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Original article

Preventive pancreatic stents in the management of acute biliary pancreatitis (PREPAST trial): Pre-study protocol for a multicenter, prospective, randomized, interventional, controlled trial

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ABSTRACT

Background: The outcome of the most common biliary form of acute pancreatitis has not changed even with the better described indications for early endoscopic intervention. It may be due to the fact that this intrevention theoretically can cause further pancreatic injury or cannot always relieve the pancreatic duct obstruction. We hypothesize that maintaining the outflow of the pancreatic duct with preventive pancreatic stents at the early ERCP improves the outcome of acute biliary pancreatitis.

Methods/Design: PREPAST is a prospective, randomized, controlled, multicenter trial. Patients with acute biliary pancreatitis with coexisting cholangitis are randomized to undergo urgent endoscopic intervention with or without pancreatic stenting within 48 h from the onset of pain, and in addition patients without signs of cholangitis but cholestasis are randomly allocated to recieve conservative treatment or early endoscopic intervention with or without pancreatic stenting within 48 h from the onset of pain. Patients without acute cholangitis and signs of cholestasis recieve conservative treatment. 230 patients are planned to be enrolled during a 48 months period from different centers. The primary endpoint is the outcome of acute biliary pancreatitis as described by the latest guidelines. Secondary endpoints include mortality data, and other variables not analyzed as a primary endpoint but related to the pancreatitis or the pancreatic stenting.

Discussion: The PREPAST trial is designed to show whether early endoscopic intervention with the usage of preventive pancreatic stenting improves the outcome of acute biliary pancreatitis. The study has been registered at the International Standard Randomised Controlled Trial Number (ISRCTN) Register (trial ID: ISRCTN13517695).

Background

Acute pancreatitis (AP) is one of the most common diseases of the gastrointestinal tract that leads to hospitalization causing major financial and healthcare problems. It was the most common gastrointestinal cause for hospitalization in the USA in 2009 with a total annual cost of 2.6 billion USD. The incidence of AP varies between 4.9 and 73.4 cases per 100,000 worldwide

Abbreviations: ABP, acute biliary pancreatitis; AE, adeverse event; ALT, alanine aminotransferase; AP, acute pancreatitis; AST, aspartate aminotransferase; CBD, common bile duct; CECT, contrast-enhanced computer tomography; CRF, case report form; DSMB, Data Safety and Monitoring Board; ERCP, endoscopic retrograde cholangiography; ES, endoscopic sphincterotomy; ICU, intensive care unit; PPS, preventive pancreatic stent; SAE, serious adverse event; SIRS, systemic inflammatory response syndrome; ULN, upper limit of normal; US, ultrasound.

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and is increasing. Hospital admissions for AP inceased by 30% between 2000 and 2009 [1,2]. Gallstones accounts for the cause of AP in 30–55% of cases in most western countries which is referred to as acute biliary pancreatitis (ABP) [3]. Although the pathogenesis of ABP is not fully understood it is generally accepted that prolonged or transient obstruction of the papilla of Vater caused by gallstones may lead to increased intrapancreatic ductal pressure and early intraductal activation of the pancreatic enzymes. It seems from experimental models that the acinar-ductal tango plays an important role in the pathogenesis [4–6].

Early endoscopic intervention in terms of endoscopic retrograde cholangiopancreatography (ERCP), endoscopic sphincterotomy (ES) and clearance of the common bile duct (CBD) within 72 h calculated from the onset of pain became the gold standard therapy for ABP patients with predicted severe course since the first randomized controlled trial proved better outcome, reduced morbidity and shorter hospital stay for these patients [7]. The usefulness of early endoscopic intervention was debated in 2008, when a meta-analysis concluded that early ERCP in ABP patients without cholangitis did not lead to significant reduction of morbidity and mortality [8]. A year later a prospective trial by the Dutch Pancreatitis Study Group showed fewer complications in severe ABP patients with cholestasis treated with early ERCP [9]. These findings suggest that not the predicted severity but the presence of obstructive signs are more important in determining those patients who would benefit from early ERCP. The most recent published guidelines incorporated this approach to their treatment recommendations [2,10].

On the other hand two important factors should be noted. First, the prediction of CBD stones in the early course of ABP with the standard biochemical and radiological methods is unreliable [11]. Second, in the available previous and recent guidelines early endoscopic intervention concentrates only on clearance of the common bile duct however the main pathogenetic events take place in the pancreatic duct and acinar-ductal tango [5,6]. Data from previous publications demonstrated beneficial effect of small caliber pancreatic stenting as a rescue procedure in the prevention of evolution of post-ERCP pancreatitis and it was also feasibile and safe as a bridging procedure in ABP but difficult sphincterotomy [12,13]. Based on these results we hypothesized that early ERCP, ES and CBD stone extraction did not always relieve the pancreatic duct obstruction in ABP (eg. presence of peripapillary edema, inflammation or prolonged spasm of the pancreatic sphincter, etc) and manipulation of the Vater papilla could cause further pancreatic injury similarly to post-ERCP pancreatitis. Therefore we conducted a prospective non-randomized trial where we inserted preventive pancreatic stents (PPS) temporarily for those ABP patients in whom biliary cannulation proved to be difficult. We could demonstrate that adequate pancreatic drainage with PPS inserted temporarily at early ERCP led to better overall outcome and siginficantly less complications compared to ERCP, ES and CBD stone extraction alone [14].

