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Timing of CHolecystectomy In Severe PAncreatitis (CHISPA): study protocol for a randomized controlled trial

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ABSTRACT

Acute pancreatitis is the recurrent reason for gastrointestinal admission in a clinical urgent setting, it happens secondary to a wide array of pathologies out of which biliary disease stands as one of the most frequent causes for its presentation. Approximately 20% of pancreatitis are of moderate or severe severity. Currently, there is not a clear recommendation on timing for cholecystectomy, either early or delayed.

CHISPA is a randomized controlled, parallel-group, superior clinical trial. An intention-to-treat analysis will be performed. It seeks to evaluate differences between patients taken to early cholecystectomy during hospital admission (72 hours after randomization) versus delayed cholecystectomy (30±5 days after randomization). The primary endpoint is major complications associated with laparoscopic cholecystectomy defined as a Clavien-Dindo score of over III/V during the first 90 days after the procedure. Secondary endpoints include recurrence of biliary disease, minor complications (Clavien-Dindo score below III/V), days of postoperative hospital stay, and length of stay in an intensive therapy unit postoperatively (if it applies).

The CHISPA trial has been designed to demonstrate that delayed laparoscopic cholecystectomy reduces the rate of complications associated to an episode of severe biliary pancreatitis compared to early laparoscopic cholecystectomy.Trial registration number: NCT06113419.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ There is scarce and low-quality evidence supporting interval cholecystectomy after moderately severe and severe pancreatitis.

WHAT THIS STUDY ADDS

⇒ High-quality evidence to define the timing of cholecystectomy after moderately severe and severe pancreatitis.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ With higher-quality evidence, a higher-quality recommendation could be provided in clinical practice guidelines.

BACKGROUND

Acute pancreatitis is an important cause of morbidity with growing incidence rates.[1] Pancreatitis severity is classified according to Atlanta's revised criteria into mild, moderately severe, or severe.[2] The etiology for acute pancreatitis is mostly of biliary origin and as a result performing cholecystectomy is part of the treatment to avoid recurrent episodes.[3 4]

In mild acute pancreatitis, laparoscopic cholecystectomy is recommended during the same hospital admission (also referred to as early cholecystectomy) due to evidence that reports it as a safe procedure associated with a reduction in complications relating to biliary disease.[5] Modern guidelines for the management of mild acute pancreatitis recommend early cholecystectomy with a Grade 1A recommendation.[4]

However, in the approximately 20% of cases classified as moderately severe and severe acute pancreatitis there is not a clear current recommendation on timing of cholecystectomy.[6] The WSES guidelines (World Journal of Emergency Surgery) recommend delayed cholecystectomy on patients diagnosed with pancreatitis with peripancreatic collections until they are resolved or when the patient is clinically and hemodynamically stable and inflammation subsides, with a Grade 2C recommendation (very weak recommendation; other alternatives may be equally reasonable).[4] This recommendation was included based on a study that compared early versus delayed cholecystectomy on patients with moderately severe or severe pancreatitis and peripancreatic collections, finding a higher rate of complications in the early cholecystectomy group.[7] A recently published retrospective study on which surgical outcomes for laparoscopic cholecystectomy after pancreatitis were compared evidenced that

performing cholecystectomy is a safe procedure regardless of the severity of pancreatitis.[8]

There is not any current evidence that dictates clear recommendations on an ideal timing for performing laparoscopic cholecystectomy in patients diagnosed with severe pancreatitis. The aim of this study is to establish whether there is a difference in surgical outcomes between patients diagnosed with severe pancreatitis on which cholecystectomy was performed during the same hospital admission versus patients on which interval cholecystectomy was performed (4 weeks after recovery of pancreatitis).

METHODS

Design

CHISPA is a randomized controlled, parallel-group, superior clinical trial. Patients will be randomly allocated to receive early laparoscopic cholecystectomy (within 72 hours after randomization) or interval laparoscopic cholecystectomy (30±5 days after randomization). All data and interventions will be recollected and performed in Hospital Universitario Mayor Méderi, a fourth-level high-complexity hospital in Bogotá Colombia. We followed the Standard Protocol Items: Recommendations for Interventional Trials guidelines to report this protocol.[9]

Study objective

To establish whether there is a difference in surgical outcomes comparing patients diagnosed with severe or moderately severe pancreatitis on which early cholecystectomy was performed versus performing interval cholecystectomy.

Endpoints

The primary endpoint will be to evaluate major complications, defined as a Clavien-Dindo score greater than or equal to III/V.[10]

Secondary endpoints include evaluating minor complications (defined as a Clavien-Dindo score I/II), biliary disease recurrence (defined as either acute cholecystitis, biliary colic, acute pancreatitis, jaundice, or cholangitis diagnosis), postoperative hospital stay length and postoperative stay length in an intensive therapy unit to those who apply.

