

Efficacy and safety of aggressive hydration for preventing post-endoscopic retrograde cholangiopancreatography pancreatitis: study protocol for a phase 3, multicenter, open-label, randomized controlled study

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Study protocol

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Abstract

Background

Endoscopic retrograde cholangiopancreatography (ERCP), a procedure to treat pancreaticobiliary disorders, is generally safe. However, adverse events (AEs) of post-ERCP pancreatitis (PEP) can occur, which can be fatal. Physicians performing ERCP can take measures to prevent PEP, including endoscopic pancreatic duct stents and pharmacological prophylaxis. Periprocedural aggressive hydration has been investigated for its potential for reducing PEP risk. This study aims to evaluate the efficacy and safety of periprocedural aggressive hydration plus intrarectal diclofenac versus standard hydration therapy plus intrarectal diclofenac in preventing PEP onset in Japanese patients.

Methods

This phase 3, multicenter, open-label, randomized controlled study is being conducted at an anticipated 27 sites in Japan. The study plans to enroll 780 adults (aged ≥ 18 years) who are scheduled to receive an ERCP procedure. Patients will be randomized 1:1 to the aggressive hydration or standard hydration group. Approximately 8 h prior to the ERCP procedure, patients in both groups will be administered the main infusion (≤ 1.5 mL/kg/h). The aggressive hydration group will receive a bolus of 500 mL Ringer's solution at the start of the ERCP procedure (500 mL/h) followed by Ringer's solution administered at 3mL/kg/h for 8 h. The standard hydration group will be administered Ringer's solution at 1.5 mL/kg/h initiated at the start of the ERCP procedure and continuing for 9 h. Within 30 min of completing the ERCP procedure, patients in both groups will receive intrarectal diclofenac sodium (standard, 50 mg; patients weighing < 50 kg or aged ≥ 80 years, 25 mg). The primary endpoint is the incidence of PEP (serum amylase ≥ 400 U/I after ERCP completion and persistent abdominal pain for ≥ 24 h). Secondary endpoints include the incidence of PEP by severity, the incidence of hyperamylasemia (increase in amylase ≥ 400 U/I), and the incidence of infusion-related AEs. AEs will be monitored throughout the study.

Discussion

This study aims to clarify whether aggressive hydration reduces PEP incidence versus standard hydration, and to compare PEP incidence by severity, and the incidence of hyperamylasemia and infusion-related AEs. Safety will be determined in both groups.

Trial registration:

Japan Registry of Clinical Trials (jRCT: s041230145; registered February 6, 2024; <https://jrct.mhlw.go.jp/latest-detail/jRCTs041230145>)

Administrative Information

Note: the numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers. The order of the items has been modified to group similar items (see <http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/>).

Title {1}	Efficacy and safety of aggressive hydration for preventing post-endoscopic retrograde cholangiopancreatography pancreatitis: study protocol for a phase 3, multicenter, open-label, randomized controlled study
Trial registration {2a and 2b}.	Japan Registry of Clinical Trials (jRCT: s041230145; registered February 6, 2024; https://jrct.mhlw.go.jp/latest-detail/jRCTs041230145)
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Name and contact information for the trial sponsor {5b}

Mie University Hospital Special Clinical Research Incentive Fund Operational Grants from the Department of Gastroenterology and Hepatology, Mie University Hospital

Role of sponsor {5c}

The sponsor is responsible for the overall design, management, and conduct of the study.
Mie University Hospital oversees study coordination, data management, and quality assurance.
The sponsor will have no role in patient recruitment or data analysis and will not influence the interpretation of study results.

Introduction

Background and rationale {6a}

Endoscopic retrograde cholangiopancreatography (ERCP) is an important procedure that is mainly used to treat pancreaticobiliary disorders [1]. Although the procedure is considered generally safe, several adverse events (AEs) are associated with ERCP, including post-ERCP pancreatitis (PEP), bleeding, cholangitis, cholecystitis, and perforation [2]. Among these, PEP is the most common. A meta-analysis of randomized controlled trials reported that PEP occurs at a cumulative incidence of 10.2% overall, with 0.5% of patients experiencing severe PEP and 0.2% of patients experiencing fatal PEP [3].

