Study Protocol

Comparison between local cryoprevention associated with NSAIDs versus NSAIDs alone for reducing the incidence of post-ERCP pancreatitis: a randomized clinical trial.

Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo - Brazil

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COLD AND NSAID TRIAL – Comparison between local cryoprevention associated with NSAIDs versus NSAIDs alone for reducing the incidence of post-ERCP pancreatitis: a randomized clinical trial.

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Investigator Responsibility

The investigator will start the protocol only after written approval from CAPPesq - Ethics Committee for Research Project Analysis of HCFMUSP. This approval must be in the investigator's name and a copy sent to the Gastrointestinal Endoscopy Service of HCFMUSP, along with the Informed Consent Form (ICF) approved by CAPPesq, before the start of the protocol.

The Principal Investigator must also:

1. Conduct the study according to the established Protocol, with CAPPesq approval and the signed ICF;

2. Ensure that the products used are regulated by ANVISA;

3. Ensure that written ICF is obtained from each participant before the start of any study-related activity;

4. Provide all necessary data and reports, as well as patient charts with proper medical notes to CAPPesq, when requested;

5. Allow study members or the Principal Investigator's designee, as well as ANVISA representatives, to inspect and copy any documents related to this clinical investigation;

6. Provide adequate resources to ensure compliance with all study-related procedures and prompt submission of all case notification forms to CAPPesq;

7. Communicate protocol requirements to requesting physicians;

The Principal Investigator may delegate one or more of the above functions to a Participating Investigator, provided the latter signs the INVESTIGATOR term and receives adequate information. However, the Principal Investigator has global responsibility for approval with CAPPesq and the proper conduct of the study, including obtaining and documenting the participant's ICF, and compliance with the study protocol, in addition to signing the clinical investigation, collecting all necessary data, and ensuring that everyone involved in the study is adequately trained before any data collection.

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Abstract

The standard prophylaxis for post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP) is performed with rectal non-steroidal anti-inflammatory drugs (NSAIDs). A recent Japanese study demonstrated the efficacy of irrigating the periampullary region with ice water, however without the concomitant use of NSAIDs. The proposed study is a randomized, single-center, single-blind clinical trial that aims to compare the efficacy of rectal NSAIDs alone versus NSAIDs associated with ice water in the prevention of PEP.

Introduction

PEP is the most common and feared adverse event associated with endoscopic retrograde cholangiopancreatography (ERCP), occurring in about 3.5% to 9.7% of cases in unselected patients, reaching higher rates in high-risk groups [1, 2]. Although most cases are mild, PEP can progress to severe forms, with pancreatic necrosis, multi-organ failure, and death, impacting patients' quality of life and healthcare system costs. Currently, rectal administration of NSAIDs, such as indomethacin or diclofenac, is the main pharmacological strategy recommended by international guidelines [European Society of Gastrointestinal Endoscopy (ESGE) and American Society for Gastrointestinal Endoscopy (ASGE)] for PEP prevention [3, 4, 5, and 6]. Other measures such as hyperhydration with lactated Ringer's and pancreatic stent placement can also be used for PEP prevention, depending on the clinical context, whether or not a guidewire passed into the main pancreatic duct during ERCP, and the presence of contraindications to NSAID use [5].

Cryoprevention, or the use of ice/cooling, is an intervention widely used in acute musculoskeletal injuries to reduce edema and inflammation through vasoconstriction and decreased local metabolic activity [7, 8]. Based on this physiological principle, it is hypothesized that topical cooling of the duodenal papilla after endoscopic manipulation may reduce post-procedure papillary edema, one of the main pathophysiological mechanisms of pancreatic flow obstruction and consequent PEP [9, 10].

A recent Japanese randomized clinical trial demonstrated that irrigation of the papilla with ice water (4 to 5°C) significantly reduced the incidence of PEP (3.2% vs 6.8% in the control group), suggesting that this simple and low-cost technique can be a valuable tool for PEP prevention [10]. Although rectal NSAIDs are recommended for preventing such an adverse event, they were not used in conjunction with the cooled water in the study in question.

