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Effect of endoscopic transpapillary biliary drainage with/without endoscopic sphincterotomy on post-endoscopic retrograde cholangiopancreatography pancreatitis in patients with biliary stricture (E-BEST): a protocol for a multicentre randomised controlled trial

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ABSTRACT

Introduction The effect of endoscopic sphincterotomy prior to endoscopic biliary stenting to prevent post-endoscopic retrograde cholangiopancreatography pancreatitis remains to be fully elucidated. The aim of this study is to prospectively evaluate the non-inferiority of non-endoscopic sphincterotomy prior to stenting for naïve major duodenal papilla compared with endoscopic sphincterotomy prior to stenting in patients with biliary stricture.

Methods and analysis We designed a multicentre randomised controlled trial, for which we will recruit 370 patients with biliary stricture requiring endoscopic biliary stenting from 26 high-volume institutions in Japan. Patients will be randomly allocated to the endoscopic sphincterotomy group or the non-endoscopic sphincterotomy group. The main outcome measure is the incidence of pancreatitis within 2 days of initial transpapillary biliary drainage. Data will be analysed on completion of the study. We will calculate the 95% **confidence intervals** (CIs) of the incidence of pancreatitis in each group and analyse weather the difference in both groups with 95% CIs is within the non-inferiority margin (6%) using the Wald method.

Ethics and dissemination This study has been approved by the institutional review board of Hokkaido University Hospital (IRB: 016–0181). Results will be submitted for presentation at an international medical conference and published in a peer-reviewed journal.

Trial registration number The University Hospital Medical Information Network ID: UMIN000025727 Pre-results.

Strengths and limitations of this study

- The first prospective study to confirm the non-inferiority of non-endoscopic sphincterotomy before insertion of a biliary stent in patients with biliary stricture that include not only cases with distal BD strictures, but also those with hilar strictures.
- Only including the cases with the naïve major duodenal papilla.
- Prospective designed, multicentre, large sample size protocol.
- Not including the cases drained by a metallic stent.
- The cases using non-steroidal anti-inflammatory drugs and an endoscopic pancreatic stent will not be excluded.

INTRODUCTION

Pancreatitis following endoscopic retrograde cholangiopancreatography (ERCP) is known as post-ERCP pancreatitis (PEP) and occurs in approximately 3%–4% of patients who have undergone transpapillary endoscopic biliary stenting (EBS).[1] PEP can lead to life-threatening adverse events; therefore, endoscopic sphincterotomy (ES) prior to EBS is often performed to prevent PEP by separating the orifice of the pancreatic duct (PD) and the bile duct (BD), which likely results in a decrease in the pressure on the PD orifice.

However, the effect of ES prior to EBS has not yet been fully elucidated. Although a previous study indicated that ES prior to metallic stent (MS) placement for distal BD stricture due to pancreatic cancer did not reduce the risk of PEP,[2] several limitations were associated with that study. First, hilar biliary obstruction cases were not included.

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PD obstruction in the cases with hilar BD stricture is rare, and EBS could cause PEP in such cases.[3 4] Second, used stents were limited to MS, which is not commonly used for initial drainage, especially not in surgical cases. In the initial drainage setting, a plastic stent (PS) or endoscopic nasobiliary drainage (ENBD) is generally suitable and commonly used.

Moreover, few studies analysed the efficacy of ES prior to PS placement, and the results are controversial. Giorgio *et al*. questioned the efficacy of ES before PS placement,[5] whereas Simmons *et al*. reported that the incidence of pancreatitis was 2.4% in the ES group, but it was 13.0% in the non-ES group.[6] However, the above-mentioned two studies analysed only cases in which 10-Fr PS was used. Moreover, the study by Giorgio *et al*. did not include any cases with hilar BD stricture, and that by Simmons *et al*. was a retrospective analysis.

Therefore, a prospective study including cases the distal BD stricture and the hilar BD stricture and using PS or ENBD for initial drainage is strongly warranted to elucidate the effect of adding ES prior to biliary drainage.

The aim of this study is to prospectively evaluate the non-inferiority of non-ES prior to EBS (PS or ENBD) for the naïve major duodenal papilla compared with ES prior to EBS in patients with biliary stricture.

