Original Article

Multicenter prospective cohort study of adverse events associated with biliary endoscopic retrograde cholangiopancreatography: Incidence of adverse events and preventive measures for post-endoscopic retrograde cholangiopancreatography pancreatitis

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Objectives: The reported incidence of adverse events (AEs) in endoscopic retrograde cholangiopancreatography (ERCP) varies between 2.5% and 14%. The aim of this study was to evaluate the incidence and severity of AEs in biliary ERCP and to specify the risk factors and preventive measures for post-ERCP pancreatitis (PEP).

Methods: Patients with biliary disease with intact papilla were prospectively enrolled at 36 hospitals between April 2017 and March 2018. The primary outcomes were the incidence and severity of AEs.

Results: A total of 16,032 ERCP procedures were performed at the 36 hospitals during the study period and 3739 patients were enrolled. The overall incidence of AEs was 10.1% and ERCP-related mortality was 0.08%. PEP developed in 258 cases (6.9%), bleeding in 33 (0.9%), instrumental AEs in 17 (0.5%), infections in 37 (1.0%), cardiovascular AEs in eight (0.2%), pulmonary AEs in eight (0.2%), drug reaction AE in one (0.03%), pain in 15 (0.4%), and other AEs in 15 (0.4%). Multivariable analysis showed significant risk factors for PEP were: female of younger age, pancreatic guidewire-assisted biliary cannulation, temporary guidewire insertion into the pancreatic duct, total procedure time >60 min, and post-ERCP administration of non-steroidal anti-inflammatory drugs. Effective preventive measures were prophylactic pancreatic stenting (PPS) and epinephrine spraying onto the papilla.

Conclusions: In patients with intact papilla who underwent biliary ERCP, the incidence of AEs was 10.1% and the mortality was 0.08%. PPS and epinephrine spraying may prevent PEP.

Registration: This study was registered in the University Hospital Medical Information Network (UMIN000024820).

Key words: cholangiopancreatography, endoscopic retrograde, pancreatitis

INTRODUCTION

ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY (ERCP) is an invaluable procedure in the diagnosis and management of pancreaticobiliary

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diseases. However, it occasionally causes adverse events (AEs) such as pancreatitis, bleeding, perforation, or infection. The reported incidence of ERCP-related AEs varies between 2.5% and 14% due to differences in clinical settings, definitions, and study design.[1,2]

In ERCP procedures, selective cannulation and prevention of AEs are critical issues, and they are closely related.[3,4] In patients with prior sphincterotomy, the incidence of post-ERCP pancreatitis (PEP) is lower because the biliary orifice is separated from the pancreatic orifice and selective biliary cannulation is easier. Bleeding is a serious AE after endoscopic sphincterotomy for patients with intact papilla.[5,6] Thus, the incidence of ERCP-related AEs is markedly influenced by the proportion of patients with intact papilla.

ERCP procedures of the biliary and pancreatic tracts are often discussed indistinguishably; however, they have different roles in pancreatic procedures such as pancreatic injection and pancreatic stenting. Pancreatic injection may occur accidentally in biliary ERCP, whereas it is intentional and indispensable in pancreatic ERCP. Pancreatic stenting is a prophylactic procedure in biliary ERCP, whereas it is a therapeutic procedure in pancreatic ERCP. Analysis of ERCP without distinction of the biliary and pancreatic tracts may lead to inappropriate results. Thus, they should be discussed separately in the analysis of risk factors.

We aimed to determine the incidence and severity of AEs associated with biliary ERCP in patients with intact papilla, and to evaluate risk factors and preventive measures for PEP.

MATERIAL AND METHODS

Setting/participants

THE PRESENT STUDY was a prospective multicenter cohort study. The study enrolled patients who were registered between April 2017 and March 2018 at 36 hospitals. General acute hospitals (n = 20), university hospitals (n = 14), and cancer centers (n = 2), which employed pancreatobiliary specialists, were included in this study.

Patients who underwent ERCP for biliary diseases with intact papilla were enrolled. Among them, those with comorbid acute pancreatitis, altered gastrointestinal anatomy, a history of pancreatic surgery, or a severe life-threating systemic disease with an American Society of Anesthesiologists Physical Status (ASA-PS) of four or greater were excluded. In addition, each patient was enrolled only once.