There are several measures that clinicians can use to prevent PEP. For example, endoscopic pancreatic duct stents have been shown to reduce the incidence of PEP in high-risk patients [4]. As such, Japanese, European, and American guidelines recommend pancreatic duct stents for patients at high risk of PEP [5–7]. Of note, the non-therapeutic use of pancreatic duct stents is not reimbursed by the national insurance system in Japan. Pharmacological prophylaxis for PEP is also available. Randomized clinical trials have demonstrated that rectal administration of nonsteroidal anti-inflammatory drugs (NSAIDs) either immediately before or after ERCP significantly lowers the incidence of PEP [8, 9], and guidelines support routine prophylactic rectal administration of NSAIDs for patients undergoing ERCP [5–7].

Periprocedural aggressive hydration is a measure that has been gaining attention for its potential to reduce the risk of PEP. Both a pilot study (N = 62) and a randomized, double-blind study (N = 150) that used the same protocol for aggressive hydration (intravenous [IV] lactated Ringer's solution 3 mL/kg/h during the procedure, IV bolus 20 mL/kg immediately after the procedure, IV 3 mL/kg/h for 8 h after the procedure) found that this method significantly reduced the incidence of PEP compared with standard hydration [10, 11]. A meta-analysis of randomized controlled trials found that periprocedural aggressive hydration reduced the incidence of PEP by 56% compared with standard hydration (5.1% vs 11.1%; odds ratio 0.44; $p = 0.0004$), with no significant difference in the incidence of fluid overload-related AEs between the two approaches [12]. Although this is promising, a standard protocol for aggressive hydration has yet to be established. The Department of Gastroenterology and Hepatology at Mei University Hospital in Japan conducted a single-arm study, RESOLUTION-PEP, in 231 patients to evaluate the efficacy and safety of aggressive hydration with lactated Ringer's solution combined with intrarectal diclofenac sodium (diclofenac) for PEP prevention [13]. The study used an IV bolus administration of lactated Ringer's solution (5 mL/kg) at the start of the ERCP procedure, with a continuous IV infusion of 3 mL/kg/h for 8 h after the procedure. The PEP incidence rate was 5.6%, which was similar to that reported in the meta-analysis (5.1%) [12]. No severe AEs due to aggressive hydration were reported.

Objectives {7}

This randomized, controlled study is being conducted to further evaluate the efficacy and safety of periprocedural aggressive hydration plus intrarectal diclofenac versus standard hydration plus intrarectal

diclofenac in preventing the onset of PEP in Japanese patients.

Trial design {8}

This is a phase 3, multicenter, open-label, randomized (1:1) controlled study (**Fig. 1**).

Methods: Participants, interventions, and outcomes

Study setting {9}

The study is being conducted in Japan between 6 February 2024 and 31 March 2028 and is expected to include 27 study sites (**Table 1**) and 780 patients.

[Place Table 1 here]

Eligibility criteria {10}

This study will include patients aged ≥ 18 years who are scheduled to receive an ERCP procedure. Patients with any of the following will be excluded from the study: previous ERCP with a history of papillary procedures, reduced cardiac function (New York Heart Association grade ≥ 2 cardiac function, left ventricular ejection fraction $< 40\%$, or a serum brain natriuretic peptide [BNP] ≥ 100 pg/mL or serum N-terminal pro-BNP ≥ 400 pg/mL), reduced renal function (estimated glomerular filtration rate < 60 mL/min/1.73m²), respiratory failure (peripheral oxygen saturation $< 90\%$ in room air), concomitant pancreatitis, suspected dehydration or shock, hyponatremia (serum sodium > 147 mEq/L), Eastern Cooperative Oncology Group performance status ≥ 3 , a colostomy rendering it impossible to rectally administer diclofenac, contraindications to diclofenac, history of allergy to iodine contrast media, postoperative reconstructed intestinal tract, organic stenosis of the gastrointestinal tract that makes papillary access impossible, scheduled from the outset to undergo transpapillary cannulation of the bile duct or pancreatic duct via percutaneous transhepatic biliary drainage-assisted rendezvous or endoscopic ultrasonography-guided rendezvous, or who are pregnant or may become pregnant.