Box 1 Participating institutions

- Aichi Cancer Center
- Fukushima Medical University, Aizu Medical Center
- Gifu University
- Gifu Municipal Hospital
- Hakodate Municipal Hospital
- Hokkaido University
- Iwamizawa Municipal General Hospital
- Kitami Red Cross Hospital
- Kumamoto University
- Kushiro Rosai Hospital
- Miyazaki University
- NHO Hakodate Hospital
- NHO Hokkaido Medical Center
- NTT East Sapporo Hospital
- Obihiro Kosei Hospital
- Okayama University
- Okinawa Prefectural Chubu Hospital
- Sapporo Medical University
- Sendai City Medical Center, Sendai Open Hospital
- Teine Keijinkai Hospital
- Toho University, Ohashi Hospital
- The University of Tokyo
- Tokyo Medical University
- Tomakomai Municipal Hospital
- Urasoe General Hospital
- Yamanashi University

MATERIAL AND METHODS

Design

To evaluate our research question, we designed a multicentre randomised controlled trial. The research protocol of this study was registered with the University Hospital Medical Information Network (UMIN) Clinical Trial Registry (UMIN000025727). The study stage is 'Pre-results'.

Setting

This study is conducted by the Department of Gastroenterology and Hepatology, Hokkaido University Hospital, Japan, and 25 other high-volume institutions in the field of pancreaticobiliary intervention in Japan are participating (box 1).

Participants and recruitment

Patients with biliary obstruction (distal biliary obstruction or hilar biliary obstruction) requiring endoscopic biliary drainage by means of PS or ENBD will be enrolled. Patients will be recruited among those referred to the 26 participating institutions for endoscopic biliary drainage.

Inclusion criteria

The inclusion criteria for the study are as follows: (1) clinical diagnosis of biliary stricture confirmed by imaging examination (CT, MRI, ultrasound or endoscopic ultrasound); (2) requirement for endoscopic biliary drainage via PS (7 Fr, 8.5 Fr or 10 Fr) or ENBD (5 Fr, 6 Fr, or 7 Fr); (3) being ≥20 years of age and (4) providing informed consent.

Exclusion criteria

The exclusion criteria for the study are as follows: (1) history of ERCP; (2) history of gastrointestinal tract reconstruction except Billroth I reconstruction; (3) acute pancreatitis; (4) the major duodenal papilla unreachable by a duodenal endoscope; (5) bleeding diathesis (prothrombin time and international normalised ratio ≥1.5, platelets <50 000/mm^3 and/or treatment with antiplatelet or anticoagulant drugs that cannot be ceased); (6) severe cholangitis; (7) Eastern Cooperative Oncology Group Performance Status (ECOG-PS) 4; (8) pancreaticobiliary maljunction; (9) severe cardiopulmonary disease; (10) pregnancy or breastfeeding; (11) ampullary tumour and (12) unsuitable for inclusion at the discretion of the physician.

Study outline and intervention

Figure 1 shows the proposed study flow. At first, all potential participants will be asked to provide written informed consent by the physicians in charge of this study in each institution. Preregistration is performed by identifying whether the patient fulfils the inclusion criteria and whether any exclusion criteria are applicable. When successful biliary cannulations are accomplished on ERCP, participants will be randomised into the non-ES group or the ES group by means of dynamic allocation (allocation factors comprise institution, location of stricture (distal or hilar), age (≥50 or<50 years) and sex) using the web-based randomised allocation system.

