Title page

Title

Combination of Diclofenac and Sublingual Nitrates is Superior to Diclofenac Alone in Preventing Pancreatitis After Endoscopic Retrograde Cholangiopancreatography

Short title

Sublingual nitrate with rectal NSAIDs for PEP

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Abbreviation

ERCP, endoscopic retrograde cholangiopancreatography; NSAIDs, nonsteroidal anti-inflammatory drugs; PEP, post ERCP pancreatitis; RCT, randomized controlled trials; EPST, endoscopic pancreatic sphincterotomy; EPBD, endoscopic papillary balloon dilation; SOD, sphincter of oddi dysfunction; AE, adverse effect; NNT, number needed to treat; OR, odds ratio; CI, confidence interval

Authors contributions

TT and HK took part in the conception, design, and drafting of the article. TU, YA, HH, MF, RH, TO, MW. MT, MM, YK participated in the analysis and interpretation of the data. HO participated in the final approval of the article.

Abstract

Background & Aims: Acute pancreatitis is a major adverse event of endoscopic retrograde cholangiopancreatography (ERCP). Rectal administration of non-steroidal anti-inflammatory drugs (NSAIDs) decreases the incidence of post-ERCP pancreatitis (PEP). Little is known about the combined effects of sublingual nitrate and NSAIDs. We performed a randomized trial to assess whether the combination of NSAIDs and sublingual nitrate is more effective than NSAIDs alone in preventing PEP.

Methods: In a prospective superiority trial, eligible patients underwent ERCP at 12 endoscopic units in Japan, from March 2015 through May 2018. Patients were randomly assigned to groups given diclofenac suppositories (50 mg) within 15 minutes after the endoscopic procedure alone (diclofenac alone group, n=442) or in combination with sublingual isosorbide dinitrate (5 mg) 5 minutes before the endoscopic procedure (combination group, n=444). The primary endpoint was the occurrence of PEP.

Results: Post-ERCP pancreatitis developed in 25 patients in the combination group (5.6%), and in 42 patients in the diclofenac alone group (9.5%) (relative risk, 0.59; 95% CI, 0.37–0.95; *P*=.03). Moderate to severe pancreatitis developed in 4 patients (0.9%) in

the combination group, and 10 patients (2.3%) in the diclofenac alone group (relative risk, 0.12; 95% CI, 0.13–1.26; P = 0.12). There was no serious adverse event related to the additional administration of sublingual nitrate.

Conclusions: In a randomized controlled trial, we found that prophylaxis with rectal diclofenac and sublingual nitrate significantly reduces the overall incidence of PEP compared with diclofenac suppository alone. ClinicalTrials.gov, no: UMIN 000016274

KEY WORDS: pancreas, inflammation, smooth-muscle relaxant, drug

Introduction

Acute pancreatitis is the most important adverse event (AE) of endoscopic retrograde cholangiopancreatography (ERCP). Generally, post-ERCP pancreatitis (PEP) occurs in 1–25% of patients [1-2]. PEP is usually mild or moderate; however, some cases may develop severe pancreatitis, which requires further intervention and leads to death in 0.3–0.6% of the patients [3-6].

Numerous pharmacological agents have been evaluated for the prevention of PEP. Several randomized trials, including a high-profile multicenter study, have confirmed the efficacy of rectal non-steroidal anti-inflammatory drugs (NSAIDs) in preventing PEP [7-10]. Routine rectal administration of diclofenac or indomethacin, immediately before or after an ERCP has been recommended to minimize the risk of PEP in the European Society of Gastrointestinal Endoscopy (ESGE) and Japanese Society of Hepato-Biliary-Pancreatic Surgery (JHBPS) guidelines [11] [12]. Moreover, in 2 randomized controlled trials (RCTs), positive results have been reported by administering sublingual nitrate to prevent PEP [13, 14]. Nitrate is a smooth-muscle relaxant, and increases pancreatic parenchymal blood flow [15]. Recently, it was demonstrated in a RCT that a combination of sublingual nitrate and rectal NSAIDs is more effective than NSAIDs alone in preventing PEP [16]. The study showed that the relative risk of PEP reduced by 56.2%

with this treatment, which is simple, inexpensive, and well tolerated. Although the trial reported the efficacy of the combination therapy in preventing PEP, the trial was a single-center study with small sample size. Therefore, we conducted a multicenter, prospective, randomized controlled trial to evaluate the efficacy of a combination of rectal NSAIDs and sublingual nitrate in preventing PEP.

