Protocol

Supplement to: Rectal Indomethacin to Prevent Post-ESWL Pancreatitis: The RIPEP Randomized Clinical Trial

1 Title

Rectal Indomethacin to Prevent Post ESWL-pancreatitis

2 Trial registration

NCT02797067, registered on May 29th, 2016, and was initially released on May 31st, 2016

3 Protocol version and summary of amendments to the original protocol and SAP through course of study

Version: 20171220A

Issue date: 20 December 2017

5/10/2017:

1. Sample size increased from 1116 total subjects to 1370 total subjects because statistical power was recalculated.

12/20/2017:

The definition of the primary outcome, post-ESWL pancreatitis, is changed to the Revised Atlanta International consensus from Cotton's criteria. Patients were identified as post-ESWL pancreatitis if meeting two out of three criteria: pain consistent with acute pancreatitis; amylase or lipase>3 times normal limit; characteristic findings on imaging.

4 Roles and responsibilities

YYQ and NR drafted the manuscript. NR and JYG participated in the enrollment of patients in the study. YYQ and CW performed the sample size calculation. WBZ, LX, JP and XYT participated in the acquisition of data. HC, LHH, HW and BL lead the site-specific recruitments and carried out the study interventions. ZDJ, DW, YQD and LWW participated in the design of the study. ZL and ZSL conceived the project and led the study. ZL obtained funding of the study. All authors had access to the study data and reviewed and approved the final manuscript.

5 Background

Chronic pancreatitis encompasses a wide range of progressive fibro-inflammatory processes of the exocrine pancreas that eventually lead to damage of the gland, leading to abdominal pain, endocrine (diabetes) and exocrine insufficiency (steatorrhea). Pancreatic duct stones, a common complication of chronic pancreatitis, develop during the natural course of disease and are observed in 90%

patients [1]. Current treatment options include endoscopic therapy, extracorporeal shock wave lithotripsy (ESWL) and surgery. ESWL disintegrates the stones as a compensatory role thus facilitating main pancreatic duct (MPD) sphincterotomy, stricture dilatation, stone extraction and MPD stenting during endoscopic retrograde cholangiopancreatography (ERCP) [2,3]. The European Society of Gastrointestinal Endoscopy (ESGE) recommends ESWL as a first step, immediately followed by endoscopic extraction of stone fragments for treating patients with uncomplicated, painful chronic pancreatitis and radiopaque stones of 5 mm or more obstructing the MPD [4]. Although proved as safe, effective and noninvasive in stone fragmentation [5–8], ESWL can still cause adverse events, which can be classified as complications and transient adverse events (TAEs), depending on the severity. Based on previous published studies, major complications were classified into five groups: post-ESWL pancreatitis, bleeding, infection, steinstrasse and perforation [6, 9]. It is reported that the rate of post-ESWL pancreatitis ranges from 6.3 to 12.5% [1]. According to previous data in our center, post-ESWL pancreatitis was the most common complication, with an overall occurrence rate of 6.8% for the first ESWL sessions. Some cases may need specific medical treatment or prolonged hospitalization, high medical expenditure and may even be life-threatening [9].

Compared to ESWL, complications of ERCP have been widely studied and the prevention strategies have been particularly analyzed by prior studies. Post-ERCP pancreatitis (PEP) also proved to be the most common complication with a reported incidence ranging from 3.6 to 15.1% in large-scale studies [10]. To date, various prophylactic procedures have been applied while prophylactic pancreatic stent (PPS) placement and rectally administered nonsteroidal anti-inflammatory drugs (NSAIDs) are promising for decreasing the rate and severity of PEP [11–16]. The strongly prophylactic effect of NSAIDs has prompted the European Society of Comparative Gastroenterology (ESGE), the Japanese Society of Hepato-Biliary-Pancreatic Surgery and The Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy (ASGE) to recommend the intrarectal administration of NSAIDs in all cases undergoing ERCP without contraindications [17–19]. Furthermore, Luo et al. have conducted a multicenter randomized controlled trial and demonstrated that pre-procedural rectal administration of indomethacin in unselected patients reduced the overall occurrence of PEP compared with a risk-stratified and post-procedural strategy [20].

As there are few research regarding the incidence and prophylaxis of post-ESWL complications and given the potential clinical and economic benefit, we designed this prospective, randomized, double-blinded, placebo-controlled trial to investigate whether rectally administered indomethacin can effectively decrease the incidence and severity of post-ESWL pancreatitis as well as any associated adverse events, thus benefiting patients treated with pancreatic ESWL.

