Prophylactic endoscopic sphincterotomy in patients unfit for cholecystectomy after an acute biliary pancreatitis episode – study protocol for an open-label, two-armed, randomized controlled trial

This is the first version of the trial's protocol, completed according to the SPIRIT 2013 guideline (2023).

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All authors provided critical conceptual input and approved the article's final version.

**CONFLICT OF INTEREST**

None to declare.

**FUNDING**

None to declare.

**ETHICAL APPROVAL**

The study has been approved by the Scientific and Research Ethics Committee of the Hungarian Medical Research Council (XX).

**PATIENT CONSENT**

Patient consent for publication is not required. The medical personnel will provide informed consent to all participants.

**DATA AVAILABILITY STATEMENT**

The datasets generated during and/or analyzed during the current study will be available from the corresponding author upon reasonable request. All data necessary to interpret and support the result of the trial will be published in the supplementary material.

STRENGTHS AND LIMITATIONS OF THIS STUDY

**Strengths:**

The study is designed as a prospective randomized controlled trial to provide the highest evidence level to guide the clinical decision-making concerning the possible benefits of prophylactic endoscopic sphincterotomy (ES) after acute biliary pancreatitis in frail patients unfit for cholecystectomy.

Our study will be a (I) multicentric, (II) internationally registered trial, and (III) the study protocol will be published.

**Limitations:**

Only high-volume expert centers can join the study. Trained gastroenterologists with >50 ES completed within a year must be on duty.

The estimated sample size is relatively large in the context of the specific patient group meeting the inclusion criteria.

ABSTRACT

**Background**

**Methods, design**

**Hypothesis**

**Keywords:** ERCP, prophylactic sphincterotomy, biliary pancreatitis

**INTRODUCTION**

Background

Acute pancreatitis is one of the leading gastrointestinal causes of acute hospital admissions, with an overall mortality rate of 3% (1). In most Western countries, approximately 30-55% of the cases are caused by gallstones or sludge, referred to as biliary pancreatitis (2). International guidelines recommend that in case of cholangitis or choledocholithiasis, an endoscopic retrograde cholangiopancreatography (ERCP) should be performed to clear the bile duct with endoscopic sphincterotomy (ES) (3). After ERCP/ES is completed, the common bile duct is cleared, and the complications caused by the gallstones are significantly reduced (4).

After acute biliary pancreatitis (ABP), patients may experience a recurrent episode of biliary pancreatitis or other biliary events, such as acute cholecystitis, common bile duct obstruction, cholangitis, or biliary colic, associated with a high hospital readmission rate (5).

Cholecystectomy is recommended after an ABP episode to prevent the recurrence of pancreaticobiliary events (6).

However, some patients with gallbladder stones are elderly or frail and often have major medical problems, making them unsuitable candidates for surgery. It is still unclear whether elective ES may prove beneficial in preventing the recurrence of ABP in these patients,even if the therapeutic procedure itself is not recommended by the current guidelines.

In August 2023, we systematically searched for available studies in the literature. Cohort studies with relatively low sample sizes suggested the importance of ES in the study population (7, 8). However, no randomized controlled trials were identified comparing prophylactic ES with conservative treatment.

Objectives

We aim to provide grade-A evidence for the efficacy and safety of prophylactic ES in frail patients unfit for cholecystectomy after an ABP episode.

We hypothesize that patients undergoing prophylactic ES will experience fewer medical events and have lower mortality rates than those receiving conservative treatment during the one-year follow-up period.

Trial design

We will conduct a prospective, multicenter, open-label, two-armed RCT with a superiority study design. Study participants will be randomly assigned to group A ("prophylactic ES") and group B ("conservative treatment") in a 1:1 ratio.

The study protocol was conducted following the Standard Protocol Items: Recommendations for Interventional Trials 2013 statement (9).

METHODS

Sample size

Ninety-four participants will be randomized to the intervention and the conservative care arms (47 participants in each arm). All eligible patients will be offered to participate in the study.

After including 50% of the study participants, we plan to conduct an interim analysis to reassess the estimated sample size and analyze the collected data.

Study setting

The leading study site will be the Institute of Pancreatic Diseases, Semmelweis University, Budapest, Hungary.

Initially, the trial will be launched in ... Hungarian (Institute of Pancreatic Diseases, Semmelweis University; First Department of Medicine, Medical School, University of Pécs; Department of Medicine, University of Szeged) and X (…) centers, after which the study will be open to other centers. In all cases, the International Data Management Board (IDBM) will audit the center and report to the Steering Committee (SC). The SC maintains the right to decide whether a center meets the required quality requirements for joining the study.