Methods

Study design

The study was a 2-arm, multicenter, prospective, randomized, superiority unblinded trial to evaluate the combined effect of nitrate and diclofenac in the prevention of PEP, in comparison with the efficacy of diclofenac alone. The study was conducted between March 2015 and May 2018 at 12 centers in Japan; more than 200 ERCPs per year were performed in each center. A total of 900 eligible patients were randomly assigned to receive a 50 mg diclofenac suppository either alone or in combination with a 5 mg isosorbide dinitrate sublingual tablet. The sublingual isosorbide dinitrate tablets which showed maximum blood concentrations at 18.2 min, and the biphasic elimination with an initial half-life of 7.5 minutes and a longer terminal half-life of 55.2 minutes [17] were administered 5 minutes before the endoscopic procedure, and the diclofenac

suppositories were administered within 15 minutes after the endoscopic procedure.

Ethical consideration

The study protocol was approved by the institutional review board of each of the participating institutions before initiating the study. This trial was registered with the University Hospital Medical Information Network (Clinical Trial Registry no. UMIN000016274).

Endpoints

Primary and secondary endpoints

The primary endpoint was the occurrence of PEP. PEP was defined by the criteria set by Cotton et al. [18], as the development of abdominal pain and elevation of serum amylase levels by more than 3 times the upper normal limit (hyperamylasemia) within 24 h after an ERCP. Serum amylase level was measured before the ERCP, and at any time when the patient complained of abdominal pain within 24 h after the ERCP; otherwise, it was routinely measured 24 h after the ERCP. Secondary endpoints included the development of moderate or severe PEP, the frequency of PEP in the patients with the risk factors for PEP, AE related to the study drugs. The severity of PEP was graded according to the

extension of the planned fasting period after the ERCP as follows, mild: PEP requiring an extension of the planned fasting period of less than 3 days; moderate: requiring an extension of the planned fasting period of 4–10 days; and severe: requiring an extension of the planned fasting period of more than 10 days, necessitating a surgical or intensive treatment, or resulting in death. This definition of PEP severity was modified based on the criteria of Cotton et al (18). The following factors were considered to be high-risk for the occurrence of PEP: (1) pre-cut sphincterotomy (a procedure performed to facilitate the biliary access when standard cannulation techniques are unsuccessful); (2) endoscopic pancreatic sphincterotomy (EPST); (3) endoscopic papillary balloon dilation (EPBD) of the intact biliary sphincter; (4) difficult cannulation (more than 10 minutes elapsed for the successful selective cannulation, or in failed cannulation, (5) injection of contrast agent into the pancreatic duct; (6) female patient, and age < 60 years, (7) clinical suspicion of sphincter of Oddi dysfunction (SOD); (8) history of recurrent pancreatitis; and (9) history of PEP [11,19]. The patients- and procedure-related factors were recorded at the end of procedures. Patient-related factors included the following: (1) age, (2) sex, (3) presence of juxtapapillary diverticulum and (4) indication for ERCP. Procedure-related factors include the following: (1) pancreatography; (2) EPST; (3) pre-cut sphincterotomy; (4) endoscopic biliary sphincterotomy; (5) EPBD of the intact biliary

sphincter; (6) endoscopic biliary drainage(EBD) without endoscopic sphincterotomy ; (7) pancreatic duct stenting; (8) common bile duct-intraductal ultrasonography; (9) pancreatic duct-intraductal ultrasonography; (10) common bile duct tissue sampling ; cytology and brush; (11) pancreatic duct tissue sampling - cytology and brush; (12) time for selective cannulation to the targeted duct which was initiated when cannulation was attempted ; (13) total time for the ERCP procedure; and (14) concomitant endoscopic ultrasound sonography (EUS) / fine needle aspiration (FNA).

Eligibility Criteria

The inclusion criteria were applied to patients who were scheduled to undergo an ERCP. The exclusion criteria are as follows: (1) evaluated 4 or 5 levels according to the Eastern Cooperative Oncology Group Performance Status (ECOG PS)[20];(2) age younger than 20 years; (3) body weight less than 50 kg; (4) those cases that were expected to have duodenal papilla which were inaccessible by endoscopy; (5) not native papilla; (6) presence of acute pancreatitis; (7) presence of chronic pancreatitis; (8) presence of pancreatic head cancer with occlusion of the main pancreatic duct; (9) contraindication to NSAIDs or nitrate; (10) case of post gastrectomy; (11) serum creatinine level, >1.4 mg per deciliter; (12) presence of active peptic ulcer disease; (13)

presence of closed angle glaucoma; (14) presence of aspirin-induced asthma; (15) currently on nitrate medication; (16) inability to provide written informed consent; (17) the subjects deemed inappropriate for the trial.