Who will take informed consent? {26a}

Potential study participants will be given a thorough explanation of the study in writing and orally by the principal investigator or an assistant investigator, and written informed consent will be obtained.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

Not applicable. There is no collection of data or biological specimens for ancillary studies.

Interventions

Explanation for the choice of comparators {6b}

Normal hydration was selected as the comparator because it reflects the current standard clinical practice during ERCP procedures. At present, patients undergoing ERCP typically receive routine intravenous hydration, and this approach is widely accepted as the standard of care. Therefore, comparing the

loading infusion strategy against normal hydration will allow us to evaluate the additional benefit of fluid loading over the established standard treatment.

Intervention description {11a}

The infusion protocol for each group is described below and the study observation schedule is shown in **Table 2**. For both groups, during the 8 h prior to the ERCP procedure, the main infusion will be administered at a rate of ≤ 1.5 mL/kg/h. Side-tube infusions may be administered with a total volume of ≤ 100 mL up to two times, separately from the main infusion. Patients in the aggressive hydration group will receive a bolus of 500 mL Ringer's solution (adjusted to 10 mL/kg for patients weighing < 50 kg) at the start of the ERCP procedure. The infusion will be administered at 500 mL/h using an infusion pump, and the bolus will be terminated after 1 h even if the entire volume has not been administered. At the end of the bolus administration, patients will receive Ringer's solution at 3 mL/kg/h for 8 h. Patients in the standard hydration group will receive Ringer's solution at 1.5 mL/kg/h, which will be initiated at the start of the ERCP procedure and continued for 9 h. Within 30 min of completing the ERCP procedure, patients in both groups will receive intrarectal diclofenac 50 mg (adjusted to 25 mg for patients weighing < 50 kg or aged ≥ 80 years). Additionally, at the conclusion of the infusion specified for each treatment group, until the blood test for determining the onset of PEP is performed (when blood sampling is conducted 9–24 h after ERCP), any ongoing infusion, if administered, will be given at a rate not exceeding 1.5 mL/kg/h for the main infusion, regardless of the type of fluid. Side-tube infusions may be administered with a total volume of ≤ 100 mL up to three times, separately from the main infusion. Patients should undergo the ERCP procedure within 14 days of enrollment in the study.

[Place Table 2 here]

Criteria for discontinuing or modifying allocated interventions {11b}

During the treatment period, a change in the infusion load will be implemented if considered necessary due to the onset of acute pancreatitis, hypotension (systolic blood pressure < 90 mmHg) or insufficient circulating plasma volume, hypertension (systolic blood pressure > 180 mmHg) or excessive circulating plasma volume, or in the case of serum electrolyte values outside of the normal range (normal range: sodium 135–147 mEq/L; potassium 3.6–5.0 mEq/L; chloride 98–108 mEq/L; calcium 8.8–10.2 mg/dL).

Strategies to improve adherence to interventions {11c}

Adherence to the intervention will be ensured by verifying the residual volume after each infusion to confirm whether the prescribed volume has been fully administered.

Relevant concomitant care permitted or prohibited during the trial {11d}

Temporary pancreatic ductal stenting for PEP prophylaxis should not be performed unless one or more of the following are true: suspected or confirmed papillary insufficiency, history of post-ERCP pancreatitis or acute pancreatitis, difficulty in cannulation, pancreatic duct insertion or pancreatic duct angiography, pre-cut sphincterotomy of the major duodenal papilla during ERCP, pancreatic duct stent placement before or during endoscopic papillary resection, or when the purpose of the ERCP is pancreatic duct stenting. The following concomitant medications are prohibited: protease inhibitors, nitrates, and nafamostat mesylate.