The main hypothesis of this study is the efficacy of instilling ice-cold distilled water (4ºC to 5ºC) into the second duodenal portion as an adjunct to the standard practice of NSAID use for reducing the incidence of PEP in our setting.

1. Objectives

This study aims to evaluate, in an unprecedented way, the efficacy of instilling ice-cold distilled water (4ºC to 5ºC) into the second duodenal portion as an adjunct to the standard practice of using NSAIDs, comparing it with a group using NSAIDs only to reduce the incidence of PEP in our setting.

2. Hypothesis

The main hypothesis of this study is the efficacy of instilling ice-cold distilled water (4ºC to 5ºC) into the second duodenal portion as an adjunct to standard practice for reducing the incidence of PEP in our setting.

3. Methodology

3.1. Study Setting

The study will be conducted at a single center - Gastrointestinal Endoscopy Service of the Hospital das Clínicas of the University of São Paulo Medical School, Brazil. Av. Dr. Enéas de Carvalho Aguiar, 255 - ICHC - 6th floor - Room 3 - São Paulo - SP - 05403-000 tel (11) 2662-6460.

3.2. Study Design

This is a randomized, sequential, blinded, 1:1 paired clinical trial conducted at a single tertiary center.

3.3. Randomization and Pairing

Random sequence generation will be performed with online software in a 1:1 ratio in blocks of 4.

The randomization sequence will be computer-generated in permuted blocks. Allocation concealment will be guaranteed through an online system or opaque sealed envelopes, opened only immediately before the procedure.

3.4. Blinding

Patients will not know which group they are allocated to, nor will the researchers responsible for data extraction and statistical analysis. However, there will be no blinding of the performing physicians, as the endoscopist will handle the device and will therefore be aware of whether ice water was used or not.

3.5. Sample Size and Statistics

An initial sample of 530 participants was calculated; considering a 10% drop-out, the final calculation was 583 people, based on the last clinical trial that showed an approximate PEP incidence of 3.0% in the ice water instillation group [10] and based on an 8.5% approximate PEP incidence in patients who used indomethacin without ice water instillation [11]. A power of 80% and a 95% confidence interval (CI) (statistical significance of 5%) were considered.

An intention-to-treat analysis will be used. Differences will be expressed as relative risk with a 95% CI. Categorical variables were described by frequency counts and percentages; chi-square and Student's t-tests will be used to compare categorical and continuous variables between the two groups, respectively. Quantitative variables will be described using means and standard deviations. Using Poisson regression, incidence rates will be calculated to assess the relationship between study arm, age, sex, and ERCP indication. Multivariate estimates of prevalence ratios will be obtained via log-binomial regression; adjustments will be made for age, sex, and colonoscopy indication. Mixed-effects models may be adjusted with a random intercept and treatment as a fixed effect. A $p < 0.05$ will be considered statistically significant.

4. Eligibility Criteria

Inclusion Criteria

Patients aged 18 years or older.

Clinical indication for ERCP.

Presence of native major duodenal papilla without previous manipulation.

Ability of the patient or companion to provide informed consent.

Exclusion Criteria

Contraindication to ERCP (e.g., severe hemodynamic instability, visceral perforation).

Ongoing acute pancreatitis (except mild biliary where ERCP is therapeutic and pain has already resolved).

Inaccessibility of the duodenal papilla, whether due to altered surgical anatomy preventing access to the papilla (e.g., Gastrectomies with Billroth II and Roux-en-Y reconstruction, except Billroth I) or gastroduodenal obstructions (pyloric or duodenal stenoses).

Pregnant women.

Refusal to participate in the study or inability to sign the ICF.

Contraindication to NSAID use.

5. Recruitment

Patients will be recruited consecutively at the participating center before the procedure.

Sampling method: non-probability sample. Patients will be included consecutively.

5.1. Investigators

Clinical investigators will be appointed as participating researchers in the study, and physicians who perform endoscopic evaluations related to the Hospital das Clínicas of the University of São Paulo Medical School.