Randomization

After confirming the fulfillment of the eligibility criteria, investigators conducted a registration to the Data Center by a web-based system. The patients were then randomly assigned to receive a 50 mg diclofenac suppository, either alone (diclofenac alone group) or in combination with a 5 mg isosorbide dinitrate sublingual tablet (combination group) in a 1:1 ratio by a minimization method to maintain a balance among the institutions and the patients' characteristics, namely, age, sex, and primary disease (biliary disease vs. pancreatic disease). Investigators and patients were not blinded to treatment allocation.

Treatment methods

Intervention

Before the endoscopy, the history of each patient was recorded, and a physical examination was performed. ERCP was performed with the patients in a prone or

semi-prone position, under conscious sedation, and with CO_2 insufflation. Pharyngeal anesthesia was induced by a topical anesthetic using a lidocaine spray; whereas, conscious sedation was induced by an intravenous medication, mainly pethidine hydrochloride, and diazepam or midazolam, just before the procedures. We administered 20 mL of ulinastatin (150,000 U) solution, a protease inhibitor, by intravenous infusion immediately after the ERCP, which is routinely used in our institution with the expectation that it will prevent PEP. The ERCP devices used were not limited to any specific types. We used a conventional cannulation technique involving contrast injection in the first attempt without the use of a guidewire. A standard monomer-ionic, iodinated, radiological contrast agent with 60% iodine was used as a contrast medium. Injection of the contrast medium allowed visualization of the bile duct or pancreatic duct to confirm whether selective cannulation was achieved. The cases in which it was difficult to cannulate, we performed a pancreatic guidewire placement or pre-cut sphincterotomy to achieve selective cannulation. Pancreatic duct stenting was performed to prevent pancreatitis at the endoscopist's discretion. After the procedures, the endoscopists recorded the results, and the patients fasted until the blood tests performed the following day confirmed the absence of pancreatitis or other AEs. For the purpose of observation, all of the patients in this study were hospitalized

for at least 48 hours after the procedure. We assessed the patients the morning after the procedure and at any time the patients complained of pain. Abdominal pain was defined as new or worsening persistent pain in the epigastric region. Decisions regarding the evaluation of AEs following the procedure were left to the discretion of the endoscopist. All the authors had access to the study data, and they reviewed and approved the final manuscript.

Adverse events

AEs of the study drugs were monitored during their hospital stay. The AE of diclofenac, including gastrointestinal bleeding and renal failure; and that of nitrates, including headache, dizziness, and hypotension (systolic blood pressure <90 mmHg or decreased by 20%) were monitored. Other post-ERCP AEs, including biliary infection, bleeding, and perforation were also monitored in addition to PEP. AE were defined in accordance with the American Society for Gastrointestinal Endoscopy lexicon for endoscopic AEs [21].

Statistical consideration

Sample size

Previous data from a meta-analysis conducted by Puig et al. [22] indicated that a prophylactic administration of rectal NSAIDs reduces the incidence of PEP from 14.5% to 7.4%, and the relative risk reduction is 50.7%. Sotoudehmanesh et al. [16] also reported that combining rectal NSAIDs with sublingual nitrate reduces the incidence of PEP from 15.3% to 6.7%, as compared to that with the administration of NSAIDs alone, and the relative risk reduction is 56.2%. We assumed that the incidence of PEP in the patients who did not receive any prophylactic medicine for PEP would be 14.6% (estimated from previous 5 years' data obtained from our institutions). We estimated that 892 patients (446 per study group) would show at least 80% reduction in the overall incidence of PEP (56.2% in both the groups), from 7.4% (in the diclofenac alone group) to 3.2% (in the combination group), while performing the Fisher's exact test with a 2-sided significance level of 0.05.

Statistical analysis

Statistical analysis was performed on the basis of modified intention-to-treat analysis after excluding cases who were randomized mistake. The Wilcoxon rank sum test was performed to compare the continuous data, and the Fisher's exact test was performed to evaluate the non-continuous variables. No interim analysis was done. A $P<0.05$ was

considered statistically significant. All the statistical analyses were performed using a JMP Pro 12 (SAS Institute Inc., Cary, NC, USA). The ranges of the continuous values were shown as interquartile ranges.