Based on these preliminary data a prospective, randomized, controlled trial is needed to confirm that in ABP patients insertion of a PPS at the early ERCP is superior to ERCP and ES alone not just for patients with difficult biliary cannulation. The PREPAST trial was designed to investigate whether using PPS reduces the morbidity and mortality of ABP patients with cholangitis compared to ES and CBD stone extraction alone irrespective of predicted severity and to investigate whether using these stents in ABP patients without cholangitis, but cholestasis provides better outcome compared to either conservative treatment, or early ERCP and ES.

Methods/design

Design

The PREPAST trial is a prospective, randomized, controlled, multicenter study organized by members (authors of this article) of the organizing and steering committee of this study as a part of the Hungarian Pancreatic Study Group. The above mentioned investigators signed a declaration of intention to participate in this study on 7th October 2013 in Kecskemét, Hungary.

Patients with ABP and acute cholangitis irrespective of the predicted severity of AP will be randomized to recieve urgent ERCP, ES and bile duct clearance (within 48 h from the onset of pain) or PPS insertion on top of these (study arm A – group A1: ERCP, ES and bile duct clearance only; group A2: ERCP, ES, bile duct clearance + PPS insertion).

Patients with ABP but without signs of acute cholangitis will be assessed for evidence of cholestasis. Those patients in whom cholestasis is present will be randomized into one of the following three groups (study arm B): group B0: conservative treatment, group B1: early ERCP, ES and bile duct clearance (within 48 h) or group B2: early ERCP, ES, bile duct clearance and PPS insertion (within 48 h). Those patients in group B0 who show clinical and biochemical markers of prolonged cholestasis at 48 h after randomization will be crossed over to recieve endoscopic intervention (to group B1) while those who show spontaneous signs of improvement will stay in group B0 receiving conservative treatment. ABP patients without signs of acute cholangitis and cholestasis will recieve conservative treatment.

Primary endpoint

The outcome of each group will be calculated, using a composite endpoint. All complicated course of ABP will be included. A complicated course will be described as any of the following three:

- Moderate and severe AP (including temporary and persistent organ failure),
- Any complications including systemic (exacerbation of pre-existing co-morbidity) and all local complications (acute peri-pancreatic fluid collection without tendency of spontaneous resolution, pancreatic pseudocyst, acute necrotic collection, walled-off necrosis) of AP as described in the revised Atlanta classification and
- Mortality [15].

Secondary endpoints

Secondary endpoints related to ABP outcome:

- Multi organ failure in each subgroup;
- Mortality rate in each subgroup;
- Pain score on admission, 24 and 72 h after ERCP (or after randomization in group B1);
- New onset of sepsis;
- The proportion of patients with severe course of ABP;
- The proportion of patients with severe organ failure requiring respiratory support (mechanical ventilation) and/or cardiac support (vasopressors) and/or renal support (haemodyalisis);

Secondary endpoints related to endoscopic treatment:

- PPS insertion success rate;

- Consequences of attempted but failed pancreatic stenting (this subgroup will be analyzed separately);
- Endoscopist's experience on PPS success rate and ABP outcome;
- The influence of the endoscopic technique used on the outcome of ABP;
- Influence of patient and procedure related risk factors of post-ERCP pancreatitis (published by the European Society of Gastrointestinal Endoscopy – ESGE) on outcome of ABP patients who underwent ERCP and on success rate of PPS insertion [16].

Study population

All adult patients admitted with ABP to one of the participating hospitals of the Hungarian Pancreatic Study Group and international collaborators will be assessed for eligibility. Patients who fulfill all inclusion and exclusion criteria will be assessed for acute cholangitis. Those with acute cholangitis complicating their ABP will be randomized to recieve urgent ERCP and bile duct clearance within 48 h from the onset of pain (study group A1) or urgent ERCP, bile duct clearance and PPS insertion (study group A2). Those ABP patients who have no signs of acute cholangitis will be assessed for evidence of cholestasis. Patients with signs of cholestasis will be randomized into one of three groups: conservative treatment (group B1), early ERCP, ES and bile duct clearance within 48 h (group B2) or early ERCP, ES, bile duct clearance and PPS insertion within 48 h (group B3). Those patients in the conservative treatment arm who show clinical and laboratory signs of prolonged cholestasis at 48 h after randomization will be crossed over to recieve ERCP, ES and bile duct clearance, while those who show spontaneous resolution will stay in the original group receiving conservative treatment. Patients without signs of cholestasis (and acute cholangitis) will recieve conservative treatment (Fig. 1).

