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Clinical Study Protocol

A Multicenter, Prospective, Randomized Controlled Trial Evaluating the Efficacy of Rectal Diclofenac and Sublingual Nitroglycerin as a Combined Prophylactic Treatment for Post-ERCP Pancreatitis

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Acute pancreatitis is the major complication of endoscopic retrograde cholangiopancreatography (ERCP). A preliminary research suggested that the administration of nonsteroidal anti-inflammatory drugs (NSAIDs) with nitroglycerin might reduce the incidence of post-ERCP pancreatitis (PEP) more effectively than NSAIDs alone. We conduct a two-arm, multicenter, prospective, randomized, superiority trial to evaluate the additional effect of nitroglycerin for prevention of PEP. A total of 900 patients randomly receive 50 mg diclofenac suppository either alone or with 5 mg isosorbide dinitrate sublingual tablet. The primary endpoint is the occurrence of PEP. This study will clarify whether NSAIDs plus nitroglycerin can prevent PEP.

Key words: post-ERCP pancreatitis, NSAIDs, nitroglycerin

Acute pancreatitis is the most important complication 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 involve the development of severe pancreatitis, which requires further intervention and leads to death in 0.3-0.6% of the patients [3-6].

Numerous pharmacological procedures have been evaluated for the prevention of PEP. Several randomized trials including a high-profile multicenter study have confirmed the efficacy of rectal nonsteroidal anti-inflammatory drugs (NSAIDs) in preventing PEP [7-10]. Therefore, routine rectal administration of diclofenac or indomethacin, immediately before or after ERCP is recommended to minimize the risk for PEP [11]. Moreover, in two randomized controlled trials (RCTs), positive results were obtained by administering sublingual nitroglycerin to prevent PEP [12,13]. Nitroglycerin is a smooth-muscle relaxant, which may lower the sphincter of Oddi pressure and increase pancreatic parenchymal blood flow [14].

Recently, it was demonstrated in an RCT that a combination of sublingual nitroglycerin and a rectal NSAIDs was more effective than only NSAIDs for preventing PEP [15]. The study showed that the relative risk for PEP was reduced by 56.2% with the treatment, which is simple, inexpensive, and well tolerated. Although the trial showed efficacy of the

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combination therapy for preventing PEP, the trial was a single-center study with small sample size. Therefore, we conduct a multicenter, prospective, randomized controlled trial to evaluate the efficacy of a combination of rectal NSAIDs and sublingual nitroglycerin for preventing PEP.

Methods

Study design. The study is a two-arm, multicenter, prospective, randomized, superiority trial to evaluate the additional effect of nitroglycerin with diclofenac for prevention of PEP, and compare it with that of diclofenac alone. The study is conducted at the Okayama University Hospital and 11 other hospitals affiliated to the Okayama University. A total of 900 eligible patients are randomly assigned to receive 50 mg diclofenac suppository either alone or with 5 mg isosorbide dinitrate sublingual tablet. The sublingual tablets are administered 5 min before ERCP and the diclofenac suppositories are administered in 15 min after ERCP (Fig. 1).

Ethical consideration

The study protocol is approved by the institutional review board of each participating institution before the study is initiated (no. m02027). This trial is registered with the University hospital Medical Information Network Clinical Trial Registry (no. UMIN000016274).

Endopoints

Primary and secondary endpoints. The primary endpoint is the occurrence of PEP. PEP is defined by the criteria set by Cotton *et al.* [16], 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 ERCP. Serum amylase level is measured before ERCP and at any time when the patient complains of abdominal pain within 24 h after ERCP; otherwise, it is routinely measured 24 h after ERCP. Secondary endpoints include the development of moderate or severe PEP, the frequency of PEP in patients with risk factors for PEP, risk factors for PEP in this study, and adverse effects related to the study drugs. The severity of PEP is graded according to the duration of fasting period after the ERCP. Mild PEP required 2–3 days; moderate PEP required 4–10 days; and severe PEP required more than 10 days, necessitating a surgical or intensive treatment, or resulting in death. The following procedures are considered high-risk for PEP: (1) precut sphincterotomy (a procedure performed to facilitate biliary access when standard cannulation techniques are unsuccessful), (2) endoscopic pancreatic sphincterotomy (EPST), (3) endoscopic papillary balloon dilation (EPBD) without endoscopic sphincterotomy (EST), (4) difficult cannulation (more than 10 min elapsed for successful cannulation, (5) failed cannulation, (6) injection of contrast agent into the pancreatic duct, (7) female sex and age $<$ 60 years, (8) clinical suspicion of sphincter of Oddi dysfunction (SOD), (9) history of recurrent pancreatitis, and (10) history of PEP (11,17). The patients- and procedure-related factors are recorded at the end of procedures and risk factors for PEP are evaluated. Patient-related factors include following: (1) age, (2) sex, (3) presence of parapapillary diverticulum, and (4) indication of ERCP. Procedure-related factors include following: (1) pancreatography, (2) pancreatic acinarization on radiography, (3) EPST, (4) precut sphincterotomy, (5) EST, (6) EPBD without EST, (7) endoscopic biliary drainage without EST, (8) pancreatic duct stenting, (9) pancreatic duct-intraductal ultrasonography, (10) common bile duct-intraductal ultrasonography, (11) common bile duct tissue sampling; cytology and brush, (12) pancreatic duct tissue sampling; cytology and brush, (13) time of cannulation, and (14) total time of procedure.