Eligibility criteria

*Inclusion criteria:*

1. adult patients (above 18 years)
2. naïve papilla
3. evidence of AP based on the Atlanta criteria:

* pain in the upper abdomen
* serum amylase or lipase concentration > 3 times the upper limit of normal
* imaging features of acute pancreatitis on abdominal imaging

1. high probability of a biliary etiology:

* gallstones or biliary sludge on imaging (any type)
* dilated common bile duct on imaging defined as > 8 mm in patients ≤ 75 years or > 10 mm in patients > 75 years
* abnormal liver enzymes (GPT > two times the upper limit of normal)

1. patients unfit for surgery due to the attending physician's decision e.g. ASA ≥ III; severe heart failure with reduced ejection fraction <40%, severe uncontrolled hypertension, chronic kidney disease stage four or five

Exclusion criteria:

1. previous cholecystectomy
2. previous endoscopic sphincterotomy or pancreatobiliary stenting
3. ERCP/ES is recommended by the guidelines (3)

* sign of cholangitis
* presence of CBD stone on any imaging
* signs of stone in endoscopic ultrasonography or magnetic resonance imaging in case of abnormal liver enzymes (persistently elevated GPT and GOT with less than a 20% decrease over four days) or dilated CBD (defined as above)

1. chronic pancreatitis
2. estimated life expectancy < 12 months
3. ERCP is contraindicated, e.g. the procedure cannot be carried out safely due to the patient's comorbidities or physical status; high risk of bleeding or contraindication of the discontinuation of the anticoagulation therapy.
4. ERCP is technically not feasible due to altered anatomy, e.g., total gastrectomy, Roux-en-Y gastric bypass anatomy
5. pancreatobiliary malignancy

Interventions

Patients will be randomized to group A (prophylactic sphincterotomy) or group B (conservative treatment).

Papillary cannulation and sphincterotomy techniques will be performed in adherence to the recommendations outlined in the ESGE guideline (10).

All recommended measures for post-ERCP pancreatitis prevention must be implemented, including the use of prophylactic pancreatic stents, rectal NSAIDs, and optimal hydration protocols where appropriate.

All rescue techniques may be utilized if necessary, in accordance with clinical judgment and guideline recommendations.

ERCP/ ES will be performed by or under the direct supervision of an experienced endoscopist, defined as someone who has done more than 400 ERCPs in their lifetime and has completed more than 50 ERCPs yearly on average in the previous three years.

If the ES cannot be performed during the initial ERCP, the number of further attempts is under the discretion of the endoscopist.

Outcomes

*Primary outcome:*

Composite endpoint –recurrent pancreatobiliary events in 12 months

- cholangitis – Tokyo guidelines

- cholecystitis – Tokyo guidelines

- recurrent APB – defined as above

- choledocholithiasis

- pyogenic liver abscess

*Secondary outcomes:*

The following outcomes will be assessed at 3, 6, 9, and 12-months:

- the composite primary outcome

- individual endpoints of the composite primary outcome

- number of pancreatobiliary events requiring intensive care unit admission

- mortality associated with pancreatobiliary events

- all-cause mortality

- post-ERCP pancreatitis, with a focus on moderate or severe cases

- other post-ERCP complications, including bleeding, cholangitis and perforation

- length of hospitalization, defined as the time between admission and the first day of medical fitness for discharge

Participant timeline

An attending physician will inform the patients about the trial in detail, and participants must complete a written informed consent.

Before randomization, all patients must undergo imaging (e.g., ultrasound or CT scan).

The study will start after randomization.

Randomization will occur after the acute pancreatitis episode has improved, as indicated by reduced abdominal pain and a sustained decrease in inflammatory markers for at least 48 hours (11).

On the intervention arm, prophylactic ES will be carried out during the index admission for the acute biliary pancreatic episode.

The patient or their representative (e.g., primary caregiver, family doctor) will be asked to note every biliary event during the follow-up period and will be contacted on the phone at 3, 6, 9, and 12 months after discharge to collect information.

The study will end 12 months after discharge or in case of any automatic dropout criteria.

Additional data collected at baseline

Additional data on demographics, comorbidities and medical history, especially focusing on previous biliary events, will be collected.

The reason for the decision that a patient is unfit for surgery will be noted.

Randomization

A random sequence generator will allocate the patients to group A ("prophylactic ES") and group B ("conservative treatment") with an allocation ratio of 1:1 and randomly varying multiple block sizes. Randomization will be stratified by participating centers and patient gender.

Blinding

To prevent the selection bias of patients for Groups A and B, trial participants, care providers, and outcome assessors will be blinded until the allocation, as they will have no access to the randomization sequence. Blinding from group assignment to intervention cannot be maintained due to the nature of the intervention (e.g., performing or not performing ES). Therefore, no sham procedure is planned in the control arm. Statisticians will receive anonymized data records.