This will be further classified into short-term (≤30 days) complications and long-term (>30 days) complications.

Inclusion criteria

Inclusion criteria are: age ≥18 years, diagnosis of pancreatitis according to Atlanta guidelines, moderately severe or severe pancreatitis (Acute Physiology And Chronic Health Evaluation II (APACHE II) score ≥8 on admittance), biliary pancreatitis diagnosed on imaging (be it ultrasound, MRI and/or CT), recovery of pancreatitis by oral intake (defined as 24 hours of food consumption of any consistency without emetic episodes and pain defined as <4/10 on the Visual Analog Score of pain) and written informed consent. If the patient's scholarity does not allow them to properly read the written informed consent, it will be read aloud by a member of the research team in order to affirm the subject's understanding and consent to the study.

Exclusion criteria

Exclusion criteria are: pregnancy, history of cholecystectomy, planned open cholecystectomy, pancreatitis-associated complication before laparoscopic cholecystectomy (compartment syndrome, bleeding and/or need for peripancreatic collection drainage), chronic pancreatitis, more than one episode of pancreatitis, active malignant disease, septic shock, choledocholithiasis not resolved by endoscopic retrograde cholangiopancreatography (ERCP), post-ERCP perforation and post-ERCP concomitant pancreatitis.

Sampling method

A stratified randomized sampling would be performed considering the covariables that influence the different outcomes. Posteriorly, a generalized, computer-generated randomization list will be created to assign patients to the intervention (laparoscopic cholecystectomy) in the early or interval group. The randomizaton sequence will be created on R. The patient assignation process is described in the sample size section.

Sample size calculation

Multiple sample size calculations were performed for each primary and secondary outcome so as to use the largest sample size calculated. The biggest sample size calculated was the one for the primary outcome and as such was decided as the sample size for the study.

To calculate the sample size for the primary outcome, we considered a retrospective study performed in Colombia in which two patient cohorts with a diagnosis of severe acute pancreatitis were taken to either early cholecystectomy (during the same hospitalization) or interval cholecystectomy (4 weeks after hospital discharge). Complication rates (overall, as the study does not distinguish or specify types of complications) for the early cholecystectomy group were 14% while they were 1.8% for interval cholecystectomy.[11] Considering these percentages, the sample size was calculated to obtain a clinical superiority for interval cholecystectomy versus early cholecystectomy. Taking into account an alpha value of 0.05, a beta value of 0.2 and an expected sample loss of 15%, a result of 67 patients per group was calculated for a total of 134 patients. The sample size was calculated considering a statistical equation of superiority where H0 : $\varepsilon \leq \delta$ versus Ha : $\varepsilon > \delta$, in which the p values represent the proportions for each group, ε is the significative clinical difference between both groups and δ represents the margin of superiority. As such, $\delta>0$ indicates the superiority of the experimental group over the control group. The formula can be seen in figure 1.

$$n1 = n2 = \frac{(Z\alpha + Z\beta)^2(p1(1 - p1)) + p2(1 - p2)}{(\varepsilon - \delta)^2}$$

Figure 1 Formula for sample size calculation.

The sample size was performed using the interface *r* studio V.2022.7.2, with the statistical package TrialSize.[12] This package implements specific formulas for sample size calculation for superiority studies.[13] The adjustment for sample size loss was performed with the recommended equations for clinical trials.[14]

Sample group assignation

The following scenarios were considered for patient assignation into the study using a stratification method by steps (table 1). First, the sample size was assigned taking into account the variable "Age" and second the variable "Collections" (referring to the presence of local pancreatic or peripancreatic collections).

For the stratification of the variable "Age", we used the reported variables by a study by Ramírez *et al*.[15] Appearance of severe complications (Clavien-Dindo score III/V) percentages were calculated as 82% (28/34) for the group ≥60 years and 18% (6/34) for the group <60 years.

For the second variable the percentage of patients with collections in the pancreatitis group was used (10/95).

Time of randomization

After eligibility is confirmed and written informed consent has been obtained, randomization will take place after pancreatitis is resolved, defined by the following criteria:

- Oral tolerance is defined by food consumption of ≥24 hours without vomit.
- Modulated pain (<4/10 on the pain Visual Analog Scale).
- No signs of organ failure.

Randomization

Randomization will be stratified following these parameters: if endoscopic sphincterotomy was performed, if the patient is of older age (>60 years) and if local complications were documented. A computer-generated randomized list will be used in order to assign patients to the procedure (laparoscopic cholecystectomy) by interval (4 weeks after recovery of pancreatitis) or during hospital admission. The randomized sequence will be created using R. The main investigator will oversee defining randomization according to the established sequence.