All ERCP patients stayed in the hospital for at least 24 h following the procedure and received standard intravenous hydration (60–100 mL/h) until the next morning. The day after ERCP, blood tests were administered to test for pancreatitis or other AEs. Antithrombotic drugs were administered in accordance with the Guidelines for Gastroenterological Endoscopy in Patients Undergoing Antithrombotic Treatment.[7,8] The indications and methods for preventive measures were not specified in the protocol.

Outcomes

The primary outcomes were the incidence and severity of AEs associated with biliary ERCP. Secondary outcomes included the practice of selective biliary cannulation, the duration of cannulation attempts and prognostic factors for PEP.

Adverse events are events that prevent the completion of the planned procedure and/or result in admission to the hospital, prolongation of existing hospital stay, another procedure (needing sedation/anesthesia), or subsequent medical consultation.[9] This study included all AEs occurring intra-procedure (from entering the preparation area through to leaving the endoscopy room) and post-procedure (up to 14 days), with a definite or probable causal relationship.

The AEs were categorized as pancreatitis, bleeding, instrumental injuries, infection, cardiovascular events, pulmonary events, pain, thromboembolism, drug reaction, and others.[9] A diagnosis of PEP was based on the consensus definition: new or worsened abdominal pain, new or prolonged hospitalization for at least 2 days, and a serum amylase level measured more than 24 h after the procedure that was three times or greater than the upper limit of normal range.[5,10,11] The diagnosis and severity of AEs were defined by the American Society for Gastrointestinal Endoscopy (ASGE) lexicon for endoscopic AEs except for the diagnosis of PEP.[9]

Exposure factors

We collected data on patient-related factors, operator-related factors, procedure-related factors, and preventive measures. Patient-related factors included age, sex, ASA-PS, previous pancreatitis, suspected sphincter of Oddi dysfunction (SOD), cholangitis, obstruction of the main pancreatic duct (MPD) at the pancreatic head, serum amylase before ERCP, serum bilirubin before ERCP, diameter of the extrahepatic bile duct, and periampullary diverticulum. Operator-related factors included operators' expertise and institutional case volume. Procedure-related factors included pancreatic guidewire (PGW)-assisted biliary cannulation, precut sphincterotomy, cannulation attempts duration, unsuccessful biliary cannulation, biliary sphincterotomy, endoscopic papillary balloon dilation, endoscopic papillary large balloon dilation, pancreatic injection, temporary guidewire insertion into the pancreatic duct, endoscopic biliary stenting, endoscopic nasobiliary drainage, self-expandable metallic stent, extraction of biliary stones, brushing cytology, forceps biopsy, intraductal ultrasonography, and total

procedure time. Preventive measures included wire-guided cannulation, prophylactic pancreatic stenting (PPS), endoscopic nasopancreatic drainage (ENPD), administration of protease inhibitors, administration of glyceryl trinitrate, rectal administration of non-steroidal anti-inflammatory drugs (NSAIDs) immediately before or after ERCP, epinephrine spraying onto the papilla, and use of isotonic contrast agents.

Intact papilla was defined as that without previous sphincterotomy, papillary balloon dilation, or stenting. Cholangitis was diagnosed using the Tokyo Guidelines for the management of acute cholangitis and cholecystitis based on systemic inflammation, cholestasis, and imaging.[12] Obstruction of the MPD was defined as the disappearance of the MPD and dilation of the upstream pancreatic duct on imaging due to pancreatic head carcinoma or chronic pancreatitis. The operator was judged as having low experience in ERCP if they had performed fewer than 200 procedures or the current number of procedures was <40 per year.[13] A low-volume center was defined as fewer than 400 ERCPs per year. Exposure factors associated with guidewire insertion into the pancreatic duct were divided into the "PGW-assisted biliary cannulation" and "temporary guidewire insertion into the pancreatic duct" in order to control for multicollinearity, and to distinguish leaving guidewire and temporary guidewire insertion.

Data collection

The planning group of this study created a common case report form (CRF). Clinical data on the CRF were accumulated in the database of each institution prospectively. Eligibility for this study was determined before ERCP, and ERCP information was recorded immediately after ERCP. The incidence of AEs was assessed one week after ERCP and patient outcomes were assessed one month later.

Statistical analysis

Categorical data are presented as numbers (percentage) and continuous data as means (standard deviation [SD]) for normally distributed data or medians (interquartile range [IQR]) for non-normally distributed data.

Missing data was found in 231 items in 210 patients. Missing data were complemented with the most frequent variables for categorical data and mean or median values for continuous data. Those that could be estimated from other variables were complemented by regression imputation.