Provisions for post-trial care {30}

No post-treatment is specified.

Outcomes {12}

The primary endpoint is the incidence of PEP, defined as serum amylase ≥ 400 U/l after the completion of the ERCP (whether or not the patient had an elevated level prior to ERCP) and persistent abdominal pain (≥ 24 h) according to the criteria of the American Society for Gastrointestinal Endoscopy (ASGE) [14], with the blood sampling timing modified to facilitate blood sampling in real-world clinical practice ($16 \text{ h} \pm 8 \text{ h}$ after ERCP completion). Abdominal pain is defined as the occurrence of epigastric pain with a score of ≥ 3 on an integer visual analogue scale (VAS; 0–10) within 48 h after the start of ERCP, or an increase of ≥ 3 points compared with the pre-ERCP score, which persists for at least 24 h.

The secondary endpoints are the incidence of PEP by severity, the incidence of hyperamylasemia (increase in amylase ≥ 400 U/l), and the incidence of infusion-related AEs. The severity of PEP will be assessed using the 2012 Atlanta Classification [15]. AEs will be monitored throughout the study and will be classified per the Japanese translation of the Common Terminology Criteria for Adverse Events version 5.0 (Japan Clinical Oncology Group Shared Criteria Scope) [16].

Participant timeline {13}

Table 2 provides procedures at each timepoint.

Sample size {14}

The sample size was calculated as follows. Under the assumption that the incidence of PEP in the aggressive hydration group and the standard hydration group will be the same as reported in a 2019 meta-analysis (5.1% and 11.1%, respectively) [12], and assuming a two-sided α significance level of 0.05

and a power of $1-\beta = 0.8$, the number of patients required to detect a significant difference between the two groups was 714 total, with 357 patients in each group. Considering that some patients will be ineligible, withdraw from the study, or be lost to follow-up, the expected number of enrolled patients was set at 780.

Recruitment {15}

Eligible patients scheduled for ERCP will be identified during outpatient visits or upon hospital admission, and will be approached for study participation after providing informed consent.

Assignment of interventions: allocation

Sequence generation {16a}

The Nagoya University Registration and Randomization System will be employed to perform randomization using a minimization method with the following stratification factors to ensure balance between the treatment groups: age (< 50 years, ≥ 50 years), sex (male, female), purpose of ERCP (with or without the intent of pancreatic duct cannulation), and study site.

Concealment mechanism {16b}

The allocation will not be concealed, as this is an open-label study. The details of the random assignment procedure will not be made available to the principal investigator or assistant investigators.

Implementation {16c}

Patients will be registered by physicians at each participating study site using the Nagoya University Registration and Randomization System, which will randomly allocate patients 1:1 to the aggressive hydration group or standard hydration group. The randomization process will be independently monitored and overseen by the Mei University Data Center.

Assignment of interventions: Blinding

Who will be blinded {17a}

No blinding will be performed.

Procedure for unblinding if needed {17b}

Not applicable. This was an open-label study.

Data collection and management

Plans for assessment and collection of outcomes {18a}

During the observation period, patients will be monitored for the presence and severity of PEP, post-ERCP AEs other than PEP (hyperamylasemia, acute cholangitis, gastrointestinal bleeding, and gastrointestinal

perforation according to the ASGE) [14], and infusion-related AEs (cerebral edema, respiratory failure, peripheral edema, and hyponatremia). Data collection will be performed using electronic case report forms (eCRF) implemented in the study's electronic data capture (EDC) system, which is managed by the Mie University Data Center.

Plans to promote participant retention and complete follow-up {18b}

This study will be completed within the index hospitalization, and all outcomes will be assessed until discharge. Therefore, no long-term follow-up is required. For patients who discontinue or deviate from the intervention protocol, outcome data including the occurrence and severity of PEP, post-ERCP AEs, and infusion-related AEs will still be collected until discharge to ensure completeness of outcome assessment.