Inclusion criteria

Inclusion criteria are: age $\geq$18 years; diagnosis of acute biliary pancreatitis; written informed consent; possibility of performing ERCP within 48 h calculated from the onset of pain.

Diagnosis of acute pancreatitis is based on the deifinition of IAP/APA guideline. „2 out of 3″ of the following criteria present: upper abdominal pain; serum amylase or lipase >3x upper limit of normal range (ULN); characteristic findings on imaging studies (abdominal ultrasound (US)/CT/MRI); however those patients without abdominal pain will be excluded because the onset of AP cannot be assessed [10].

Biliary origin of AP is based on the criteria suggested by the Dutch Pancreatitis Study Group [9]. The origin is suspected to be biliary if one of the following three definitions present: gallstones and/or sludge diagnosed on imaging; in the abscence of gallstones and/or sludge a dilated CBD on US (>8 mm in patients $\leq$75 years old or >10 mm in patients >75 years old); alanine aminotransferase (ALT) level >2xULN with ALT > aspartate aminotransferase (AST).

Exclusion criteria

Exclusion criteria are: pregnancy; AP due to alcohol, malignancy or post-ERCP pancreatitis; pain onset >48 h; abscence of abdominal pain (the onset cannot be assessed); liver cirrhosis Child score C; pancreatic fluid collections or necrosis on initial imaging at presentation; INR>1.6 and uncorrectable by the time of ERCP, previous ES.

Treatment protocol

Initial assessment and therapy

All patients with ABP who are referred to the gastroenterology/endoscopy teams of the participating hospitals will be assessed for eligibility to PREPAST trial. We are not intended to perform a full search of our hospitals' admission registry for complete cover of AP patients.

The referred patients will be started on initial, goal directed intravenous fluid resuscitation therapy with isotonic crystalloid solution (Ringer-lactate preferred, however other crystalloid solutions used by the ambulance or emergency department does not exlcude patients from the study) at a rate of 5–10 ml/kg/h (or 250–500 ml/h) over the first 12–24 h. The response is mainly based on non-invasive clinical (heart rate <120/min, mean arterial pressure between 65 and 95 mmHg, urinary output >0.5–1 ml/kg/h) and biochemical targets (hematocrit 35–44%, blood urea nitrogen decreasing on therapy). Fluid requirements will be reassessed every 6–12 h for the first 24 h, and daily thereafter while needed.

In the meantime (preferably at the emergency department, but within 6 h from admission) laboratory tests and abdominal ultrasound scan will be performed for all referred patients to assess inclusion and exclusion criteria. The aim of the abdominal US is to detect gallstones and/or sludge in the gallbladder, to determine the diameter of CBD and determine suspicion of pancreatic fluid collections or necrosis. Contrast-enhanced computer tomography (CECT) is only performed at admission if the diagnosis of AP is unclear or if presence of an already complicated disease suspected on US (ie. pancreatic fluid collections or necrosis). The onset of pain will be accurately determined and documented. A written informed consent will be obtained for all potentially eligibile patients before randomization.

The presence of acute cholangitis will be assessed at admission based on the updated (TG13) Tokyo guidelines (Table 1) [17]. We slightly modified the diagnostic criteria of „definite diagnosis” for our study as we require the presence of both items in group A, plus one item in both B and C. The Tokyo guidelines were developed for patients not having acute pancreatitis, where increased inflammatory laboratory markers can be caused by the pancreatitis itself. Furthermore signs of cholestasis can be caused by gallstones migrating through the CBD in ABP patients. Leaving the original criteria of TG13 may lead to false diagnosis of acute cholangitis in ABP patients. In cases of „suspected diagnosis” (as termed by the TG13) a reassessment of the presence of acute cholangitis is allowed in 6–12 h, except for those cases when the patient's clinical status warrants more urgent intervention. If acute cholangitis could be safely excluded, the patient can be randomized to group B. Those patients with definitive diagnosis of acute cholangitis are randomized to group A.

Randomization, endoscopic and conservative treatment groups

Not blinded randomization will be applied in the present study. The allocation of participants into randomization groups will be carried out based on predefined randomization lists. Randomization lists will be prepared separately for each centrum; furthermore each centrum will receive separate randomization lists for patients in group A and B.

Patients with ABP and co-existing acute cholangitis will recieve early endoscopic intervention **(group A)**. Patients in group A will be randomized either into group A1 (ERCP, ES treatment) or into group A2 (ERCP, ES + PPS treatment). Randomization lists will be prepared with a block size of 4 and with an allocation ratio of 1:1. In case of withdrawn of a volunteer, he/she will be substituted by a new one. For this purpose, an additional sample size will be randomized for each centrum, which can be applied if needed.