6 Objectives

To investigate whether rectal indomethacin can effectively decrease the incidence and severity of post-extracorporeal shock wave lithotripsy (ESWL) pancreatitis as well as associated transient adverse events, thus benefiting patients treated with pancreatic ESWL.

7 Trial design

The RIPEP trial is designed as a prospective, randomized, double-blinded, placebo-controlled clinical trial.

8 Study setting

The study is conducted in Changhai Hospital, which is a tertiary referral center and the largest digestive endoscopy center performing pancreatic ESWL in China.

9 Eligibility criteria

Inclusion criteria

All patients (aged 18 years or older) with chronic pancreatitis treated with ESWL for pancreatic stones. ESWL is performed for the clearance of radiopaque obstructive MPD stones larger than 5 mm located at the head/body of the pancreas.

Exclusion criteria

1) Readmitted to the hospital during enrollment of the study;
2) Suspected or established malignancy;
3) Pancreatic ascites;
4) Receiving NSAIDs within 7 days;
5) Contraindications to ESWL;
6) Contraindication or allergy to NSAIDs (including gastrointestinal hemorrhage within 4 weeks or renal dysfunction with serum creatinine > 120 μmol/L);

7) Presence of coagulopathy or received anticoagulation therapy within 3 days;

8) Acute pancreatitis within 3 days;

9) Known active cardiovascular or cerebrovascular disease;

10) Unwilling or unable to provide consent;

11) Pregnant or breastfeeding women;

12) Being without a rectum (i.e., status post-total proctocolectomy).

10 Interventions

If inclusion/exclusion criteria are met and written informed consent has been obtained, the subject will be randomized to receive either a 100-mg indomethacin suppository or identical-appearing placebo. Glycerin suppositories used in our study are produced by department of pharmacy, Changhai Hospital, making them identical in appearance to indomethacin suppositories. Patients enrolled receive suppositories without packaging, making it possible that patients enrolled and performing endoscopists are all blinded to the assignment despite of the different packaging. The suppository will be administered within 30 min before ESWL by a trained research nurse blinded to the type of suppository labeled with allocation sequence. Randomization will occur in a 1:1 fashion with a random number table generated by the investigator, making it possible that all the patients and staff endoscopists are blinded to the treatment assigned to each participant.

ESWL will be performed by two endoscopists (HC and HW) using an electromagnetic lithotripter with bi-dimensional fluoroscopic targeting facility. The pretreatment procedure is similar to that for ERCP. Intravenously administered remifentanil combined with dexmedetomidine is administered for analgesia during the procedure.

Patients are to be placed in the supine position or tilted to their right side at an angle of 30°. An intensity ranging from 1 to 6 was used with a frequency of 60–120 shocks per min during the procedure, and the exposure is limited to a maximum of 5000 shock waves per session. The duration of each session is 60–90 min. Routinely, it was set at an intensity of 6 with a frequency of 120 shocks per min and a total of 5000 shock waves per session. The fragmentation of the stones is monitored by fluoroscopy during the pancreatic ESWL session. Vital signs of the patients will be closely monitored and procedure related parameters, intensity, frequency, duration and fragmentation efficacy, will be recorded by the performing endoscopists during and right after

ESWL.

After the ESWL, patients will be kept under surveillance for up to 24 h. A Visual Analogue Scale (VAS) before and after the procedure will be recorded. Serum amylase, routine hematology and biochemical tests will be measured in all study patients 3 and 24 h after the procedure and subsequently at clinical discretion. If new abdominal pain appears at any moment during the surveillance period, the amylase level will be measured. If abdominal pain suggests strongly that acute pancreatitis is present, but the serum amylase activity is less than three times the upper limit of normal, as may be the case with delayed presentation, imaging will be required to confirm the diagnosis of acute pancreatitis. All complications will be captured during hospitalization. Repeated ESWL sessions will be performed over consecutive days until the stones have been successfully fragmented, which is defined as stones broken into fragments ≤2 or 3 mm, or by the demonstration at X-ray of decreased stone density, increased stone surface, and heterogeneity of the stone which may fill the MPD and adjacent side branches. ERCP is routinely performed one or two days after the last session of ESWL or after complete recovery from post-ESWL complications for the clearance and visualization of the MPD.