Results

Patients

Between March 2015 and May 2018, 10188 patients were scheduled to undergo ERCP and assessed for eligibility across 12 centers. After screening, 9288 patients met the exclusion criteria and 44 declined to participate. Patients were deemed to be inappropriate for trial when their health was unstable due severe cholangitis (n = 55), advanced cancer (n = 26), severe comorbidity (n = 15), decompensated cirrhosis (n = 11), or advanced age (> 85 years) (n = 36). The remaining 900 patients were enrolled for the study (Figure 1). Further, 14 patients (1.6%) were excluded because, they had been randomized by mistake; some either fulfilled one of the exclusion criteria (n=7) (2 presented with contraindication for the NSAIDs, 2 had a history of endoscopic biliary sphincterotomy , 1 had the body weight less than 50 kg, 1 presented with contraindication for nitrate, 1 manifested the presence of chronic pancreatitis), some declined to give their consent just before the ERCP (n=4), and

some were registered twice (n=3). These patients were ineligible for the trial because, determining the effect of the treatment would have been impossible in those.

In the combination group, 2 patients (0.5%) did not undergo ERCP, since hypotension and rash or hypoxia occurred immediately after the administration of nitrate, which was thought to be an allergic reaction to nitrate. In the diclofenac alone group, ERCP was not performed in one patient due to the natural discharge of choledocholithiasis before the procedure; and the primary endpoint could not be evaluated in one patient, since fatal pulmonary infarction occurred after the ERCP. These four patients were included in the analysis. Finally, the total number of patients include in the analysis was 886 (444 in the combination group vs. 442 in the diclofenac alone group). The baseline characteristics were similar in both the groups (Table 1).

The procedure-related parameters in both the groups were similar (Table 2). The number of patients at high risk of PEP, defined as having one or more risk factors for PEP, were 289 (65.1%) and 300 (67.9%) in the combination and diclofenac alone groups, respectively (P = 0.39). Among them, the number of patients with one risk for post-ERCP pancreatitis were 163 (36.7%) and 167 (37.8%) (P = 0.78), two risks for post-ERCP pancreatitis were 93 (21.0%) and 103 (23.3%) (P = 0.42), and three or more risks for post-ERCP pancreatitis were 33 (7.4%) and 30 (6.8%) (P = 0.79) in

the combination and diclofenac alone groups, respectively.

Study outcomes

The primary outcome, namely, PEP occurred in 67 of the 886 patients (7.6%). Of these, 25 of the 444 patients (5.6%) developed PEP in the combination group, and 42 of the 442 patients (9.5%) developed PEP in the diclofenac alone group (relative risk, 0.59; 95% confidence interval (CI), 0.37-0.95; P=0.03); and this corresponded to an absolute risk reduction of 3.9% (number needed to treat [NNT], for preventing one episode of PEP, was 26), and a relative risk reduction of 40.8% (Table 3).In this study, all the patients were hospitalized for the ERCP procedures; and 67 patients with PEP completed the follow-up, necessary to determine the severity of PEP. Moderate or severe PEP occurred in 14 of the 886 patients (1.6%): 4 (0.9%) in the combination group and 10 (2.3%) in the diclofenac alone group (relative risk, 0.12; 95%CI, 0.13-1.26; P=0.12) (Table 3). In this trial, no one developed severe PEP. Among the high-risk patients, PEP occurred in 24 of the 288 patients (8.3%) in the combination group, and in 39 of the 301 (13.0%) in the diclofenac alone group (relative risk, 0.64; 95%CI, 0.39-1.03; P=0.08). There was no statistical significance between two groups; however, this may be due to the small sample size. The relative risk of patients with no risk factors for PEP, patients with one risk factor for PEP, patients with two risk factors for PEP,

and patients with more than 2 risk factors for PEP, were 0.31, 0.45, 0.76 and 0.78, respectively. Furthermore, the relative benefit of additional sublingual nitrate had a tendency to decline according to the number of risk factors for PEP.

Prophylactic pancreatic stent

In total, 136 patients (15.4%) were given a prophylactic pancreatic stent; all of these patients were considered a high risk for PEP. Among them, 10 of the 70 patients (14.3%) developed PEP in the combination group, and 7 of the 66 patients (10.6%) developed PEP in the diclofenac alone group (P=0.61).