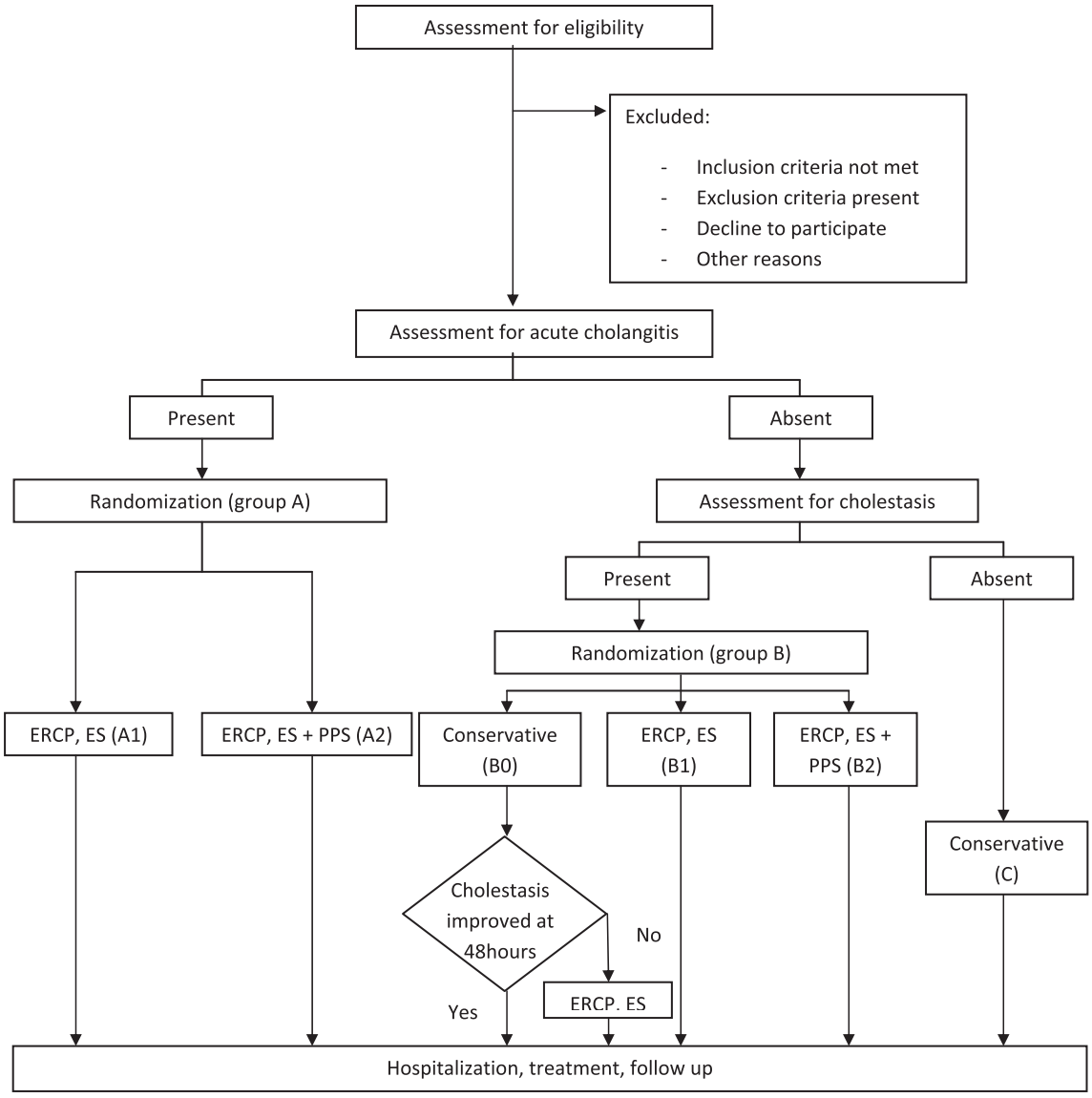

Fig. 1. Flowchart of PREPAST study.

Table 1
Diagnostic criteria for acute cholangitis as defined by the T13 Tokyo guidelines [17].

TG 13 diagnostic criteria for acute cholangitis	
A: Systemic inflammation	
A-1	Fever (>38 °C) and/or shaking
A-2	Laboratory data: evidence of inflammatory response (WBC <4 or >10 × 10^9/L, CRP≥10 mg/l and other changes indicating inflammation)
B: Cholestasis	
B-1	Jaundice (serum bilirubin ≥34.2 μmol/l)
B-2	Laboratory data: abnormal liver function tests (ALP, GGT, ALT, AST >1.5xULN)
C: Imaging	
C-1	Biliary dilatation
C-2	Evidence of the etiology on imaging (stricture, stone, stent etc.)
Suspected diagnosis: one item in A + one item in either B or C	
Definite diagnosis: one item in A, one item in B and one item in C	

Other factors which are helpful in diagnosis of acute cholangitis include abdominal pain (right upper quadrant or upper abdominal) and a history of biliary disease (gallstones, previous biliary procedures, placement of a biliary stent).