Univariable analysis was then performed by chi-squared test for each of the potential factors and candidate risk factors were selected based on *P*-values of <0.1. To focus on preventive measures, all of the preventive measures were selected as candidate factors. Next, multiple logistic regression analysis was performed using forced entry method (all possible models), and the odds ratio (OR) and its 95% confidence interval (CI) were indicated.

All tests of significance were two-tailed, and *P*-values <0.05 were significant.

Sample size calculation

The sample size was calculated considering the statistical power of the main analysis. Based on the preliminary questionnaire survey in the study group, we presumed the incidence of PEP was 7%, the proportion of biliary ERCP with intact papilla was 30% and the volume of ERCP was 380 procedures per year on average. In general, 10 events per variable are required for logistic regression analysis;[14] thus, we estimated that at least 10,000 ERCPs and 3000 eligible cases would be needed to evaluate about 20 variables. More than 27 institutions were expected to participate, enabling a sufficient number of ERCP cases would be collected during one year.

Ethics

This study was a non-invasive observational study, and we did not collect biological samples for research purposes. We informed the study subjects of the outline of this study on the website or bulletin board of each hospital, and provided an opportunity to decline participation. This study was approved by the institutional review boards of the respective institutions.

Registration of the clinical trial

This study was registered in the University Hospital Medical Information Network (UMIN000024820).

RESULTS

Baseline description of the cohort

A TOTAL OF 16,032 ERCP procedures were performed at the 36 centers during the study period and 3739 of them were registered in this study. Of the 3739 ERCP procedures, 2362 were performed at the 20 general acute hospitals, 1264 at the 14 university hospitals, and 113 at the two cancer centers.

The mean age of the study patients was 72.5 (SD 13.1) years, and 1633 were female. ASA-PS classes were class 1 (n = 1803), class 2 (n = 1352), and class 3 (n = 584). The indications for ERCP were shown in Table 1.

Table 1 Baseline characteristics of the study patients and their indications for ERCP

Patients, *n*	3739
Sex, *n*	
Male/female	2106/1633
Age	
Years, mean (SD)	72.5 (13.1)
<30, *n* (%)	32 (0.9)
30–49, *n* (%)	193 (5.2)
50–69, *n* (%)	1096 (29.3)
70–89, *n* (%)	2204 (58.9)
≥90, *n* (%)	214 (5.7)
ASA-PS, *n*	
1/2/3	1803/1352/584
Indication, *n*	
Choledocholithiasis	2106
Cholangitis (unknown)	114
Cholecystitis/Mirizzi syndrome	21
Bile leakage	41
Benign biliary stricture	85
Sclerosing cholangitis	8
Pancreaticobiliary maljunction	19
Suspected SOD	2
Other (non-neoplastic)	76
Cholangiocarcinoma	408
Gallbladder carcinoma	128
Ampullary neoplasm	62
Hepatocellular carcinoma	17
Pancreatic carcinoma	439
Other (neoplastic)	213

ASA-PS, American Society of Anesthesiologists Physical Status; SD, standard deviation; SOD, sphincter of Oddi dysfunction.

NSAIDs were administered to 618 patients, of which 383 (62.0%) were administered NSAIDs before ERCP and 235 (38.0%) immediately after ERCP. The dosage of NSAIDs was 12.5 mg (n = 1), 25 mg (n = 253), 50 mg (n = 359), 75 mg (n = 3), and 100 mg (n = 2). A low dose (50 mg or less) was administered to 613 patients (99.2%).

Incidence and severity of AEs

One-month outcome was obtained from all study patients. A total of 392 AEs developed in 377 ERCP cases (10.08%), and the severity was mild (n = 286), moderate (n = 76), severe (n = 27) and fatal (n = 3). The ERCP-related mortality was 0.08%. PEP developed in 258 cases (6.90%), it was mild (n = 201), moderate (n = 39), severe (n = 17), and fatal (n = 1). Bleeding developed in 33 cases (0.88%), it was mild (n = 23), moderate (n = 8), and severe (n = 2). Instrumental AEs developed in 17 cases (0.45%), it was mild (n = 9), moderate (n = 5), severe (n = 2), and fatal (n = 1). All instrumental AEs were perforation. Infection developed in 37 cases (0.99%), it was mild (n = 21), moderate (n = 13), severe (n = 2), and fatal (n = 1). Infections included cholangitis (n = 22), cholecystitis (n = 11), and other (n = 4). The incidence and severity of all AEs were shown in Table 2.