The clinical investigator will be responsible for following the protocol, obtaining informed consent, collecting and recording procedure data, and performing and recording patient follow-up. Case report forms will be the information record documents.

6. Procedures

Standard ERCP (Base procedure for both groups): All patients will undergo ERCP under sedation or general anesthesia and will be hydrated intravenously with lactated Ringer's (3 ml/kg/h during the procedure, 20 ml/kg/h bolus post-procedure, and 3 ml/kg/h for 8 hours post-procedure), unless contraindicated, according to institutional routine. The procedure begins with the introduction of the duodenoscope into the second duodenal portion, followed by selective cannulation of the papilla and the bile duct using a papillatome and guidewire. After the papillatome enters the extrahepatic bile duct, contrast injection is performed under radioscopy to study the biliary tree, followed by papillotomy if indicated. Therapeutic management (stone removal, dilation, stents, etc.) follows the standard treatment based on the diagnosis. *Standard Prophylaxis:* Rectal administration of NSAIDs (indomethacin 100mg) will be performed for all patients without contraindications, according to international guidelines and service routine.

Intervention Group (Ice-cold distilled water): Immediately after the end of the therapeutic ERCP and before removing the duodenoscope, irrigation of the duodenal papilla with ice-cold distilled water will be performed.

Preparation: The distilled water will be kept refrigerated at a temperature between 4ºC and 5ºC.

Technique: Using a catheter or through the working channel of the endoscope, 250 ml of ice-cold distilled water (4º to 5ºC) will be injected towards the papillary region. The infusion can be done in divided boluses (e.g., 5 syringes of 50 ml) with interleaved aspiration of the infused liquid to avoid excessive gastric/duodenal distension, as described in the protocol by Azuma et al [8].

Control Group: Patients will undergo standard ERCP and standard pharmacological prophylaxis (indomethacin 100mg), without the instillation of ice-cold distilled water at the end of the exam.

Recovery and Follow-up: After the procedure, patients will be monitored in the recovery room. Blood samples for amylase and/or lipase measurement will be collected according to institutional protocol. Clinical evaluation of abdominal pain will be performed.

7. Outcomes

Primary Outcome:

Incidence of Post-ERCP Pancreatitis (PEP): Defined according to consensus criteria (Modified Cotton Criteria): new or worsened abdominal pain consistent with pancreatitis, associated with an elevation of serum amylase or lipase of at least 3 times the upper limit of normal, occurring more than 24 hours after the procedure [5, 9, 12].

Secondary Outcomes:

PEP Severity: Classified as mild, moderate, or severe based on the length of hospital stay and local/systemic complications, according to the Modified Cotton Criteria [5, 9, 12].

Cholangitis: Defined by fever, jaundice, and/or leukocytosis with evidence of biliary obstruction or need for reintervention [5].

Bleeding: Clinical evidence of hemorrhage (melena, hematemesis) or drop in hemoglobin > 2g/dL requiring transfusion or endoscopic/surgical intervention [5].

Perforation: Radiological or surgical evidence of air or luminal content leakage into the abdominal cavity or retroperitoneum [5].

Mortality: Death from any cause up to 30 days after the procedure [5].

8. Financial Support

The study will use the endoscopy service's own resources where it will be conducted (equipment, ERCP supplies). Distilled water is a low-cost item available in hospital routine.

9. Ethical Aspects

The protocol will be submitted for approval to the Ethics Committee for Research Project Analysis (CAPPesq) of HCFMUSP. The study will be conducted in accordance with the Declaration of Helsinki and local regulations. All patients will sign the ICF before inclusion. Since the intervention (cooled water) is low risk and the control group will receive standard treatment (including NSAIDs if indicated), there is no ethical detriment to the participants.

10. Benefits

It is expected that the addition of cryoprevention will reduce the incidence of post-ERCP pancreatitis, decreasing patient suffering, hospital stay, and hospital costs, without adding significant risks to the procedure.

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