Patients with ABP but without evidence of acute cholangitis will be assessed for evidence of cholestasis. Patients without co-existing acute cholangitis but evidence of cholestasis will be randomized to recieve conservative treatment or early ERCP, ES and bile duct clearance or early ERCP, ES, bile duct clearance plus PPS insertion **(group B)**. Patients receiving conservative treatment will be assessed at 24 h after randomization (not later than 72 h from the onset of pain) for clinical and laboratory signs of persistent cholestasis. If this is present patients will recieve ERCP, ES and bile duct clearance and their data will be collected separately. Patients in group B will be randomized either into group B0 (conservative treatment), into group B1 (ERCP, ES treatment) or into group B2 (ERCP, ES + PPS treatment). Randomization lists will be prepared with a block size of 6 and with an allocation ratio of 1:1:1. In case of withdrawn of a volunteer, he/she will be substituted by a new one. For this purpose, an additional sample size will be randomized for each centrum, which can be applied if needed.

Evidence of cholestasis is diagnosed by imaging and laboratory markers. Criteria of cholestasis are the following: objective demonstration of gallbladder stones and/or sludge, or dilated CBD,

Table 2
Modified Marshall scoring system for organ failure [18].

	Score				
Organ system	0	1	2	3	4
Respiratory (PaO_2/FiO_2)	>400	301–400	201–300	101–200	<100
Renal* (serum creatinine, μmol/l)	<134	135–169	170–310	311–439	>439
Cardiovascular (systolic blood pressure, mmHg)**	>90	<90 Fluid responsive	<90 Not fluid responsive	<90, pH < 7.3	<90, pH < 7.2
For non-ventilated patients, the FiO_2 can be estimated from below:					
Supplemental Oxygen (l/min)	FiO_2	**A score for patients with pre-existing chronic renal failure depends on the extent of further deterioration of baseline renal function. No formal correction exists for a baseline serum creatinine ≥ 134 μmol/l or ≥ 1.4 mg/dl*			
Room air	21%				
2–3	25%				
4–5	30%	***Off inotropic support. For patients with the need for inotropic catecholamine support, a Marshall score of 2 is appointed for cardiovascular system and dependent on the pH a Marshall score of 3 or 4 can be appointed*			
6–8	40%				
9–10	50%				

or CBD stone on abdominal US and elevated liver function tests with an ALT, ALP and bilirubin levels more than 1.5xULN.

Patients without signs of cholestasis (and acute cholangitis) will recieve conservative treatment **(group C)**, and will not be randomized.

A three-digit unique randomization number will be assigned to each individually recruited patient, which will determine the allocation of the treatments. In each center and for each group (A, B and C) randomization numbers will be distributed in ascending order with the starting numbers of 001. Centers will also get a unique two-digit center identifier; patient groups will be identified with one-letter identifiers A, B and C.

Therefore patients will be identified with the following combination:

□□ □ □□□

two-digit centrum-ID one-letter group identifier three-digit randomization number

(Example: 01A001)

Each randomization list will consist of the above identifier; also the name of the assigned treatment will be listed. The prepared randomization lists will be sent to the centrums. In order to not compromise the randomization all started block of 4 for group A and 6 for group B are advised to be completed.

Patients in group C will also receive the above identifier, however all patients in this group will receive the same conservative treatment.

PPS insertion technique

For PPS insertion a 0.035 or 0.025-inch single use hydrophylic guidewire will be placed into the pancreatic duct with no or minimal contrast filling until the genu and a 5 Fr, 3 cm pancreatic stent with internal flaps will be introduced without any pancreatic sphincterotomy. When insertion of a PPS within 10 min and/or 5 attempts is unsuccessful, the procedure should be abandoned and defined as „failed PPS insertion". These patients will be closely followed up and analyzed separately. All stents will be removed at a second gastroscopy procedure within a few days when ABP has resolved or significantly improved.

Access into the CBD, cannulation and ES techniques and CBD clearance is left to the ERCPist discretion. The techniques and accessories used will be documented. All endoscopic procedures will be recorded in full length.

Risk stratification, prognostication

Prediction of outcome at admission will be assessed combining individual patient risk factors (age, co-morbidity, body mass index), clinical risk stratifications (presence of systemic inflammatory response syndrome (SIRS)) and thereafter with monitoring the response to initial therapy (persistent SIRS, blood urea nitrogen, hematocrit).

Signs of SIRS will be documented at admission and at 48 h (at least). SIRS is defined by presence of two or more of the following four criteria: (1) heart rate >90/min, (2) core temperature <36 °C or >38 °C, (3) white blood count $<4 \times 10^9$/L or $>12 \times 10^9$/L, (4) respiratory rate >20/min.

Severity will also be assessed with the modified Glasgow criteria (Table 3) and BISAP score (one point for each of the following criteria present: blood urea nitrogen >25 mg/dl, impaired mental status, SIRS, age >60 years, presence of a pleural effusion) [18,19].

