation time greater than 15 min (OR=1.9; 95% CI=1.20 to 3.02, $P=0.006$), total procedure time greater than 30 min (OR=1.7; 95% CI=1.03 to 2.86, $P=0.04$), pancreatic duct brush cytology (OR =2.7; 95% CI=1.40 to 4.92, $P=0.004$), and not performing EPS (OR =2.4; 95% CI=1.14 to 5.67, $P=0.02$) (Table II).

Table I. Characteristics of patients

		Number (%)	PEP
All patients		1334	115 (8.6%)
Mean age ± SD (years)		65.5 ± 12.7	
Sex	Male	857 (64.2%)	72 (8.4%)
	Female	477 (35.8%)	43 (9.0%)
Previous PEP	Presence	81(6.1%)	36 (44.4%)
	Absence	1253(93.9%)	79 (6.3%)
Previous acute pancreatitis	Presence	52(3.9%)	17 (52.7%)
	Absence	1282(96.1%)	98 (7.6%)
Suspected SOD	Presence	24 (1.8%)	8 (33.3%)
	Absence	1310 (98.2%)	107 (8.2%)
Cannulation time	< 15 min	992 (74.4%)	70 (7.1%)
	≥ 15 min	342 (25.6%)	45 (13.2%)
Total procedure time	< 30 min	464 (34.8%)	28 (6.0%)
	≥ 30 min	870 (65.2%)	87 (10.0%)
EST	Performed	175 (13.1%)	20 (11.4%)
	Not performed	1159 (86.9%)	95 (8.2%)
Precut sphincterotomy	Performed	18 (1.4%)	0 (0%)
	Not performed	1316 (98.6%)	115 (8.7%)
Pancreatic duct injection	Performed	923 (69.2%)	92 (10.0%)
	Not performed	411 (30.8%)	23 (5.6%)
Pancreatic duct IDUS	Performed	75 (5.6%)	9 (12%)
	Not performed	1259 (94.4%)	106 (8.4%)
Bile duct IDUS	Performed	120 (9.0%)	13 (10.8%)
	Not performed	1214 (91.0%)	102 (8.4%)
Pancreatic duct aspiration cytology	Performed	147 (11.0%)	14 (9.5%)
	Not performed	1187 (89.0%)	101 (8.5%)
Bile duct aspiration cytology	Performed	79 (5.9%)	10 (12.7%)
	Not performed	1255 (94.1%)	105 (8.4%)
Pancreatic duct brush cytology	Performed	108 (8.1%)	18 (16.7%)
	Not performed	1226 (91.9%)	97 (7.9%)
Bile duct brush cytology	Performed	146 (10.9%)	16 (11.0%)
	Not performed	1188 (89.1%)	99 (9.1%)
Endoscopic pancreatic stenting	Performed	131(9.8%)	9 (6.9%)
	Not Performed	1203 (90.2%)	106 (8.8%)

EPS: Endoscopic pancreatic stenting; ERCP: endoscopic retrograde cholangiopancreatography; EST: endoscopic sphincterotomy; IDUS: intraductal ultrasonography; SOD: sphincter of Oddi dysfunction.

Table II. Logistic regression analysis of risk factors for post-ERCP pancreatitis (PEP)