The overall bile duct cannulation rate was 96.9% and the median cannulation attempts time was 7 (IQR 2–15) minutes.

Univariable analysis of exposure factors for PEP

By univariable analysis, 20 candidate factors with P-values < 0.1 were selected: female sex and younger age (<50 years), ASA-PS 3, normal serum bilirubin (total bilirubin <1.2 mg/dL), hyperamylasemia before ERCP (≥130 U/L), nondilated extrahepatic bile ducts (<10 mm), cholangitis, obstruction of the MPD at pancreatic head, periampullary diverticulum, low-experienced first operator, PGW-assisted biliary cannulation, precut sphincterotomy, biliary sphincterotomy, pancreatic injection, temporary guidewire insertion into the pancreatic duct, extraction of biliary stones, brushing cytology, biopsy, intraductal ultrasonography, cannulation attempts duration >10 min, and total procedure time >60 min (Table 3). Among preventive measures, PPS, ENPD, rectal administration of NSAIDs after ERCP, and epinephrine spraying onto the papilla had P-values < 0.1 (Table 3).

Multivariable analysis of exposure factors for PEP

Multivariable logistic regression analysis was performed using 20 candidate risk factors and nine preventive measures (Table 3). The analysis yielded nine significant prognostic factors; five risk factors and four protective factors: female of younger age (OR 2.20 [95% CI 1.12–4.04]), ASA-PS 3 (OR 0.62 [95% CI 0.39–0.96]), obstruction of the MPD at the pancreatic head (OR 0.41 [95% CI 0.22–0.73]), PGW-assisted biliary cannulation (OR 2.82 [95% CI 1.92–4.15]), temporary guidewire insertion into the pancreatic duct (OR 2.50 [95% CI 1.60–3.85]), total procedure time >60 min (OR 1.73 [95% CI 1.24–2.40]), PPS (OR 0.63 [95% CI 0.42–0.93]), rectal administration of NSAIDs after ERCP (OR 1.93 [95% CI 1.22–2.96]), and epinephrine spraying onto the papilla (OR 0.60 [95% CI 0.42–0.84]).

DISCUSSION

IN BILIARY ERCP for patients with intact papilla, the overall incidence of AEs was 10.1%, that of PEP was 6.9%, the ERCP-related mortality was 0.08%, and the

Table 2 Incidence and severity of adverse events in endoscopic retrograde cholangiopancreatography

	Pancreatitis	Bleeding	Instrumental	Infection	Cardiovascular	Pulmonary	Drug reaction	Pain	Other
Mild	201	23	9	21	5	4	1	13	9
Moderate	39	8	5	13	2	1	0	2	6
Severe	17	2	2	2	1	3	0	0	0
Fatal	1	0	1	1	0	0	0	0	0
Total	258 (6.90%)	33 (0.88%)	17 (0.45%)	37 (0.99%)	8 (0.21%)	8 (0.21%)	1 (0.03%)	15 (0.40%)	15 (0.40%)

overall bile duct cannulation rate was 96.9%. These incidences and cannulation rate would be the benchmark values in biliary ERCP for patients with intact papilla.

The lack of standardized classification, definition, and severity criteria was a problem in discussing endoscopic AEs. Recently, the ASGE issued a lexicon of AEs, which proposed comprehensive classification and standardized severity criteria for endoscopic AEs.[9] Although the 2010 ASGE lexicon is useful for research and comparison, the definition of pancreatitis is insufficient, and the consensus criteria are commonly used in PEP. To maintain comparability with previous studies and to standardize the severity of AEs, this study used the consensus definition to define pancreatitis, and the ASGE lexicon to define other AEs and all severity classifications.

Multivariable analysis identified one risk factor and two protective factors among the patient-related factors, three risk factors among the procedure-related factors, one risk factor and two protective factors among the preventive measures.

Among the patient-related factors, female of younger age were risk factors that have been reported previously.[6,15] On the other hand, two protective factors, obstruction of the MPD at the pancreatic head and ASA-PS 3, were uncommon findings. Obstruction of the MPD at the pancreatic head is a reasonable factor both theoretically and empirically. The ASA-PS 3 may reflect patient background such as elderly age.

Among the procedure-related factors, PGW-assisted biliary cannulation, temporary guidewire insertion into the pancreatic duct, and total procedure time >60 min were significant risk factors. Although pancreatic injection has been reported as a definite risk factor, guidewire insertion into the pancreatic duct, especially PGW-assisted biliary cannulation, was a more influential risk factor in this study. This may reflect the pancreatic duct damage caused by leaving guidewire in the pancreatic duct and difficulty in biliary cannulation. Total procedure time >60 min may reflect the difficulties in the procedures or more complicated procedures.