Every patient, especially those with signs of SIRS and suspicion of severe ABP will be closely monitored for transient or persistent

Table 3
Modified Glasgow criteria for predicting severity of acute pancreatitis [19].

One point for each item:	
Age	>55 years
PO_2 (arterial)	<60 mm Hg
Albumine	<32 g/l
Total calcium	<2 mmol/l
Leukocytes	$>15 \times 10^9$/l
LDH	>600 U/l
Glucose (non diabetics)	>10 mmol/l
Urea after rehydration	>16 mmol/l

A Glasgow score of ≥3 is regarded as indicative of severe pancreatitis.

organ failure by the modified Marshall scoring system at admission and at least 48 h after (Table 2). When clinically required further assessments will be performed. Organ failure is defined by a Marshall score of ≥2 for at least one of three organ systems (ie. respiratory, renal, cardiovascular) [15,20].

Patients with persistent SIRS, organ failure and/or a severe course of AP will be transferred to the intensive care unit (ICU) after discussion with the intensivist on a case-by-case basis. Patients at ICU will recieve full available support and treatment, including multidisciplinary team discussions whenever needed.

Hospital treatment, discharge, follow up

Every patient will be hospitalized for treatment. Routine antibiotic prophylaxis will not be used. Initial antibiotic therapy will be administered only for patients with evidence of acute cholangitis or patients with other causes of bacterial infection (eg. pneumonia, urinary tract infections). In cases of (suspected) infected necrosis antibiotics will be administered (carbapenems, quinolones and metronidazole).

At 48 h from admission every patient will be assessed for determining further nutritional management. Oral feeding will be started in patients with mild course of ABP once abdominal pain has decreased and inflammatory markers are decreasing and reassuring. Patients in whom oral feeding cannot be started or with severe course of ABP, a nasojejunal feeding tube will be placed and enteral nutrition will be started. Patients who do not tolerate enteral feeding and nutritional goals cannot be reached, a second line parenteral nutrition will be started within the next 3–5 days.

CECT is not required initially, however patients with a suspicion of severe course of ABP and those who fail to respond to conservative treatment or clinically deteriorating will undergo a CECT at least 72–96 h after onset of symptoms.

Patients will document their pain score on a visual analog scale at admission, 24 and 72 h after endoscopic treatment (or after randomization for conservative treatment group).

Patients will be discharged once they are clinically symptom free and tolerate oral feeding. Follow up is scheduled at 3 months after discharge. Patients in stable clinical status but need for nasojejunal feeding can be discharged home with home enteral feeding but scheduled for regular follows ups at least every 2 weeks until the cause which initiated the nasojejunal feeding has resolved and oral feeding has been started and tolerated well. A final follow up then scheduled at 3 months later. Those patients on home enteral feeding who fail to improve on this therapeutic regime will be followed up every 2 weeks until the final decision for intervention (endoscopic or surgical, eg. pseudocyst drainage) has been made. They will be followed up at 3 months after their intervention.

Any further laboratory, imaging, endoscopic test, therapeutic interventions and medical therapies are left to the treating gastroenterologists discretion. An expert of the organizing and steering committee will be available for discussion via telephone or e-mail when required.

Data collection

All relevant clinical data will be collected during hospital admission using electronic case record form (eCRF), eg. patients' baseline characteristics, relevant laboratory and imaging results, endoscopy procedures, accessories used, outcomes. The eCRF will be filled out by the local treating physicians, the study coordinator or the study nurse. The study coordinator and the study nurse are allowed to correct wrongly entered data (eg. miscalculated disease severity scores). The CRFs will be checked with source data. Printed CRFs will be provided for cases of limited access to the online system. It is allowed to fill the printed CRF in first, but all data should be uploaded to the online system as soon as possible.

The data collected through the study will be entered in a validated electronic data management system, which can be assessed by the study doctors with unique usernames and secret passwords in order to treat data secretly and confidentially.

After the data entry period the database will be closed and archived; the data will be transferred into SAS or SPSS format.

Only study group personnel will have access to the unblinded source data.

Patients will be asked to contact the study coordinator or treating physician when they will be readmitted to hospital during follow up.

Safety

An independent Data Safety and Monitoring Board (DSMB) consisting of three independent experts will evaluate the clinical research data on an ongoing basis to assure patient safety and study integrity. The board will monitor the trial data and give their advice based on periodical reviews.

Adverse events (AE) are defined as “any undesirable experience occurring to a subject during a clinical trial, whether or not considered related to the intervention”. All involved physicians will repetitively be asked to report any potential AEs. These AEs will be listed and discussed by the DSMB. The organizing and steering committe will be informed of the outcome of the DSMB discussion.

Serious adverse events (SAE) are defined as “any undesirable experience occurring to a subject during a clinical trial, whether or not considered related to the intervention when the patient outcome is death, life-threatening, hospitalization, disability or permanent damage, required intervention to prevent permanent impairment or damage”, which is also in line with the Food and Drug Administration's definition.