Adverse events

The ERCP-related AEs were the following: (1) The median serum amylase level after the procedures was 88 (56–173) IU/L in the combination group and 94(62–198) IU/L in the diclofenac alone group (P=0.07); hyperamylasemia was observed in 52 patients (11.7%) in the combination group and 65 patients (14.7%) in the diclofenac group (P=0.20). (2) Sphincterotomy site bleeding occurred in 2 patients (0.5%) in the combination group, and 0 (0%) in the diclofenac alone group. Both the cases manifested

moderate bleeding and recovered with endoscopic hemostasis. Thus, there was no need of transfusion; (3) A duodenal perforation occurred in one (0.2%) patient in the combination group, and in 2 patients (0.5%) in the diclofenac group after the EST. Of the 3 patients, one patient in the diclofenac group underwent surgery 2 days after the ERCP, and the remaining 2 patients recovered spontaneously with the conservative treatment; (4) Biliary infection occurred in 3 patients (0.7%) in the combination group, and in 2 patients (0.5%) in the diclofenac alone group. (Table 3). There was no significant difference among the outcomes in both the groups.

The AEs other than the ERCP-related were the following: 35 patients (7.9%) in the combination group and 13 (2.9%) in the diclofenac alone group presented mild transient hypotension during the ERCP procedures, which improved within several minutes, and the incidence rate was significantly higher in the combination group (P=0.002). In all cases, the hypotension was treated and responded to an intravenous bolus infusion of lactated ringer's solution and/or administration of a temporary vasopressor (Table 3). Among the patients who developed PEP in the combination group, only one patient presented with transient hypotension during the procedures. In the combination group, only one patient (0.2%) complained of headache.

Hypotension and rash or hypoxia, which were thought to be an allergic reaction to nitrate, occurred in 2 patients in the combination group; however, improved promptly by the administration of temporary vasopressors, steroids, and antihistamines. There was no serious adverse effect related to the additional administration of nitrate.

One patient in the diclofenac alone group developed fatal pulmonary infarction a few hours after the ERCP. The patient had an advanced cholangiocarcinoma, and had been diagnosed with pulmonary arterial thrombosis before the ERCP.

Discussion

Rectal administration of the NSAIDs has been widely used for the prevention of PEP, and has been recommended to be administered in all patients without contraindications in the ESGE and JHBPS guidelines [11, 12].

In this multicenter, randomized controlled trial, we found that the combination therapy with diclofenac and sublingual nitrate significantly reduced the incidence of PEP as compared to that with the use of diclofenac alone; and it reduced the risk of PEP by 40.8%. The number of ERCP patients who were needed to be treated for preventing an episode of pancreatitis was 26.

Medication with nitrate, especially the sublingual administration, for prophylactic use before the ERCP reduced the incidence of PEP in meta-analysis [23,24,25]. Glyceryl trinitrate (GTN) can reduce the pressure of sphincter of Oddi [15]. Theoretically, the use of these compounds before and after an ERCP can relax the biliary and pancreatic sphincters, and minimize potential pancreatic outflow obstruction after the procedure. Moreover, nitrates produce nitric oxide that causes dilation of the microvascular vessels, which may improve pancreatic tissue circulation and nutrition [26]. These effects of nitrate may reduce the incidence of PEP. Recently, the study reported by Sotoudehmanesh showed that combination of rectal NSAIDs and sublingual isosorbide dinitrate, significantly reduces the incidence of PEP than that by the NSAIDs suppository alone (from 15.3% to 6.7%). In this study, the time and dose of administration of rectal NSAIDs varied from the previous studies; however, our result was consistent with that of the previous studies [16].

We observed a higher rate of PEP in the diclofenac alone group than that reported in previous studies [7-9]. This might have resulted from the use of low dose diclofenac or the use of a different cannulation method. In some randomized controlled trials [27-30], rectal NSAIDs showed significantly better prophylactic activity in PEP. The

recommended dose, and that used in these trials, of rectal NSAIDs is 100 mg of diclofenac or indomethacin, which is higher than the dose used in the current trial. However, 100 mg of diclofenac is not legally permitted in Japan. Previous studies reported the efficacy of 50 mg of diclofenac in the prevention of PEP, but the difference between the efficacies of 100 mg and 50 mg of diclofenac was not clear [31].
In addition, we used a conventional cannulation technique involving contrast injection in the first attempt. For this study, this was thought to be inferior in terms of the incidence of PEP [32-36]. There is no significance difference in the PEP rates in high-risk patients between the two groups (p=0.08).However, the combination group patients tended to show a low incidence of pancreatitis; it is possible that the lack of significance may be due to the small sample size.