Univariate analysis	OR (95%CI)	*P* value
Previous PEP (presence vs. absence)	11.8 (7.24-19.5)	<0.0001
Previous acute pancreatitis (presence vs. absence)	4.7 (2.55-8.49)	<0.0001
Suspected SOD (presence vs. absence)	5.6 (2.23-13.1)	0.0006
Cannulation time (< 15 min vs. ≥ 15 min)	2.0 (1.34-2.98)	0.0009
Total procedure time (< 30 min vs. ≥ 30 min)	1.7 (1.13-2.73)	0.01
Pancreatic duct injection (performed vs. not performed)	1.9 (1.18-3.06)	0.006
Pancreatic duct brush cytology (performed vs. not performed)	2.3 (1.31-3.94)	0.005
Multivariate analysis*		
Previous PEP (presence vs. absence)	12.0 (7.10-20.5)	<0.0001
Previous acute pancreatitis (presence vs. absence)	5.2 (2.54-10.2)	<0.0001
Suspected SOD (presence vs. absence)	8.7 (3.17-22.5)	<0.0001
Cannulation time (< 15 min vs. ≥ 15 min)	1.9 (1.20-3.02)	0.006
Total procedure time (< 30 min vs. ≥ 30 min)	1.7 (1.03-2.86)	0.04
Pancreatic duct brush cytology (performed vs. not performed)	2.7 (1.40-4.92)	0.004
EPS (not performed vs. performed)	2.4 (1.14-5.67)	0.02

*The odds ratio was adjusted for age, sex, previous PEP, previous acute pancreatitis, suspected SOD, cannulation time, total procedure time, pancreatic duct injection, EST, precut sphincterotomy, pancreatic duct IDUS, bile duct IDUS, pancreatic duct aspiration cytology, bile duct aspiration cytology, pancreatic duct brush cytology, bile duct brush cytology, and EPS. Backward stepwise elimination with a threshold of P = 0.05 was used to select variables for the final models.
EPS: endoscopic pancreatic stenting; ERCP: endoscopic retrograde cholangiopancreatography; EST: endoscopic sphincterotomy; IDUS: intraductal ultrasonography; SOD: sphincter of Oddi dysfunction. CI, confidence interval; OR, odds ratio.

Logistic regression analysis of risk factors for PEP in patients with or without a history of pancreatitis (PEP and acute pancreatitis)

Among the pPEP group, a cannulation time greater than 15 min (OR=2.97; 95% CI=1.10 to 8.43, *P*=0.03) and pancreatic duct injection (OR=4.28; 95% CI=1.16 to 20.78, *P*=0.03) were identified as significant risk factors for PEP. In contrast, among the pAP group, total procedure time (OR=3.93; 95% CI=1.11 to 16.46, *P*=0.03) was a significant risk factor for PEP. Among the non-preP group, suspected SOD (OR =10.48; 95% CI=3.52 to 28.08, *P*=0.0001) and a cannulation time greater than 15 min (OR=2.43; 95% CI=1.41 to 4.14, *P*= 0.002) were significant risk factors for PEP (Table III). Therefore, we hypothesized that the influence of the total procedure time or cannulation time on the occurrence of PEP may differ according to the status of previous pancreatitis (previous PEP or previous acute pancreatitis).

Table III. Logistic regression analysis of risk factors for post-ERCP pancreatitis (PEP) in patients with or without a history of pancreatitis

Patients with previous PEP	OR (95%CI)	*P* value
Univariate analysis		
Total procedure time (< 30 min vs. ≥ 30 min)	3.65 (1.33- 11.30)	0.01
Cannulation time (< 15 min vs. ≥ 15 min)	3.13 (1.22- 8.42)	0.02
Pancreatic duct injection (performed vs. not performed)	4.00 (1.15- 18.74)	0.03
Multivariate analysis*		
Cannulation time (< 15 min vs. ≥ 15 min)	2.97(1.10- 8.43)	0.03
Pancreatic duct injection (performed vs. not performed)	4.28(1.16- 20.78)	0.03
Patients with previous acute pancreatitis	OR (95%CI)	*P* value
Univariate analysis		
Total procedure time (< 30 min vs. ≥ 30 min)	3.86 (1.12- 15.90)	0.03
Multivariate analysis*		
Total procedure time (< 30 min vs. ≥ 30 min)	3.93 (1.11- 16.46)	0.03
Patients without previous pancreatitis	OR (95%CI)	*P* value
Univariate analysis		
Suspected SOD (presence vs. absence)	8.61 (2.96- 22.35)	0.0003
Cannulation time (< 15 min vs. ≥ 15 min)	2.21 (1.30- 3.70)	0.004
Multivariate analysis*		
Suspected SOD (presence vs. absence)	10.48 (3.52- 28.08)	0.0001
Cannulation time (< 15 min vs. ≥ 15 min)	2.43 (1.41- 4.14)	0.002