As preventive measures, PPS and epinephrine spraying onto the papilla were deemed to be effective, while rectal administration of NSAIDs after ERCP was associated with increased risk. Previous studies reported that PPS was a promising preventive measure for high-risk patients with easy pancreatic stenting.[15] In this analysis, PPS increased the risk in univariable analysis; however, it was preventive in the multivariable analysis. Since PPS were used for high-risk patients, this may be accounted for by reverse causality.

Epinephrine spraying onto the papilla has been proposed as a simple measure to reduce papillary edema and PEP. The results of RCTs comparing epinephrine and saline were heterogeneous, but a pooled analysis showed that topical epinephrine reduced PEP (relative risk 0.25, 95% CI 0.006–0.65; number needed to treat 15).[16–18] The present study supports the effectiveness of epinephrine spraying. We consider that large RCTs are necessary to validate the effectiveness of epinephrine spraying.

Rectal administration of low-dose NSAIDs before ERCP did not show any preventive effect. This finding was consistent with previous studies.[19,20] On the other hand, administration of NSAIDs after ERCP was significantly high risk in the multivariable analysis. This suggests that post-ERCP NSAIDs reflect various factors related to operator's choice such as the actual difficulty of the procedures and the patient conditions. Thus, we could not evaluate the efficacy of post-ERCP NSAIDs.

The main strength of this study was focusing on biliary ERCPs in patients with intact papilla, which enabled clarification of the incidence of AEs, and targeted analyses. Second, the results are highly generalizable in clinical practice because it was a prospective large-scale multicenter study that used clear definitions and unified severity assessment.

This study has some limitations. First, the preventive measures for AEs were taken under the Japanese public health insurance system; therefore, this study could not evaluate the effectiveness of high-dose NSAIDs (100 mg) as the Japanese public health insurance only covers up to 50 mg. Second, aggressive intravenous infusion, a candidate preventive measure for PEP, was not performed in this study because the evidence was not established at the time of this study. Finally, as this was an observational study based on actual clinical practice, there may be bias due to factors that were difficult to measure.