Patients who develop post ESWL/ERCP pancreatitis will be treated with standardized guideline-based management for acute pancreatitis overseen by the treating physician. Usually most of the patients developed mild to moderate post-ESWL pancreatitis based on previous treatment, and no specific strategy was provided before the procedure. The management of patients with acute pancreatitis after the procedure includes closely monitored general supportive care consisted of adequate fluid resuscitation, supplemental oxygen, correction of electrolyte and metabolic imbalances and effective pain control. Efforts to rest pancreas includes fasting, nasogastric suction, proton pump inhibitors, somatostatin, and octreotide. Gabexate mesilate is used to reduce activated proteases. Prophylactic antibiotics is also used for prevention of infection. Appropriate treatment is provided once complications occur.

11 Outcomes*

Primary outcome

The primary outcome is the incidence of post-ESWL pancreatitis.

Patients were identified as post-ESWL pancreatitis if meeting two out of three criteria: pain consistent with acute pancreatitis; amylase or lipase>3 times normal limit; characteristic findings on imaging, in according to the Revised Atlanta International consensus.

Secondary outcomes

The secondary outcomes include the incidence of moderate to severe post-ESWL pancreatitis, asymptomatic hyperamylasemia and post-ESWL complications. The related definition and stratification of post-ESWL complications is shown in Table 1.

**For patients undergoing more than one ESWL session during hospital admission, only the result of the first procedure will be included into analysis, and for patients readmitted only the first admission will be considered for enrollment.*

Table 1 Definitions of major complications of ESWL

Complications	Mild	Moderate	Severe
Post-ESWL pancreatitis	Two of the following: a) Pain consistent with acute pancreatitis; b) Amylase or lipase > 3 times normal limit; c) Characteristic imaging findings, requires admission or extension of planned admission from 2 days to 3 days	Requires hospitalization of 4 – 10 days	Hospitalization for > 10 days, pseudocyst, or intervention (percutaneous drainage or surgery)
Bleeding	Clinical evidence of bleeding, hemoglobin drop < 3 g, no transfusion	Transfusion of ≤ 4 units, no angiographic intervention, or surgery	Transfusion of ≥ 5 units or intervention (angiographic or surgical)
Infection	> 38 °C for 24 – 48 hours	Requires > 3 days of hospital treatment	Abscess, septic shock, or intervention (percutaneous drainage or surgery)
Steinstrasse	Severe abdominal pain without other post-ESWL complications	Combined with other complications, or requires > 3 days of hospital treatment	Combined with other complications; hospitalization for > 10 days, or surgery

Perforation	Possible, or very slight leak of fluid, treatable with fluids and suction for≤ 3 days	Any definite perforation treated medically for 4 – 10 days	Medical treatment for > 10 days or intervention (percutaneous or surgical)

12 Timeline

See Fig.1.

	STUDY PERIOD								
	Enrolment	**Allocation**	**Post-allocation**						**Close-out**
TIMEPOINT	$-t_1$	0	Day 1: 30 min before ESWL	Day 1: 3h post ESWL	Day 2: 24h post ESWL	Day3-®	ERCP	Hospital discharge	t_x
ENROLMENT									
Eligibility Screen	x								
Informed consent	x								
Demographics	x								
Clinical characteristics	x								
VAS score	x								
Basic test®	x								
Randomization		x							
INTERVENTION									
Rectal indomethacin			x						
Rectal glycerin			x						
ASSESSMENT									
VAS score				←	—	→			
Serum amylase				x	x	x			
laboratory test					x	x			
Radiology®				←	—	→			
Complications after ERCP							x	x	
Drug-related adverse events			←	—	—	—	—	→	
Outcomes assessment									x

Figure 1. Schedule of enrolment, interventions and assessments.

13 Sample size

This trial is a superiority trial. According to our previous retrospective studies, post-ESWL pancreatitis occurred in about 6.8% of the patients for the first ESWL sessions and accounting for 69.4% of complications in our center [9]. We estimate that 1370 patients (685 per arm), including a possible withdrawal rate of 5%, will provide a 50% reduction in the incidence of post-ERCP pancreatitis, corresponding to a relative risk of 0.5 with a two-tailed alpha of 0.05 and a power of 80%.