Several prophylactic interventions have been proved to be effective in minimizing the risk of PEP, including pancreatic stent placement [11, 37]. In the present study, pancreatic stents were used in 15.4% of all the patients. The pancreatic stent was used at the discretion of the endoscopists and the pancreatic stent placement was attempted in patients who were considered at high risk of developing PEP. Therefore, we could not accurately evaluate the usefulness of a prophylactic

pancreatic stent for preventing PEP in this study.

The only significant AE attributable to the combination group was hypotension. In the combination group, 7.9% of the patients manifested hypotension for a transient period as compared to 2.9% of the patients the diclofenac alone group who also manifested hypotension, which responded to conventional therapy. In addition, the allergic reaction related to nitrate occurred in 2 patients, which improved promptly; and no serious AEs concerning the use of nitrate were detected in our study. Prophylaxis should be cost-effective, safe, and affordable. A combination of rectally administered diclofenac and sublingual nitrate has been thought to be an ideal pharmacologic prophylaxis: it is inexpensive, safe, and easy to apply to fasting patients.

Our study has some limitations; one such limitation is the lack of a double-blind clinical setting which introduces the possibility of a bias in the evaluation of PEP and the lack of data regarding the baseline abdominal pain may be a probable confounder in terms of defining PEP. A further limitation is that the patients received a 50 mg rectal dose of diclofenac after the ERCP which is lower than that reported in the previous studies. The third limitation is that all patients were administered

ulinastatin, with the expectation that this would prevent PEP; we recognize that this may affect the incidence of PEP and introduce an additional variable into this study. The fourth limitation is that we overestimated the risk reduction rate of the additional administration of sublingual nitrate, and a larger number of cases were needed to obtain a planned statistical power. The result of this study has a possibility of a type I statistical error reflected by a confidence interval nearly 1.0. Therefore, additional confirmatory studies will be necessary to support our conclusions.

In conclusion, a combination of rectally administered diclofenac and sublingual nitrate significantly reduces the incidence of post-ERCP pancreatitis when compared with diclofenac alone.

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Table1　Patients characteristics

	Combination group n=444	Diclofenac alone group n=442
Age, year, median (range)	68(59-76)	68(59-76)
Sex, male, n (%)	286 (64.4)	286 (64.7)
Indication, n (%)		
Biliary disease	372 (83.8)	376 (85.1)
Choledocholithiasis	229 (51.6)	238 (53.9)
Suspected for SOD	3 (0.7)	0 (0)
Other benign biliary disease	49 (11.0)	52 (11.8)
Malignant biliary disease	91 (20.5)	86 (19.5)
Pancreatic disease	72 (16.2)	66 (14.9)
PDAC	31 (7.0)	20 (4.5)
IPMN	18 (4.1)	25 (5.7)
Other pancreatic disease	23 (5.2)	21 (4.8)
History of recurrent pancreatitis, n (%)	6 (1.4)	5 (1.1)
Previous history of post-ERCP pancreatitis, n (%)	1 (0.2)	1 (0.2)

SOD, sphincter of Oddi dysfunction; PDAC, pancreatic ductal adenocarcinoma, IPMN, intraductal papillary mucinous neoplasm; ERCP, endoscopic retrograde cholangiopancreatography