Data management {19}

All study data will be entered directly into eCRFs within the EDC system. Data entry will be performed by the investigators or designated research staff at each participating site. The EDC system incorporates automatic range and consistency checks to minimize entry errors and ensure data quality. Additional data validation and query management will be conducted by the Mie University Data Center, which is responsible for overseeing data management. Detailed procedures for data handling and quality control are described in the data management standard operating procedures maintained by the Mie University Data Center.

Confidentiality {27}

The principal investigator will be responsible for data management. Paper information other than medical records will be stored in lockable cabinets at each study site. Electronic data will be stored on personal computers, password protected, and stored in a lockable cabinet at each study site. Information will be stored for at least five years from the date of study completion and will be disposed of in a way that prevents identification of specific individuals.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

Blood samples will be disposed of in the usual manner after the laboratory measurements have been obtained.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

The primary and secondary endpoints will be analyzed using the full analysis set, which will comprise all patients who underwent ERCP and for whom the primary endpoint can be evaluated. Categorical variables will be summarized using frequency and proportion and continuous variables will be summarized using descriptive statistics. Fisher's exact test will be used to compare the primary, secondary, and safety outcomes between the two treatment groups. A two-sided significance level of 5% will be used. The statistical analyses will be conducted according to the statistical methods outlined in the study protocol. The full statistical methods are provided in **Additional file 1**.

Interim analyses {21b}

No interim analysis is planned.

Methods for additional analyses (e.g. subgroup analyses) {20b}

Not applicable. No subgroup analysis will be performed in this study.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

Patients with missing data related to determining the primary or secondary endpoints will be excluded from the analysis. Missing AE data will be entered as "unspecified".

Plans to give access to the full protocol, participant-level data and statistical code {31c}

The full study protocol will be made available upon reasonable request to the corresponding author. Participant-level data and statistical code will not be shared owing to privacy and institutional restrictions.

Oversight and monitoring

Composition of the coordinating center and trial steering committee {5d}

The coordinating center for this trial is the Mie University Data Center, which is responsible for patient registration, data management, and overall coordination of the study. Day-to-day operational support, including patient enrollment, completion of case report forms, and data entry, will be carried out by physicians and research staff at each participating site under the supervision of the coordinating center. Although no independent trial steering committee has been established, oversight of study conduct and data integrity will be ensured by the coordinating center. In the event of any serious issues or concerns

regarding study conduct, an independent audit will be arranged in accordance with institutional and regulatory requirements.

Composition of the data monitoring committee, its role and reporting structure {21a}

The Data Monitoring Committee will consist of persons not directly involved in the conduct of the trial. The committee will monitor the study to ensure that it is being conducted safely, in compliance with the study protocol, and that data are collected accurately. An independent Efficacy and Safety Assessment Committee will periodically review safety and efficacy information during the study and will make recommendations to the principal investigator regarding the continuation, modification, or discontinuation of the study. The committee is independent from the sponsor and has no competing interests.

Adverse event reporting and harms {22}

All serious AEs will be immediately reported to the principal investigator, who will then notify the drug provider and report to the Efficacy and Safety Evaluation Committee as necessary.

Frequency and plans for auditing trial conduct {23}

If a serious violation of relevant laws or regulations, or deviation from the study protocol is identified during monitoring, an audit will be conducted.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

Any modifications to the protocol that may impact the conduct, safety, design, population, or procedures of the study will require a formal modification to the protocol. Any modification must be approved by the relevant authorities before being implemented in the study.

Dissemination plans {31a}

The trial results will be disseminated through presentations at national and international scientific meetings and publication in peer-reviewed journals. Summaries of the study results will also be provided to the participating investigators. There are no restrictions on publication, and results will be reported in accordance with applicable guidelines for clinical trial registration and reporting.

Discussion

This study aims to address whether the use of aggressive hydration reduces the incidence of PEP compared with standard hydration. The study also aims to compare the incidence of PEP by severity, the

incidence of hyperamylasemia, and the incidence of infusion-related AEs between patients who receive aggressive hydration versus standard hydration. The study will also determine overall safety in both groups. At the end of the study, the study data will be presented at conferences and/or journal articles.