Centers and investigators willing to join and participate in the study will be assessed by the organizing and steering committee in terms of experience in the field of ERCP and PPS insertion and ABP management. On-site monitoring will be carried out when required.

Ethics

The trial protocol was approved on 13/10/2014 by the Hungarian National Ethical Committee (ETT-TUKEB ref.: 030174/2014/OTIG).

The study will be performed in accordance with the declaration of Helsinki and the principles of ICH-GCP guidelines. The trial will also be performed in keeping with local legal and regulatory requirements.

Informed consent will be obtained from each participating patient prior to randomization in oral and written form. A detailed briefing and explanation will be given to every participating patient on the nature, aim, scope and consequences of the study by a participating physician before consenting. Enough time will be given to patients to consider participation in the study and all of their questions will be discussed in detail.

Statistical aspects

Sample size calculation

Sample size estimation was based on our previous study [14].

At the time of inclusion patients will be categorized based on their clinical state, and will receive treatments according to their state. The following ABP patient groups will be examined in the present study:

- Group A1: acute cholangitis present; ERCP, ES treatment
- Group A2: acute cholangitis present; ERCP, ES + PPS treatment
- Group B0: acute cholangitis absent and cholestasis present; conservative treatment
- Group B1: acute cholangitis absent and cholestasis present; ERCP, ES treatment
- Group B2: acute cholangitis absent and cholestasis present; ERCP, ES + PPS treatment
- Group C: absent acute cholangitis and absent cholestasis; conservative treatment

The primary analysis of the study will concentrate on two patient populations considering the applied treatment; these populations are formed from the above groups:

Control group (ERCP, ES): A1 + B1
Stent group (ERCP, ES + PPS insertion): A2 + B2

The data of patients belonging to groups B0 and C will also be collected with the aim of an exploratory analysis; however hypothesis testing will not be carried out for these groups.

The primary aim of the present study is to compare the proportion of patients in the stent and control groups by whom at least one of the following events occurred:

- Moderate and severe AP (including temporary and persistent organ failure),
- Any complications including systemic (exacerbation of pre-existing co-morbidity) and all local complications (acute peripancreatic fluid collection without tendency of spontaneous resolution, pancreatic pseudocyst, acute necrotic collection, walled-off necrosis) of AP as described in the revised Atlanta classification and
- Mortality.

In our previous study at least one of the above events was recorded in 7.04% of the stent-patients and in 20.00% of the control-patients. In the course of the sample size estimation we are calculating with these results, and we assume, that the proportions will be similar in the present study.

To be able to detect this assumed proportion-difference by a two-group chi-square test with a 5% two-sided significance level calculating with a power of 80% the analyzable sample size should be 218 (109 in the control group and 109 in the stent group). Calculating with a lost to follow up rate of 5% 230 (115 in the control group and 115 in the stent group) patients should be enrolled into the study.

Analyses

The data of all patients who met the inclusion and exclusion criteria and signed a written informed consent will be analyzed.

The primary variable is the proportion of patients by whom at least one of the following events occurred:

- Moderate and severe AP (including temporary and persistent organ failure),
- Any complications including systemic (exacerbation of pre-existing co-morbidity) and all local complications (acute peripancreatic fluid collection without tendency of spontaneous resolution, pancreatic pseudocyst, acute necrotic collection, walled-off necrosis) of AP as described in the revised Atlanta classification and
- Mortality.

The primary variable will be compared between the stent and control groups. The analysis will be carried out by a two-group chi-square test with a 5% two-sided significance level.

Secondary efficacy parameters will be analyzed by descriptive statistical methods including the frequency and proportion for categorical variables, the case number, mean, standard deviation, median, minimum and maximum values for continuous variables. All secondary parameters will be evaluated for the total population, and separately for the stent and control groups, as well as for group A1, A2, B0, B1, B2 and C. Since sample size was estimated only for the stent and control groups, the interpretation of the secondary endpoints will be carried out in a descriptive manner.

Premature termination of the study

Safety issues, AEs and SAEs will be monitored continuously by the DSMB. In addition, an interim analysis will be performed after half of the expected patients have been recruited. If the DSMB suspects harm there will be a meeting between the DMSB and the organizing and steering committee and an independent statistician. During this meeting the potential harm will be discussed. The trial will not be stopped for futility, because this is the first randomized trial on using PPS in ABP and the current guidelines will be influenced by the results.

Participation and publication policy

Expert Centers throughout the world are welcome to participate in the PREPAST trial. “Online Call for Centers” is available at http://www.pancreas.hu/en/studies. Completion of the “LETTER OF INTENT” form will be mandatory for registering participation of each institution. The organizing and steering committee will acknowledge receipt of the “LETTER OF INTENT” form and will contact centers providing them with additional study information. The final decision whether a centre (investigator) will be accepted to join into the trial will be made upon endoscopic experties of both the centre and investigator.