Table2 Procedure-related parameters

	Combination group n=444	Diclofenac alone group n=442	P-value
Parameters related to cannulation			
Main target duct, n (%)			0.85
Common bile duct	374 (84.2)	375 (84.8)	
Pancreatic duct	70 (15.8)	67 (15.2)	
Success rate of selective cannulation, n (%)	438 (98.7)	431 (97.5)	0.23
Common bile duct	368/374 (98.4)	364/375 (97.1)	0.33
Pancreatic duct	70/70 (100)	67/67 (100)	0
Precut sphincterotomy, n (%)	20 (4.5)	15 (3.4)	0.49
Endoscopic pancreatic sphincterotomy, n (%)	14 (3.2)	12 (2.7)	0.84
Time for selective cannulation, min (range)	5 (2-11)	5 (2-11)	0.84
Difficult cannulation, n (%) *	142 (32.0)	139 (31.4)	0.89
Presence of juxtapapilla diverticulum, n (%)	122 (27.6)	99 (22.5)	0.09
Parameters related to biliary procedures			
Endoscopic biliary sphincterotomy, n (%)	277 (62.4)	278 (62.9)	0.89
Common bile duct-intraductal ultrasonography, n (%)	103 (23.2)	93 (21.0)	0.44
Common bile duct-tissue sampling, n (%)	52 (11.7)	59 (13.4)	0.48
Endoscopic biliary drainage without endoscopic sphincterotomy, n (%) †	48 (10.8)	41 (9.3)	0.50
Endoscopic papillary balloon dilation of intact biliary sphincter, n (%)	21 (4.7)	18 (4.1)	0.74
Parameters related to pancreatic duct procedures			
Pancreatic injection, n (%)	215 (48.4)	228 (51.6)	0.38
Placement of pancreatic duct stent, n (%)	70 (15.8)	66 (14.9)	0.78
Pancreatic duct-intraductal ultrasonography, n (%)	10 (2.3)	15 (3.4)	0.32
Pancreatic duct-tissue sampling, n (%)	7 (1.6)	4 (1.0)	0.55
Others			
ERCP procedure time, min (range)	28 (18-47)	30 (19-46)	0.40
Concomitant EUS/FNA, n (%)	72 (16.2)	87 (19.7)	0.19

*: Difficult cannulation is defined as cases where more than 10 minutes elapse before successful selective cannulation, or those with failed cannulation to the target duct.

†: Endoscopic biliary drainage without endoscopic sphincterotomy is defined as the deployment of plastic or metallic stents to the bile duct without biliary sphincterotomy.

ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound;　FNA, fine needle aspiration

Table3 The incidence of post-ERCP pancreatitis and other adverse events

	Combination group n=444	Diclofenac alone group n=442	P-value	Relative risk	95%CI
Post-ERCP pancreatitis in all patients, n (%)	25 (5.6)	42 (9.5)	0.03	0.59	0.37-0.95
Mild	21 (4.7)	32 (7.2)	0.12	0.65	0.38-1.11
Moderate	4 (0.9)	10 (2.3)	0.12	0.40	0.13-1.26
Severe	0 (0)	0 (0)			
Post-ERCP pancreatitis in patients with no risk factor	1/155 (0.7)	3/142 (2.1)	0.27	0.31	0.03–2.90
Post-ERCP pancreatitis in patients with risk factor	24/288 (8.3)	39/301 (13.0)	0.08	0.64	0.39–1.03
Post-ERCP pancreatitis in patients with 1 risk factor	7/163(4.3%)	16/167(9.6%)	0.08	0.45	0.19-1.06
Post-ERCP pancreatitis in patients with 2 risk factors	11/93(11.8%)	16/103(15.5%)	0.54	0.76	0.37-1.56
Post-ERCP pancreatitis in patients with more than 2 risk factors	6/33 (18.2)	7/30 (23.3)	0.76	0.78	0.29–2.06
Adverse events related to ERCP					
Bleeding, n (%)	2 (0.5)	0 (0)	0.50	N/A	
Mild	0	0			
Moderate	2	0			
Perforation, n (%)	1 (0.2)	2 (0.5)	0.62	0.50	0.05-5.47
Moderate	1	1			
Severe	0	1			
Biliary infection, n (%)	3 (0.7)	2 (0.5)	1.0	1.49	0.25-8.89
Mild	1	1			
Moderate	2	1			
Adverse events other than the ERCP-related					
Hypotension, n (%)	35 (7.9)	13 (2.9)	0.002	2.69	1.44-5.01
Headache, n (%)	1 (0.2)	0 (0)	1.0	N/A	
Drug allargic reaction, n (%)	2 (0.5)	0 (0)	0.50	N/A	
Pulmonary infarction, n (%)	0 (0)	1 (0.2)	0.50		

ERCP, endoscopic retrograde cholangiopancreatography; CI, confidence interval; N/A, not available

Figure legends

Figure 1: Patient flow diagram showing the combined use of rectal diclofenac with sublingual isosorbide dinitrate vs. diclofenac alone for the prevention of post-ERCP pancreatitis.

ECOG PS, Eastern Cooperative Oncology Group Performance Status; NSAIDs, non-steroidal anti-inflammatory drugs; ERCP, endoscopic retrograde cholangiopancreatography. AE, adverse event