The study is expected to determine whether aggressive hydration plus intrarectal diclofenac effectively and safely reduces the incidence of PEP. PEP is the most common and serious AE of ERCP [2]. Thus, it is of interest to evaluate prophylactic and perioperative interventions to reduce the incidence of PEP. A meta-analysis supports a reduced incidence of PEP when patients receive aggressive hydration versus standard hydration in randomized controlled trials [12]. This multicenter study is expected to provide further evidence regarding the efficacy and safety of perioperative aggressive hydration in Japanese patients. A major strength of this study is its broad participation of both university and community hospitals across Japan, which enhances the generalizability of the findings. Randomization will be performed using a minimization method with stratification by age, sex, purpose of ERCP (pancreatic duct cannulation or not), and study site to minimize imbalance between groups. In addition, several important PEP-related factors have been carefully standardized to reduce potential confounding. Intrarectal diclofenac will be administered to all patients, and the indications for prophylactic pancreatic stent placement are clearly defined to prevent discretionary use. Furthermore, trainee endoscopists will be excluded, ensuring that all procedures are performed by experienced endoscopists. Procedure-related details such as difficulty of cannulation, cannulation time, type of papillary intervention, pancreatic duct injection, modified Schutz classification, and the presence or absence of transpapillary self-expandable metallic stent placement will also be recorded, allowing for detailed subgroup analyses. The study will also document whether the assigned study infusion was completed as per protocol. For the assessment of post-ERCP pain, the VAS will be used to provide an objective and standardized endpoint rather than a subjective evaluation. Taken together, this study has been designed to enable an accurate comparison of the pure effect of aggressive hydration on the incidence of PEP, under rigorously controlled and clearly defined clinical conditions.

Although this multicenter study is being conducted only at study sites in Japan, which may limit the generalizability of the findings to other populations, the participation of diverse institutions across a wide geographic area is expected to mitigate this limitation. In conclusion, this study aims to clarify whether aggressive hydration is effective for reducing the incidence of PEP compared with standard hydration and will evaluate the safety of this intervention.

Trial status

Study Protocol version 1.1 (April 24, 2025) will be used to conduct the trial. Recruitment began on 20 May 2024 and is expected to be completed on 31 March 2028.

Abbreviations

eCRF

Electronic case report form

ERCP
Endoscopic retrograde cholangiopancreatography
AE
Adverse event
PEP
Post-endoscopic retrograde cholangiopancreatography pancreatitis
NSAID
Nonsteroidal anti-inflammatory drug
IV
Intravenous
BNP
Brain natriuretic peptide
jRCT
Japan Registry of Clinical Trials
ASGE
American Society for Gastrointestinal Endoscopy
ECOG PS
Eastern Cooperative Oncology Group performance status
EUS
Endoscopic ultrasonography
ERCP
Endoscopic retrograde cholangiopancreatography
GI
Gastrointestinal
PRBD
Percutaneous transhepatic biliary drainage
EDC
Electronic data capture
NT-proBNP
N-terminal pro-B-type natriuretic peptide
VAS
Visual analogue scale

Declarations

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Authors' contributions {31b}

RY and KN conceived and designed the study. YI provided guidance on the electronic data capture (EDC) system for conducting a multicenter study, and ST advised on the development of the study protocol in compliance with regulatory requirements. All authors contributed to patient enrollment and data collection. KN and TO performed the statistical analysis. RY drafted the manuscript and critically revised it for important intellectual content. All authors contributed to the interpretation of the data and approved the final version of the manuscript.

Funding {4}

This study was supported by Mie University Hospital Specified Clinical Trial Promotion Grant S2023-002. The funding body is responsible for the overall design, management, and conduct of the study and will have no role in patient recruitment or data analysis, and will not influence the interpretation of the study results.