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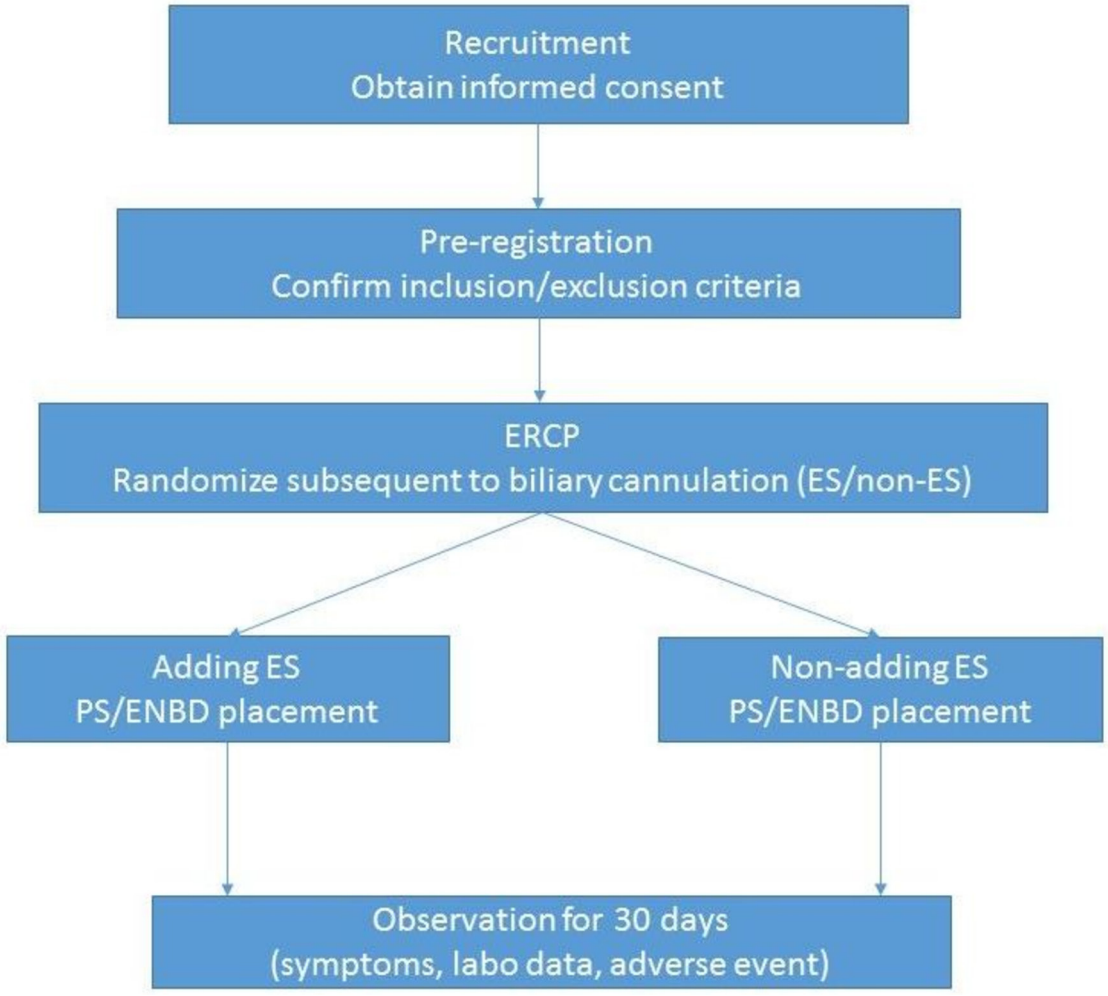

Figure 1 Proposed study flow chart. ENBD, endoscopic nasobiliary drainage; ERCP, endoscopic retrograde cholangiopancreatography; ES, endoscopic sphincterotomy; PS, plastic stent.

Patients randomised to the non-ES group will undergo insertion of PS or ENBD for BD without ES and those randomised to the ES group will undergo ES prior to insertion of PS or ENBD tube. The details of the proposed procedure are summarised in box 2.

Patient backgrounds (including sex, age, medical history, ECOG-PS and history of antiplatelet or anticoagulant drug treatment), medical information (disease (result of pathological examination, if possible), malignant or benign stricture, location of stricture, existence of main PD obstruction) and procedural characteristics (biliary cannulation time, cannulation methods, devices used, category of the operator (trainee/fellow/expert), performance of pancreatography/guidewire insertion to PD/BD biopsy/brushing cytology/intraductal ultrasonography and use of a pancreatic stent and non-steroidal anti-inflammatory drugs) will be recorded in the electronic data capture system operated by Hokkaido University (North Net). Patients will be followed up for 30 days after the procedure to obtain laboratory data and data on clinical symptoms, including vital signs. These data will be collected at the scheduled times as follows: prior to the procedure, 2 hours after the procedure, 1 day after the procedure and 30 days after the procedure (table 1).