*The odds ratio was adjusted for age, sex, suspected SOD, cannulation time, total procedure time, pancreatic duct injection, EST, precut sphincterotomy, pancreatic duct IDUS, bile duct IDUS, pancreatic duct aspiration cytology, bile duct aspiration cytology, pancreatic duct brush cytology, bile duct brush cytology, and EPS. Backward stepwise elimination with a threshold of P = 0.05 was used to select variables for the final models. EPS: endoscopic pancreatic stenting; ERCP: endoscopic retrograde cholangiopancreatography; EST: endoscopic sphincterotomy; IDUS: intraductal ultrasonography; SOD: sphincter of Oddi dysfunction. CI, confidence interval; OR, odds ratio.

Relationship between PEP and the cannulation time or total procedure time on the occurrence of PEP in patients stratified by previous PEP or acute pancreatitis

We conducted a multivariate logistic regression analysis to assess the relationship between PEP and the cannulation time or total procedure time and occurrence of PEP in the pPEP and pAP groups (Table IV, Table V). Longer cannulation times (≥15 min) correlated with the occurrence of PEP in the pPEP group (OR=2.97; 95% CI=1.10 to 8.43, *P*=0.03) and non-preP group (OR=2.43; 95% CI=1.41 to 4.14, *P*= 0.002), but not in the pAP group (OR=2.78; 95% CI=0.50 to 22.42, *P*= 0.25). In contrast, longer procedure times correlated with the occurrence of PEP in the pAP group (OR=3.93; 95% CI=1.11 to 16.5, *P*= 0.03), but not in the pPEP group (OR=2.79; 95% CI=0.92 to 9.18, *P*= 0.068) or non-preP group (OR=0.71; 95% CI=0.39 to 1.24, *P*= 0.23).

Table IV. Logistic regression analysis assessing the relationship between post-ERCP pancreatitis and cannulation times in patients stratified by previous post-ERCP pancreatitis or acute pancreatitis

				Post-ERCP pancreatitis (Outcome variable†)	
		No. of patients	No. of PEP (%)	Univariate OR (95% CI)	Multivariate OR (95% CI)*
Previous post-ERCP pancreatitis (+)		81			
Cannulation time	< 15 min	54	19 (35.2%)	1 (reference)	1 (reference)
	≥ 15 min	27	17 (63.0%)	3.13 (1.22-8.42)	2.97(1.10-8.43)
	P value			0.02	0.03
Previous acute pancreatitis (+)		52			
Cannulation time	< 15 min	44	15 (34.1%)	1 (reference)	1 (reference)
	≥ 15 min	8	2 (25%)	1.55 (0.31-11.5)	2.78 (0.50-22.42)
	P value			0.61	0.25
Previous pancreatitis (-)		1201			
Cannulation time	< 15 min	894	36 (4.0%)	1 (reference)	1 (reference)
	≥ 15 min	307	26 (8.5%)	2.21 (1.30-3.70)	2.43 (1.41-4.14)
	P value			0.004	0.002

† 0(absent); 1+ (present).

*The odds ratio was adjusted for age, sex, suspected SOD, pancreatic duct injection, EST, precut sphincterotomy, pancreatic duct IDUS, bile duct IDUS, pancreatic duct aspiration cytology, bile duct aspiration cytology, pancreatic duct brush cytology, bile duct brush cytology, and EPS. Backward stepwise elimination with a threshold of *P* = 0.05 was used to select variables for the final models. EPS: endoscopic pancreatic stenting; ERCP: endoscopic retrograde cholangiopancreatography; EST: endoscopic sphincterotomy; IDUS: intraductal ultrasonography; SOD: sphincter of Oddi dysfunction. CI, confidence interval; OR, odds ratio.