Availability of data and materials {29}

The final trial dataset will be accessible only to the principal investigator and authorized members of the Mie University Data Center responsible for data management. Participating investigators will have access to the data pertaining to their own patients. There are no contractual agreements that limit access to the dataset for investigators beyond these restrictions.

Ethics approval and consent to participate {24}

All patients must provide written informed consent prior to study enrollment, which will be collected by the study investigator or research assistant at each study site. This study will comply with the principles outlined in the Declaration of Helsinki. The study protocol was approved by the Clinical Research Review Board at Mei University Hospital (CRB4180006). The responsible regional bureau of health and welfare was the Takai–Hokuriku Regional Bureau of Health and Welfare. The study was prospectively registered with the Japan Registry of Clinical Trials (jRCT: s041230145; registered February 6, 2024; <https://jrct.mhlw.go.jp/latest-detail/jRCTs041230145>).

Consent for publication {32}

Not applicable, as no patient data are presented in this manuscript.

Competing interests {28}

The authors have no competing interests to declare.

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Tables

Table 1. List of study sites and investigators

Study site	Principal investigator
Jichi Medical University Hospital	Atsushi Kanno
Juntendo Hospital, Juntendo Medical School, Juntendo University	Hiroyuki Isayama
University of Toyama Hospital	Ichiro Yasuda
Gifu University Hospital	Shinya Uemura
Gifu Municipal Hospital	Keisuke Iwata
Gifu Prefectural Tajimi Hospital	Fumihiko Okumura
Gifu Prefectural General Medical Center	Kensaku Yoshida
Hamamatsu University Hospital	Ken Sugimoto
Aichi Medical University	Tadahisa Inoue
Nagoya City University Hospital Graduate School of Medical Sciences	Yasuki Hori
Nagoya City University Eastern Medical Center	Kazuki Hayashi
Fujita Medical College Hospital	Eizaburo Ohno
Fujita Medical College Bantane Hospital	Senju Hashimoto
Fujita Medical College Okazaki Medical Center	Yoshihiko Tachi
Mie University Hospital	Reiko Yamada
Kagawa University Hospital	Hideki Kamada
Kumamoto University Hospital	Motohiro Yoshinari
Kumamoto City Hospital	Shunpei Hashigo
Kuwana City General Medical Center	Yumi Oya
Yokkaichi Hazu Medical Center	Ryohei Sakaguchi
Mie Prefectural General Medical Center	Isao Moritani
Suzuka Kaisei Hospital	Shunsuke Tano
Matsusaka Central General Hospital	Hiroaki Naota
Okanami General Hospital	Hajime Imai
Shizuoka Prefectural General Hospital	Shinya Kawaguchi
Matsunami General Hospital	Mitsuru Okuno
Shiga University Hospital, Shiga University of Medical Science	Takuji Iwashita

Table 2. Study observation schedule

	STUDY PERIOD			
	Enrollment/Allocation		Post-allocation	
	Enrollment	Day before ERCP (Day 1) ^a	Day 2	Day 3 through discharge date
Obtain consent, registration, and allocation	○			
Disease requiring ERCP, pre-existing conditions, antithrombotic medications	○			
Confirmation of PEP risk factors	○			
Self-reported and other symptoms		○	Physical examination findings	Δ
Physical findings	○		○	Δ
Blood and biochemical tests ^b	○		BNP or NT-pro-BNP	Δ
BNP or NT-proBNP	○			
Chest X-ray	Δ		Δ	
Imaging tests	Δ		Δ	
Electrocardiogram	Δ			
Echocardiography	(only when performed to evaluate cardiac function)			
Diclofenac administration		○		
Infusion with therapeutic prescription		○	○	
ERCP		○		
Availability of PEP		○		
AE evaluation		○		
Outcome				○
Length of hospital stay				○

^aThe period from registration to the first ERCP should not exceed 14 days. If pancreatitis or other incidental changes in the patient's condition occur after the ERCP, and the patient is not enrolled in the study treatment period, the ERCP must be performed within 14 days of the initial ERCP. If a change in the main infusion is necessary during the infusion period (up to 9 hours before the start of ERCP for both groups), the study treatment should be stopped immediately, and the infusion should be changed to a clinically appropriate intravenous fluid at the discretion of the treating physician.