Box 2 The detail of proposed procedure. ENBD, endoscopic nasobiliary drainage; ES, endoscopic sphincterotomy; PS, plastic stent.

- Antispasmodic agent, intravenous or intramuscular injection
- Sedative and analgesic agent, intravenous injection
- Insertion of a duodenal endoscope and biliary cannulation
- Allocation to the ES* or non-ES* group
- To perform ES* in ES* group
- Placement of PS* or 1/2 ENBD* tubes
- Removal of a duodenal scope

The incidence of adverse events related to the procedure (pancreatitis, cholangitis, cholecystitis, perforation, bleeding, and stent occlusion) and the severity of these will be recorded according to the American Society for Gastrointesinal Endoscopy criteria.[7] The definitions of adverse events are as follows: pancreatitis, typical abdominal pain with amylase/lipase >3 times

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Table 1 Observation and follow-up schedule

Timing of evaluation	Before ERCP	2 hours after ERCP	A day after ERCP	30 days after ERCP
Day	−28–0	0	1	30
Consent	○	—	—	—
Patients background	○	—	—	—
Imaging (US, CT, MRI, EUS)	○	—	—	—
Pathology, biopsy		←Δ→*		
Symptoms	○	○	○	○
Vital signs	○	○	○	○
Laboratory data	○		○	○
Adverse event	—		←○→†	

*not mandatory.
†evaluate depending on the ASGE criteria.
ASGE, American Society for Gastrointestinal Endoscopy; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; US, ultrasound.

normal; cholangitis, fever spiking over 38°C continuing for 24 hours with cholestasis; cholecystitis, right upper quadrant pain with fever spiking, typical ultrasonography findings; perforation, evidence of air or luminal contents outside the gastrointestinal tract; bleeding, haematemesis and/or melena or haemoglobin drop >2 g/dL.

Primary outcome measure

The primary outcome measure is the incidence of pancreatitis within 2 days after the initial transpapillary biliary drainage.

Secondary outcome measures

Secondary outcome measures include the incidence of (1) cholangitis or cholecystitis after the initial transpapillary biliary drainage, (2) adverse events related to ES (perforation and bleeding) and (3) recurrent biliary obstruction (stent occlusion, dislocation or migration).

Sample size

A sample size of 370 is required, consisting of 185 patients for the intervention group (non-ES group) and 185 patients for the control group (ES group). The method for calculating the sample size is as follows. According to a previous report, the incidence of pancreatitis after transpapillary EBS was 3.66% in the group with ES and 3.33% in the group without ES.[1] Therefore, we estimated that the incidence of pancreatitis related to stent placement is approximately 4%. The non-inferiority margin was set to 6% based on a report and meta-analysis that described a higher bleeding risk in the patients with ES compared with those without ES (6%, 8/133 vs 0%, 0/133; OR 8.89; CI 2.76 to 28.73)[1 8] The power was set to 0.8 (β error, 0.2), whereas the α error was set to 0.025 (one-sided analysis). The calculated sample size is 168 for each group. We finally set the total sample size to 370, taking into account a potential 10% dropout rate.

Data management and monitoring

All sampled data will be stored in the password-protected university server (North Net), which is accessible only by the permitted physicians, according to internal information governance rules. Data will be analysed on completion of the study and no interim analysis is planned. We will calculate 95% CIs of the incidence of pancreatitis in each group and analyse if the difference between the values with 95% CIs for the two groups is within the non-inferiority margin (6%) using Wald method. The χ^2 test will be used for analysing the secondary outcome data. We will also perform analyses depending on subgroups, such as location of stricture, the main pancreatic duct (MPD) obstruction, stent calibre and multivariate analysis adjusted for confounders for searching risk factors of adverse events. All statistical procedure will be performed on per-protocol population, because this study is non-inferiority trial.

Monitoring will be performed by an independent monitor for every participating institution, and the results will be reported to the research representative and the director of Hokkaido University Hospital. Severe adverse events will immediately be reported to the research representative and the director of Hokkaido University Hospital.

Study timeline

This study started in February 2017 and enrolment will be completed by August 2019. One month follow-up period is required after the enrolment, therefore, final completion date of this study will be September 2019 at the latest.