Table 1 Stratification per group

Multistage sampling			
Sample size: 67 per group, 134 total			
	Age <60	Age ≥60	Marginal total
Collections - yes	2	6	8
Collections - no	11	48	59
Marginal total	13	54	67

The researcher or research assistant enrolling a subject must communicate with the main investigator or the trial's statistician so that whoever of the two assigns the group to which the subject will be randomized.

Intervention

All patients will receive standard treatment according to the management of pancreatitis indicated in the World Journal of Emergency Surgery guidelines.[4] When pancreatitis resolves and laparoscopic cholecystectomy is decided the patient will be informed of the group they will be assigned to, be it either early or interval (4 weeks after resolution of pancreatitis).

Laparoscopic cholecystectomy is part of the medical and surgical management of biliary pancreatitis. All patients coursing with this disease must be taken to this procedure independently of the moment it is realized. Investigators will not be able to change the conduct defined by the treating physician group or place their authority (this study) over it. Moreover, participants in this study will be provided with a more rigorous follow-up while receiving the conventional intervention for the disease.

Laparoscopic cholecystectomy will be performed using the standard American 4-port technique, insufflation will be achieved using CO_2 to 15 mm Hg of pressure. Calot's triangle will be dissected until the critical view of safety is reached, being careful to dissect above the R4U line. After reaching the critical view of safety, two proximal and one distal clip will be placed on both the cystic conduct and artery separately, cutting the clips and then dissecting the gallbladder in a cystfundic direction.[16] When the critical view of safety is not reached, the surgeon may perform a fundus-first cholecystectomy, subtotal cholecystectomy, conversion to open procedure, intraoperative cholangiography or cholecystostomy at their own discretion. It will also be the surgeon's criteria to employ or not a drain system in the surgical site. The decision for these interventions will be taken intraoperatively and will be according to findings during the procedure.

Follow-up

After performing laparoscopic cholecystectomy there will be an in-person follow-up consultation using the following sequence: every 15 days during the first month and every month after until 90 days after the procedure is completed. If the patient is in the delayed cholecystectomy group a weekly telephonic follow-up will be performed until their admittance for the scheduled procedure. Postoperative follow-up in this group will be done as described in the first group (figure 2).

Data collecting and monitoring

Written informed consent will be signed before performing randomization of the subject into its assigned subgroup . The digital database employed will be using Research Electronic Data Capture with a specifically designed case report form document. It will only include

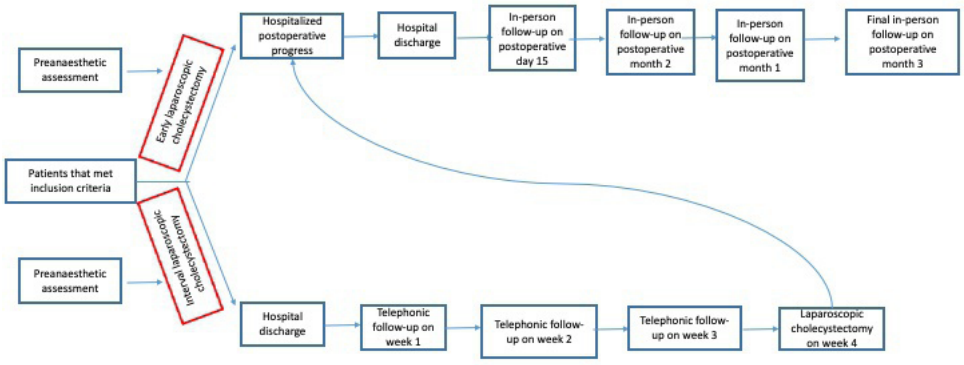

Figure 2 Flow chart that describes the data collection process.

variables of interest for the trial and is designed according to the trial stage the participant is in.

The main source of information for data collection includes the interview with the patient and reviewing clinical history, laboratory tests and diagnostic imaging available in our institution's electronic patient database.

Data will be collected, anonymized, codified and documented digitally. The research team oversees inputting data on CRF and will guarantee data safety. Confidentiality about patient information will be kept at all times. The database will be stored in files on the researcher's computers and will be password-protected.

Statistical analysis

To determine statistical differences for the primary endpoint (percentage of severe complications defined by a Clavien-Dindo score over III/V), the Pearson χ^2 test will be implemented. An intention-to-treat analysis will be performed. A two-tailed p value<0.05 will be considered statistically significant.

To characterize the sample size both clinically and demographically, a descriptive analysis will be performed where continued variables with a normal distribution will be represented by their mean and SD and non-normal distributions will be represented by their median and IQR. Categorical variables will be described as frequencies, proportions or percentages using a relative risks model.

An analysis by subgroups will be performed if ERCP was previously performed.

Most of the statistical analysis will be performed using the statistical software package Stata V.17.