^bIf PEP or other AEs occur, blood samples should be collected from day 3 to the day of discharge, and the highest amylase value during that time should be reported.

○ = mandatory (to be collected as part of the EDC).

Δ = items that are not collected in the EDC but should be implemented to ensure safety, or depending on the course of events.

AE, adverse event; BNP, brain natriuretic peptide; EDC, electronic data capture; ERCP, endoscopic retrograde cholangiopancreatography; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PEP, post-ERCP pancreatitis

Figures

Figure 1

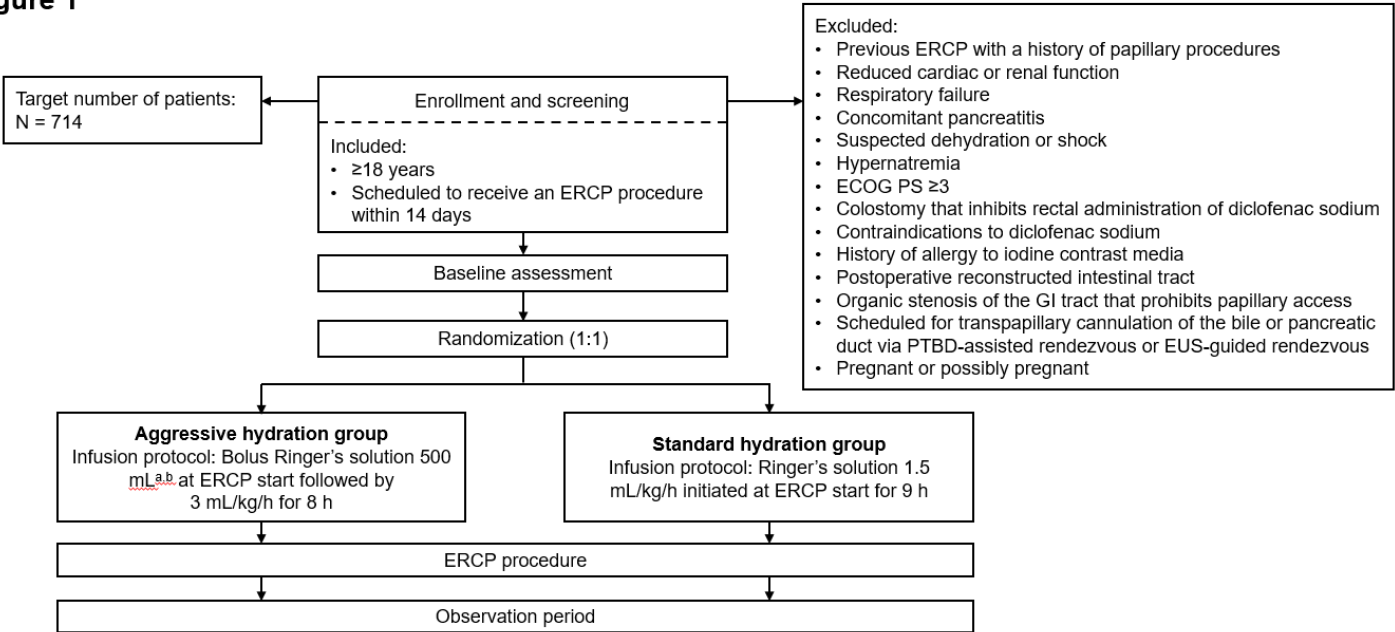


Figure 1

Study flow diagram

^aAdjusted to 10 mL/kg for patients weighing <50 kg.

^bAdministered at 500 mL/h, to be terminated after 1 h even if the entire volume has not been administered.

ECOG PS, Eastern Cooperative Oncology Group performance status; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasonography; GI, gastrointestinal; PRBD, percutaneous transhepatic biliary drainage

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