Ethics and dissemination

This study was approved by the Institutional Review Board of Hokkaido University Hospital (approved number: IRB: 016–0181, date: 23 January 2017) and each participating institutions. Results will be submitted for presentation at an international medical conference and expected to be published in a peer-reviewed journal.

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DISCUSSION

This study was designed for confirming the non-inferiority of non-ES before insertion of PS or ENBD tube with regard to the incidence of PEP in patients with biliary stricture. We chose the incidence of PEP as the primary outcome because pancreatitis is the most remarkable and potentially life-threatening adverse event related to stent placement. In addition, the theoretical background for performing ES prior to stent placement is based on the hypothesis that the separation of PD and BD orifice by ES could reduce the pressure on PD due to stent placement; however, ES can also cause adverse events, such as haemorrhage and perforation. Therefore, in terms of adverse events, it is relevant to compare non-ES with ES.

With the confirmation of the non-inferiority of non-ES before stent placement, it will be possible to omit an invasive procedure that increases the risk of adverse event. Moreover, it would lead to a decrease in medical expense. If non-inferiority is not confirmed, the results will provide clear evidence in favour of performing ES prior to stent placement, ensuring an adequate medical process.

Compared with the former study, the novelty and advantage of this study are linked to the fact that it will include not only cases with distal BD strictures, but also those with hilar BD strictures in the absence of PD obstruction, irrespective of whether the stricture is malignant or benign.

This study will include only cases with the naïve major duodenal papilla, and the stent used will be PS or ENBD tube, which is commonly chosen as the initial drainage device, especially in Japan.

In this study, blinding of participants and assessors will not be performed. However, the endpoint of this study (the occurrence of pancreatitis) is assessed objectively according to clear diagnostic criteria, we think that the risk of bias can relatively be low despite a non-blinding study design.

In conclusion, this study will provide further insight and beneficial information on the efficacy and issues of performing ES prior to transpapillary EBS in patients with biliary stricture for the prevention of PEP.

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Contributors SK designed the study and drafted the protocol. MK also contributed to design the study. RS, IS, KK edited the protocol. KO conducted the statistical design. NS supervised and edited the protocol.

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Competing interests None declared.

Ethics approval Hokkaido University Hospital.

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REFERENCES

1. Sofi AA, Nawras A, Alaradi OH, *et al*. Does endoscopic sphincterotomy reduce the risk of post-endoscopic retrograde cholangiopancreatography pancreatitis after biliary stenting? A systematic review and meta-analysis. *Dig Endosc* 2016;28:394–404.
2. Hayashi T, Kawakami H, Osanai M, *et al*. No benefit of endoscopic sphincterotomy before biliary placement of self-expandable metal stents for unresectable pancreatic cancer. *Clin Gastroenterol Hepatol* 2015;13:1151–8.
3. Kaffes AJ, Hourigan L, De Luca N, *et al*. Impact of endoscopic intervention in 100 patients with suspected postcholecystectomy bile leak. *Gastrointest Endosc* 2005;61:269–75.
4. Kawakubo K, Kawakami H, Kuwatani M, *et al*. Lower incidence of complications in endoscopic nasobiliary drainage for hilar cholangiocarcinoma. *World J Gastrointest Endosc* 2016;8:385–90.
5. Giorgio PD, Luca LD. Comparison of treatment outcomes between biliary plastic stent placements with and without endoscopic sphincterotomy for inoperable malignant common bile duct obstruction. *World J Gastroenterol* 2004;10:1212–4.
6. Simmons DT, Petersen BT, Gostout CJ, *et al*. Risk of pancreatitis following endoscopically placed large-bore plastic biliary stents with and without biliary sphincterotomy for management of postoperative bile leaks. *Surg Endosc* 2008;22:1459–63.
7. Cotton PB, Eisen GM, Aabakken L, *et al*. A lexicon for endoscopic adverse events: report of an ASGE workshop. *Gastrointest Endosc* 2010;71:446–54.
8. Wilcox CM, Kim H, Ramesh J, *et al*. Biliary sphincterotomy is not required for bile duct stent placement. *Dig Endosc* 2014;26:87–92.