Table V. Logistic regression analysis assessing the relationship between post-ERCP pancreatitis and total procedure times in patients stratified by previous post-ERCP pancreatitis or acute pancreatitis

				Post-ERCP pancreatitis (Outcome variable†)	
		No. of patients	No. of PEP (%)	Univariate OR (95% CI)	Multivariate OR (95% CI)*
Previous post-ERCP pancreatitis (+)		81			
Total procedure time	< 30 min	25	6 (24.0%)	1 (reference)	1 (reference)
	≥ 30 min	56	30 (53.6%)	3.65 (1.33-11.3)	2.79 (0.92-9.18)
	P value			0.01	0.068
Previous acute pancreatitis (+)		52			
Total procedure time	< 30 min	23	4 (17.4%)	1 (reference)	1 (reference)
	≥ 30 min	29	13 (44.8%)	3.86 (1.12-15.9)	3.93 (1.11-16.5)
	P value			0.03	0.03
Previous pancreatitis (-)		1201			
Total procedure time	< 30 min	416	18 (4.3%)	1 (reference)	1 (reference)
	≥ 30 min	785	44 (5.6%)	0.76 (0.42-1.31)	0.71 (0.39-1.24)
	P value			0.33	0.23

† 0 (absent); 1+ (present).

*The odds ratio was adjusted for age, sex, suspected SOD, pancreatic duct injection, EST, precut sphincterotomy, pancreatic duct IDUS, bile duct IDUS, pancreatic duct aspiration cytology, bile duct aspiration cytology, pancreatic duct brush cytology, bile duct brush cytology, and EPS. Backward stepwise elimination with a threshold of P = 0.05 was used to select variables for the final models.

EPS: endoscopic pancreatic stenting; ERCP: endoscopic retrograde cholangiopancreatography; EST: endoscopic sphincterotomy; IDUS: intraductal ultrasonography; SOD: sphincter of Oddi dysfunction.

CI, confidence interval; OR, odds ratio.

Preventive effects of EPS on the occurrence of PEP in the pPEP group and pAP group.

We also evaluated the effects of EPS on the relationship with previous PEP or acute pancreatitis in patients who underwent ERP (Table VI). EPS appeared to prevent PEP in the pPEP group (*P*=0.07) and pAP group (*P*=0.18).

Table VI. Effects of EPS in patients with previous pancreatitis or acute pancreatitis

		Post-ERCP pancreatitis†		
	EPS	+	-	*P* value*
Previous post-ERCP pancreatitis (+)	Performed	2 (22.2%)	7 (77.8%)	0.07
	Not performed	31 (45.6%)	26 (54.4%)	
Previous acute pancreatitis (+)	Performed	3(20.0%)	12 (80.0%)	0.18
	Not performed	12 (40.0%)	18 (60.0%)	
Previous pancreatitis (-)	Performed	4 (3.8%)	102 (96.2%)	0.42
	Not performed	40 (5.7%)	666 (94.3%)	

† + (present); - (absent).

*P values were calculated by Fisher's exact test.

EPS: endoscopic pancreatic stenting; ERCP: endoscopic retrograde cholangiopancreatography.

DISCUSSION

In the present study, we focused on the effects of differences in a previous history of PEP and acute pancreatitis on the occurrence of PEP. Longer cannulation times correlated with the occurrence of PEP in the pPEP and non-preP groups, but not in the pAP group. In contrast, longer procedure times correlated with the occurrence of PEP in the pAP group, but not in the pPEP or non-preP group. To the best of our knowledge, this

is the first study to examine the effects of procedure-related factors and previous pancreatitis on the development of PEP, including a comparison of a previous history of PEP and acute pancreatitis.

Various risk factors for PEP have been identified using multivariate analyses. A previous study showed that multiple patient-related risk factors increased the occurrence of PEP and a cumulative effect was demonstrated in patients with multiple risk factors(14). That study focused on the cumulative effects of multiple risk factors, but did not investigate the relationship between patient-related risk factors and procedure-related risk factors. Our results demonstrated that procedure-related risk factors were affected by previous pancreatitis.