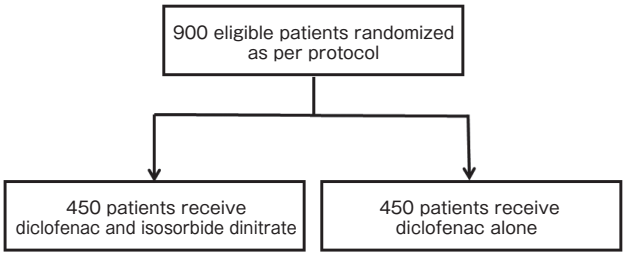

Fig. 1 Flow diagram of rectal diclofenac and sublingual isosorbide dinitrate versus diclofenac alone for the prevention of post-ERCP pancreatitis.

Eligibility Criteria

All of the patients who meet the inclusion criteria and exclusion criteria, which are listed in Table 1, are enrolled in this study from March 2015 to February 2018.

Randomization

After confirming fulfillment of the eligibility criteria, registration to the Data Center is conducted by a web-based system. Patients are then randomly assigned to receive a 50 mg diclofenac suppository, either alone or in combination with a 5 mg isosorbide dinitrate sublingual tablet by a minimization method balancing the arms with institution, age, sex, and primary disease (hepatibiliary disease vs. pancreatic disease).

Treatment Methods

Intervention. Before the endoscopy, the history of each patient is recorded and a physical examination is performed. Pharyngeal anesthesia is induced with a topical anesthetic, whereas conscious sedation is induced with an intravenous medication. We administer 20 ml of ulinastatin (150,000 U) solution, a proteolytic enzyme solution, by intravenous infusion immediately after the ERCP. The ERCP devices used are not limited to any specific types. A contrast agent is injected prior to the procedures, as is the custom in Japan. In cases in which it is difficult to cannulate, we perform pancreatic guidewire placement or precut sphincterotomy to achieve selective cannulation. Pancreatic duct stenting is performed to prevent pancreatitis at the endoscopist's discretion. After the procedures, the endoscopists record the results and patients fasted until blood tests performed the following day confirmed the absence of pancreatitis or other complications. All patients are hospitalized for the ERCP procedure and observation.

Adverse effects. Adverse effects of the study drugs are monitored during their hospital stay. Adverse effects of diclofenac, including gastrointestinal bleeding and renal failure, and adverse effects of nitrates, including headache, dizziness, and reduction in systolic blood pressure are monitored. Other post-ERCP adverse events, including cholangitis, bleeding, and perforation are monitored in addition to PEP.

Table 1 Inclusion and exclusion criteria of the study

Inclusion criteria
Patients who are scheduled to undergo ERCP
Patients who can provide written informed consent
Exclusion criteria
Performance status of 4
Younger than 20 years,
Body weight less than 50 kg
Duodenal papilla not accessible endoscopically
History of EST or EPBD
Presence of acute pancreatitis
Presence of chronic pancreatitis
Presence of pancreatic head cancer with occlusion of the MPD
Contraindication to NSAIDs or nitroglycerin
Cases of post gastrectomy
Creatinine level, $>$ 1.4 mg per deciliter
Presence of active peptic ulcer disease
Presence of closed angle glaucoma
Presence of aspirin-induced asthma
Currently taking nitroglycerin
Inability to provide written informed consent
Subjects deemed inappropriate for the trial

ERCP, endoscopic retrograde cholangiopancreatography; EST, endoscopic sphincterotomy; EPBD, endoscopic papillary balloon dilation; MPD, main pancreatic duct; NSAIDs, nonsteroidal anti-inflammatory drugs.

Statistic Consideration

Sample size. Previous data from a meta-analysis conducted by Puig *et al.* [18] indicated that prophylactic administration of rectal NSAIDs reduced the incidence of PEP from 14.5% to 7.4%, and the relative risk reduction was 50.7%. Sotoudehmanesh *et al.* [15] also reported that combining rectal NSAIDs with sublingual nitroglycerin reduced the incidence of PEP from 15.3% to 6.7%, compared with NSAIDs alone, and the relative risk reduction was 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 data obtained in the previous 5 years from our institutions). We estimated that 892 patients (446 per study group) would provide a power of at least 80% to detect a 56.2% reduction in the incidence of PEP, from 7.4% (in the group administered only diclofenac) to 3.2% (in group administered the combined treatment), by Fisher's exact test with a two-sided significance level of 0.05.

Statistical analysis. Statistical analysis is performed on the basis of intention-to-treat analysis. The Wilcoxon rank sum test is performed to compare the continuous data and the chi-square test is performed to evaluate non-continuous variables. A p-value <0.05 is considered significant. Initial univariate evaluations are made for each potential risk factor by the chi-square test. Only the significant factors from the chi-square analysis are included in multivariate analyses. All statistical analyses are performed using JMP 9 (SAS Institute Inc., Cary, NC, USA). The ranges of continuous values are shown as interquartile ranges.

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