Data collection and management

Data will be collected in a personalized electronic database, and follow-up will consist of questionnaires and the review of the medical records (online supplementary file).

An identification number will be provided to each participant. Participants' identification numbers and personal data should be stored separately from other data and be only available for those directly involved in the trial.

After data collection, the information will be entered into Electronic Case Report Forms (eCRF). According to the Data Cleaning Plan, the IDMB will validate the completed electronic case data.

Detailed data flow will be described in a Data Management Plan.

The Chief Investigator will guarantee the data's completeness, quality, and reliability. Only complete or consistent data will be referred to the Investigator by a data query form.

Statistical analysis plan

Normally distributed variables will be presented as means with standard deviations (SD), while non-normally distributed variables will be described using medians with interquartile ranges (IQR). For categorical variables, p-values will be calculated using either the Chi-square test or Fisher’s exact test, depending on the data distribution. For continuous variables, group comparisons will be conducted using the t-test for normally distributed data, while the Mann-Whitney U test will be applied for non-normally distributed data. A p-value of <0.05 will be considered statistically significant.

For all outcomes, we will conduct a per-protocol analysis (regarding the participants who finished the study as the protocol requires) and an intention-to-treat analysis (for all the patients who received the intervention). In the final analysis, intention to treat analysis will be preferred over the per-protocol analysis.

The R programming language (R Core Team, 2019, Vienna, Austria, R version 4.1 or later) will be used for statistical analysis.

Sample size estimation method

According to a recent meta-analysis, the combined risk of recurrent pancreatitis was 11.9% after the first episode of acute biliary pancreatitis. For patients undergoing cholecystectomy, the risk decreased to 6.6% (12). In a prospective cohort study by Uomo et al., which focused on patients unfit for surgery after the first ABP episode and who underwent ES, the observed rate of recurrent ABP was 5% over a 2-year period (5). Considering these findings and assuming that cholecystectomy yields similar effects as ES, we estimated a 5% incidence of recurrent pancreatobiliary events in the study arm.

Based on studies reporting recurrence rates of biliary pancreatitis between 18% and 61% in patients awaiting cholecystectomy while conservatively treated at the index admission, we calculated a 30% incidence of recurrent pancreatobiliary events in the conservative treatment arm during the 12-month follow-up period (13).

With a 25% dropout rate and using a power of 80% and a significance level of 5% to measure the treatment effect, we calculated a sample size of 94.

Safety and adverse events

(1) In case of recurrent biliary acute pancreatitis after randomization, if an ERCP is necessary in the control arm, it should be carried out immediately. (2) All necessary measurements should be taken to prevent the post-ERCP adverse events. (3) After 50% of the study participants are included, as part of the interim analysis, a safety analysis will be carried out for three months to assess the risks and benefits of ES/ ERCP. If the complication rate of ERCP is lower than 10%, it should considered as a safe procedure in the study population.

Withdrawal from study

Investigators and IDMB can submit a recommendation for dropouts from the per-protocol analysis. All requests will be filed. Based on the received information, the SC can decide to exclude the patient from the per-protocol analysis if the deviation from the protocol is related to the intervention or if it influences the primary or secondary outcomes.

Automatic dropout of the study participants will be ordered if: (1) withdrawal of consent at any point; (2) the patient cannot be contacted, or the requested data cannot be assessed from the electronic medical documents during the follow-ups.

ETHICS AND DISSEMINATION

Ethical approval

The trial is registered at ClinialTrials.gov.com (XXX).

The protocol has been approved by the Scientific and Research Ethics Committee of the Medical Council (...).

The study will be performed following the declaration of Helsinki and the International Conference on Harmonization and Good Clinical Practice guidelines.

Trial organization

The guarantor of the trial is the Institute of Pancreatic Diseases, Semmelweis University, Budapest, Hungary. The following committees and boards will be involved:

The SC will be led by BE (gastroenterologist, internal medicine specialist); the members will be AV, LC, TE, and FI. The SC will decide on all relevant questions, including dropouts during the study.

International Translational Advisory Board (ITAB): The board will consist of SV, SL, MB and SC. The ITAB will continuously monitor the progress of the study and will advise the SC.

The study was designed by the SC and ITAB.

Planned start date: …

Anticipated study duration: three years

Publication policy:

We aim to publish the results in an international, highly recognized, peer-reviewed journal.

Centers providing more than X patients can provide X authors to the authorship list.

Conflicts of interest

None to declare.

**DISCUSSION**

Our study is designed to determine whether a prophylactic ES, after ABP, leads to a reduction of mortality and readmissions for biliary events in patients with ABP unfit for cholecystectomy.

If an ES proves superior to the conservative treatment in the study population, it could be recommended routinely and incorporated into the guidelines, reducing the risk of recurring biliary events.

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