14 Recruitment

All adult patients admitted with CP will be considered for inclusion into the study during their

hospital admission in Changhai Hospital. The research members will screen the electronic medical record system every day to find the appropriate patients. Once a potential subject is found, the subject will be seen and examined by the research members. Once identified meeting the eligibility criteria, he or she will be invited to participate in the study. Written informed consent will be obtained from every patient. All subjects have the right to refuse or withdraw from the study without giving any reasons.

15 Allocation

After enrollment, patients will be randomized to receive either 100 mg of indomethacin suppositories or identical-appearing glycerin suppositories in a 1:1 ratio within 30min before the procedure by a trained research nurse. The randomization schedule was generated by the investigator using a random number table, making it possible that patients enrolled and performing endoscopists are all blinded to the treatment protocol assigned.

16 Data management

Data collection

Clinical data regarding baseline characteristics (including age, sex, etiology, smoking status, complications, previous pancreatic surgery, and previous ERCP, etc., as listed in Table 2) and outcomes will be collected during hospital admission using a case record form (CRF). CRFs will be filled out by study group personnel blinded to group assignments.

All clinical data from individual subjects will be de-identified and given a study number. The study number will serve as a link between the data and the subject's identifiable information. The data will only be accessed by the primary investigator and research assistants.

Table 2 Demographic and clinical characteristics of CP patients in the study

Age
At onset of chronic pancreatitis
At diagnosis of chronic pancreatitis
At pancreas stone
At enrollment
Sex
Smoking status
Etiology

Alcoholic CP
Idiopathic CP
Hereditary (Familial) CP
Metabolic
Traumatic
Others
Complications
Diabetes
Steatorrhea
Pseudocyst
Common Bile Duct obstruction or stricture
Duodenal stenosis
Pancreatic fistula
Portal hypertension
Previous pancreas surgery
Previous ERCP
Radiolucent stone

Descriptive statistics and analysis

All analyses will be performed on an intention-to-treat basis. For continuous variables, tests of data normality will be carried out using the Shapiro–Wilk test. Normally distributed variables will be presented as mean ± standard deviation (SD) and compared using Student's t-tests. Non-normally distributed variables will be presented as median (interquartile range, IQR) and compared using Mann–Whitney *U* tests. Categorical variables will be presented as frequencies and percentages. Chi-squared analysis or Fisher's exact test will be used for comparison of categorical variables. Two-sided *P* values less than 0.05 are considered statistically significant. Post hoc subgroup analyses of the primary outcome based on potential risk factors of ESWL identified earlier will be performed, including age, sex, main etiology, diabetes, and steatorrhea. Comparisons will be represented with relative risk (RR) and nominal 95 percent confidence intervals (CI). All statistical analyses will be performed using SPSS (version 23.0).

17 Instruments

Data collection, handling, record keeping

Source documents provide evidence of participant involvement, consent and permit collection of the data acquired. Source documents will be retained at the investigator's site and may include but

are not limited to, consent forms, current medical records and laboratory results. All data will be primarily stored in a secure, locked room within the department of gastroenterology at Changhai Hospital, Shanghai. Only study staff will have access to these source documents. All study staff and investigators will endeavor to protect the rights of the study's participants to privacy and informed consent.

Case Report Forms

CRFs will be treated as confidential documents and held securely in accordance with regulations. CRFs shall be restricted to those personnel approved by the Chief Investigator. The investigator shall sign the CRF to confirm the accuracy of the data recorded.

Record Retention and Archiving

The investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 5 years, or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

18 Monitoring

The data will be monitored every twelve months by the Data Safety Monitoring Committee (DSMC) which is independent of the trial organizers. The protocol adherence, the progress of the trial and the safety parameters will be accessed by the DSMC. All physicians who are involved in the study will be asked to report any potential adverse events during the study. These adverse events will be collected and discussed with the DSMC every twelve months. The outcome of the meeting of the monitoring committee will be sent to the ethics committee and the physicians who are involved with the study. Any death will be reported directly to the DSMC and is discussed about the cause of death.

19 Ethics approval

Ethical approval is obtained from Changhai Institutional Review Board. (CHEC2016-096)

20 Informed consents

Written informed consent will be obtained from each patient before randomization by his/her attending doctor.

21 Protocol amendments

Any subsequent amendments of the protocol need to be approved by the relevant ethical bodies before the implementation.

22 Declaration of interests

The authors declare that they have no competing interests.

23 Dissemination

We aim to present the results of these findings to national and international conferences. We also hope to disseminate finding by submitting results for publication in peer-reviewed journals.

24 References

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