The mechanisms underlying the occurrence of PEP were previously considered to be mechanical injury to the papilla or pancreatic duct, thermal injury to the papilla, hydrostatic injury, chemical or allergic injury, and enzymatic injury and infection(19-21); however, the cause of PEP may be multifactorial and remains unclear(22). In addition, in patients with previous PEP or acute pancreatitis, the direct cause of secondary PEP has not yet been elucidated. It also currently remains unclear why patients with previous pancreatitis are more likely to develop PEP. We speculate that the pAP and pPEP groups had some organic potential leading to pancreatitis, which differed from the non-preP group. Therefore, the pAP and pPEP groups may have responded differently to ERCP from the non-preP group and, thus, may have different procedure-related risk factors.

In the present study, difficult cannulation (a cannulation time greater than 15 min) and a prolonged procedure time (total procedure time greater than 30 min) were identified as significant procedure-related risk factors according to previous pancreatitis. Difficult cannulation and a prolonged procedure induced papilla trauma. Furthermore, a prolonged procedure might increase the period of the continuous stimulation of the entire pancreas during ERCP, leading to parenchymal pancreatic injury. Although difficult cannulation was identified as a significant procedure-related risk factor for PEP(11-16), difficult cannulation was not a significant risk factor in the pAP group in the present study. In contrast, a prolonged procedure, which was also identified as a procedure-related risk factor(23), was a significant risk factor in the pAP group only. Our results revealed that the significance of the total procedure time was greater than that of the cannulation time for the pAP group, suggesting that parenchymal pancreatic injury has a significant influence on the occurrence of PEP in the pAP group.

In the pPEP group, difficult cannulation was identified as a significant risk factor, similar to the non-preP group. On the other hand, a prolonged procedure time was identified as a significant risk factor in the univariate analysis (OR=3.65; 95% CI=1.33 to 11.30, P= 0.01), but not in the multivariate analysis (OR=2.79; 95% CI=0.92 to 9.18, P= 0.068). Although a prolonged procedure may have influenced the occurrence of PEP in the pPEP group, the influence of difficult cannulation on the occurrence of PEP was greater than that of a prolonged procedure. Papilla trauma had a greater influence on the occurrence of the PEP than parenchymal pancreatic injury in the pPEP group, similar to the non-preP group.

We previously reported that endoscopic pancreatic stenting (EPS) is effective for preventing PEP in patients with previous pancreatitis and those with difficult cannulation(17). The results of the present study demonstrated EPS did not significantly reduce the occurrence of PEP in any of the three groups tested. Although EPS is recommended in order to improve the disturbed flow of pancreatic juice caused by papilla edema, our results showed that it did not exert significant effects in the pPEP or non-preP group, in which difficult cannulation increased the occurrence of PEP. In the pAP group, EPS only slightly reduced the occurrence of PEP.

The present study had some limitations. The number of subjects examined was small and, thus, it was not possible to accurately evaluate the effects of some risk factors for PEP, including suspected SOD (24 cases, 1.4%) and precut sphincterotomy (18 subjects, 1.3%). Furthermore, we assessed risk factors for PEP in the ASGE and ESGE guidelines; however, other factors such as serum bilirubin and guidewire insertion into the pancreatic duct were not evaluated.

In conclusion, a higher risk of PEP with previous PEP was associated with a longer cannulation time, whereas a higher risk of PEP with previous acute pancreatitis was associated with a longer procedure time. In these patients, it would be better to consider the different influence of procedure-related risk factor on the occurrence of PEP.

ACKNOWLEDGMENTS

We would like to thank the staff of the Center of Clinical Research (Dr. Omori) at Kobe University Hospital for their valuable contributions (advice on statistical analyses). The authors assume full responsibility for the analysis and interpretation of data.

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