All members of the organizing and steering committee will be mentioned as an author (also authors of this article).

For others, co-authorship will be based on the international guidelines, with a maximum of one co-author per participating site. Participating clinicans that do not fulfill these criteria will be listed as a collaborator and the journal will be asked to present the names of collaborators to be listed in PubMed.

The order of authors will be based on scientific input and determined by the organizing and steering committee.

Discussion

The PREPAST study is designed to answer the question whether temporary insertion of a PPS at the early ERCP of ABP patients leads to a better overall outcome of their pancreatitis. It is also designed to assess the technical feasibility and safety of preventive stenting in this setting, furthermore to answer the question whether using PPS can reduce morbidity in ABP patients with and without signs of cholangitis.

The utility of early ERCP and ES in ABP has been debated over the last few years as certain meta-analyses did not find better outcome (in terms of morbidity and mortality) compared to conservative treatment in ABP patients without signs of cholangitis. As a result, previous european and american guidelines suggested early endoscopic intervention only in cases of cholangitis and a predicted severe course of ABP [21,22]. It is worth considering that trials involved in the above mentioned meta-analyses are mostly 15–20 years old and very different in study design, inclusion criteria and

endpoints which might contribute to the conflicting data. The favourable result of this debate is the recognition that the indication of ERCP in ABP should not be based on the predicted severity but on the presence of cholestasis and/or cholangitis. More recent trials confirmed this approach and it has been accepted and published by the latest guidelines [9,2,10]. This is especially important as clinical or radiological scoring systems cannot reliably predict severity in the early course of ABP, in the „therapeutic window".

It should be noted that the incidence of ABP is increasing, however the morbidity and mortality are remained almost the same even with the introduction of this changed approach into clinical practice. On the other hand experimental data from recent years suggest that the acinar-ductal tango plays an important role in the pathogenesis. Therefore we hypothesize that early CBD clearance not always affects adequately and positively the pathogenetic steps which take place in the pancreatic acinar-ductal tango. We believe that maintaining the outflow of the pancreatic duct with temporary placement of PPS can further improve the outcome of ABP.

We specifically designed this study to answer our hypothesis. We intended to include ABP patients irrespective of the predicted severity of AP and the abscence or presence of acute cholangitis, however the presence of acute cholangitis warrants slightly different approach. Therefore the study has two arms. Study arm A is designed for patients with ABP and co-existing cholangitis in whom urgent ERCP is indicated and suggested by every guideline. The definition and diagnostic criteria of acute cholangitis have improved a lot since the last meta-analyses. According to the 2013 Tokyo guidelines mild acute cholangitis can be treated only with antibiotics for the first 24 h and only those patients require urgent biliary decompression who fail to respond. We do not want to influence our results by antibiotic treatment, so all patients with signs of acute cholangitis (fullfillment of Tokyo criteria) will be addressed to study arm A, and will recieve early endoscopic intervention with or without PPS insertion. Study arm B is designed for ABP patients without acute cholangitis. AP with evidence of gallbladder stones and/or sludge is classified as ABP according to the criteria of the Dutch Pancreatitis Study Group even without signs of cholestasis. These patients do not benefit from ERCP, therefore we do not include them in randomization but provide conservative treatment for them. However ABP patients without signs of acute cholangitis but evidence of cholestasis will be randomized into 3 groups to either recieve conservative treatment or early endoscopic intervention with or without PPS placement. In the randomized trial of Acosta et al. 60% of CBD stones passed spontaneously within 48 h, therefore we allowed this timeframe before crossover from the conservative treatment group to the ERCP group will take place for patients with persistent cholestasis [23].

Every patient then recieve similar treatment except that initial usage of antibiotics only allowed for acute cholangitis (and/or other bacterial infections) but not for prophylaxis. We specifically wanted to define the indications and timing for nasojejunal feeding. We specifically selected the 48 h timeframe as until then patients with mild ABP will be pain free and oral feeding can be started, furthermore patients who require enteral feeding can also be determined by this time and this timeframe is suggested by IAP/APA guideline [9].

We intentionally chose these PPSs as these have small diameter, short length and have an internal flap which prevents early stent dislodgement and ensures that they remain in place while they intended to be there. All stents will be extracted within a few days so negative consequences of these stents on pancreatic ducts are not expected.

The primary endpoint focuses only morbidity of ABP and not mortality because demonstrating a significant reduction in mortality would require a very large sample size, and the described systemic and local complications would affect the patients outcome mostly. However we would like to concentrate on several other factors described in the secondary endpoints section.

Conclusion

The PREPAST trial is a prospective, randomized, controlled, multicenter study addressed to investigate the favourable effect of using preventive pancreatic stenting at the early ERCP of acute biliary pancreatitis to show reduced morbidity.

Trial status

The PREPAST trial has been registered at the International Standard Randomised Controlled Trial Number (ISRCTN) Register (trial ID: ISRCTN13517695).

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