Table 3 Prognostic factors for PEP by univariable and multivariable analysis

Factors	*n*	PEP	PEP (%)	Univariable analysis		Multivariable analysis	
				OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Patient-related factors							
Female of younger age (<50 years old)	91	14	15.38	2.54 (1.41–4.55)	0.0012	2.2 (1.12–4.04)	0.0226
ASA-PS 3	584	24	4.11	0.53 (0.35–0.82)	0.00238	0.62 (0.39–0.96)	0.0298
Previous pancreatitis	76	7	9.21	1.38 (0.63–3.03)	0.4225		
Suspected sphincter of Oddi dysfunction	34	3	8.82	1.31 (0.40–4.31)	0.6567		
Hyperamylasemia before ERCP (≥130 U/L)	473	22	4.65	0.62 (0.40–0.97)	0.036	0.67 (0.41–1.04)	0.0763
Normal serum bilirubin (Total bilirubin <1.2 mg/dL)	1407	121	8.6	1.51 (1.17–1.95)	0.0014	1.33 (1.00–1.78)	0.0526
Nondilated extrahepatic bile ducts (<10 mm)	1976	149	7.54	1.24 (0.96–1.60)	0.0998	1.1 (0.84–1.44)	0.5107
Cholangitis	1306	60	4.59	0.54 (0.40–0.73)	<0.0001	0.79 (0.56–1.09)	0.1491
Obstruction of the MPD at the pancreatic head	360	13	3.61	0.48 (0.27–0.85)	0.0096	0.41 (0.22–0.73)	0.0018
Periampullary diverticulum	910	51	5.6	0.75 (0.54–1.02)	0.0682	0.83 (0.59–1.16)	0.2821
Operator-related factors							
Low-experienced first operator	1837	143	7.78	1.3 (1.02–1.69)	0.0361	1.19 (0.91–1.57)	0.2123
Low volume center (<400 ERCP/year)	738	45	6.1	0.85 (0.61–1.18)	0.3369		
Procedure-related factors							
PGW-assisted biliary cannulation	903	119	13.18	2.95 (2.28–3.81)	<0.0001	2.82 (1.92–4.15)	<0.0001
Precut sphincterotomy	206	24	11.65	1.87 (1.19–2.91)	0.0054	1.06 (0.63–1.73)	0.8219
Cannulation attempts duration >10 min	1276	141	11.05	2.49 (1.93–3.22)	<0.0001	1.31 (0.95–1.80)	0.0984
Unsuccessful biliary cannulation	115	12	10.43	1.6 (0.87–2.95)	0.1288		
Biliary sphincterotomy	2368	149	6.29	0.78 (0.60–1.00)	0.0531	0.91 (0.67–1.23)	0.5438
Endoscopic papillary balloon dilation	145	10	6.9	1 (0.52–1.92)	0.9986		
Endoscopic papillary large balloon dilation	122	5	4.1	0.57 (0.23–1.40)	0.2144		
Pancreatic injection	1480	154	10.41	2.41 (1.86–3.11)	<0.0001	1.32 (0.95–1.85)	0.101
Temporary guidewire insertion into the pancreatic duct	355	39	10.99	1.78 (1.24–2.56)	0.0014	2.5 (1.60–3.85)	<0.0001
Endoscopic biliary stenting	1615	121	7.49	1.17 (0.91–1.51)	0.1978		
Endoscopic nasobiliary drainage	719	43	5.98	0.83 (0.59–1.16)	0.278		
Self-expandable metallic stent	221	19	8.6	1.29 (0.79–2.10)	0.2964		
Extraction of biliary stones	1269	70	5.52	0.71 (0.53–0.94)	0.0167	0.8 (0.56–1.12)	0.1915
Brushing cytology	368	37	10.05	1.59 (1.10–2.30)	0.012	1.24 (0.81–1.88)	0.3123
Biopsy	355	41	11.55	1.91 (1.34–2.71)	0.0003	1.28 (0.83–1.96)	0.262
Intraductal ultrasonography	368	43	11.68	1.94 (1.37–2.75)	0.0001	1.34 (0.89–1.98)	0.1534
Total procedure time >60 min	509	73	14.34	2.77 (2.07–3.69)	<0.0001	1.73 (1.24–2.40)	0.0015
Preventive measures							
Wire-guided cannulation	841	65	7.73	1.17 (0.88–1.57)	0.2815	1.03 (0.74–1.43)	0.8615
Prophylactic pancreatic stenting	377	44	11.67	1.94 (1.39–2.74)	<0.0001	0.63 (0.42–0.93)	0.0196
Endoscopic nasopancreatic drainage	17	4	23.53	4.2 (1.36–12.98)	0.0067	1.22 (0.30–4.00)	0.7607
Protease inhibitors	3020	211	6.99	1.07 (0.77–1.49)	0.6688	0.98 (0.67–1.45)	0.9155
Glyceryl trinitrate	27	2	7.41	1.08 (0.25–4.59)	0.9169	0.73 (0.11–2.76)	0.6779
Rectal administration of NSAIDs before ERCP	383	28	7.31	1.07 (0.71–1.61)	0.738	1.05 (0.64–1.69)	0.8342
Rectal administration of NSAIDs after ERCP	235	33	14.04	2.38 (1.61–3.52)	<0.0001	1.93 (1.22–2.96)	0.0053
Epinephrine spraying onto the papilla	1013	53	5.23	0.68 (0.50–0.93)	0.0141	0.6 (0.42–0.84)	0.003
Isotonic contrast agent	1613	121	7.5	1.18 (0.91–1.52)	0.2064	1.3 (0.98–1.73)	0.0701

ASA-PS, American Society of Anesthesiologists Physical Status; CI, confidence interval; ERCP, endoscopic retrograde cholangiopancreatography; MPD, main pancreatic duct; NSAIDs, non-steroidal anti-inflammatory drugs; OR, odds ratio; PEP, post-ERCP pancreatitis; PGW, pancreatic guidewire.

In conclusion, the incidence of AEs, PEP and mortality in patients with biliary ERCP with intact papilla were 10.1%, 6.9% and 0.08%, respectively. To prevent PEP, guidewire insertion into the pancreatic duct and prolonged ERCP should be avoided, epinephrine spraying may be effective, and PPS should be considered in high-risk patients with easy pancreatic stenting.

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CONFLICT OF INTEREST

AUTHORS DECLARE NO conflict of interest for this article.

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SUPPORTING INFORMATION

ADDITIONAL SUPPORTING INFORMATION may be found in the online version of this article at the publisher's web site.

Appendix S1 A list of physicians and staff contributing to this study.