Ethics

This study is classified as having a risk greater than minimum according to laws established under Resolution 008430 of 1993 from Colombia's Health Ministry (scientific, technical, and administrative norms for healthcare research), where the study is taking place. It is stratified in this risk category because it involves randomization of participating subjects in therapeutical options that have temporal variability. Both ethical principles and norms established from the Belmont Report for protection of human subjects during research will be met including respect for people, beneficence, and justice.

International (World's Medic Association's Helsinki declaration) and national laws will be followed for research involving human subjects and good clinical practice.

All participating subjects depending on their clinical condition may be intervened by their treating physician or specialty in accordance with their diseases' evolution without perjuring their participation in the study. In this case, both the patients and the information obtained in the study up until that point can be eliminated and not be considered for the analysis.

Safety

This study is a clinical trial in which there is not a direct intervention against the usual conduct on the surgical or medical management of the participating subjects. Surgical conduct in this study is a part of the typical management for acute biliary patients according to both national and international guidelines, in which the moment of performing the procedure is currently not established and as a result, it remains the surgeon's responsibility to decide this based on the patient's clinical condition.

To minimize risks for the participating subject, the researchers commit to dominating knowledge, methodology, scientific techniques and practises and ethical guidelines related to the investigation process, guaranteeing ethical and scientific integrity to maximize the research's quality. The trial will be conducted following the investigation protocol approved by CIMED (our institution's research team) and CEI-UR (Universidad del Rosario's ethics committee). The main researcher will oversee, orientate, and capacitate all personnel involved in the research team and will guarantee that all criteria are being met. All changes or any breach of the study's conduction will be reported to CIMED and/or CEI-UR, while there is an insurance policy that will cover liabilities if the patient suffers any harm due to the trial. When any type of harm or considerable risk to the health of any involved in the investigation happens, any person that

Table 2 Recommendations and grade of evidence for when to perform cholecystectomy in cases of moderately severe and severe pancreatitis

Guideline	Recommendation	Grade of recommendation
2019 WSES guidelines for the management of severe acute pancreatitis.[4]	In biliary acute pancreatitis with peripancreatic collections, cholecystectomy must be deferred until collections resolve or stabilize and there are no more signs of acute inflammation.	Very weak recommendation: alternative treatments may be equally reasonable and merit some consideration (2C).
IAP/APA* evidence-based guidelines for the management of acute pancreatitis.[20]	Cholecystectomy must be deferred in patients with peripancreatic collections until collections resolve or if they persist for over 6 weeks, cholecystectomy is safe if performed from this moment on.	Very weak recommendation: alternative treatments may be equally reasonable and merit some consideration (2C).
Japanese guidelines for the management of acute pancreatitis: Japanese Guidelines 2015.[3]	No recommendation for a moment of cholecystectomy in severe pancreatitis.	Not reported.
Clinical practice guideline: management of acute pancreatitis.[21]	Cholecystectomy must be performed during the same hospital admission for mild pancreatitis and must be deferred until clinical symptoms resolve in patients with severe pancreatitis.	Strong recommendation, moderate evidence.
American College of Gastroenterology Guideline: management of acute pancreatitis.[22]	In patients with acute necrotizing pancreatitis of biliary origin, cholecystectomy must be deferred until inflammation stops or stabilizes to prevent the risk of infection.	Strong recommendation, moderate evidence.
The consensus of integrative diagnosis and treatment of acute pancreatitis-2017.[23]	Cholecystectomy must be postponed until active inflammation resolves and fluid accumulation disappears or stabilizes.	Not reported.
Consensus and controversy among severe pancreatitis surgery guidelines: a guideline evaluation based on the Appraisal of Guidelines for Research and Evaluation II tool.[24]	In patients with acute biliary pancreatitis with fluid collections around the pancreas, cholecystectomy must be deferred until fluid collections reduce or stabilize or when there is no more active inflammatory response.	Case series (and cohort studies and cases and controls of poor quality) 4C.

*International Association of Pancreatology (IAP)/American Pancreatic Association (APA)

so wills it will be removed from the study and notified to CIMED and/or CEI-UR. The decision to terminate the trial and oversee any breaches is also the responsibility of the main researcher and the CIMED and/or CEI-UR.

DISCUSSION

The CHISPA trial is designed to answer the question of whether interval cholecystectomy leads to a reduction in major complications in the management of the patient coursing with a first episode of acute biliary pancreatitis.

Most guidelines' recommendations on when to perform cholecystectomy in patients with moderately severe and severe pancreatitis are weak considering the lack of evidence on the subject. In table 2 we include a summary of the recommendations and grade of evidence in most guidelines regarding the moment of cholecystectomy.

The strongest evidence supporting the recommendations given in most guidelines is based on a retrospective study published in 2004 that included 187 patients coursing with moderate-to-severe acute pancreatitis. Out of these patients, 5.5% of those taken to deferred cholecystectomy presented complications versus 44% in the early cholecystectomy group.[7]

Recently, in 2020, a retrospective study comparing surgical outcomes in patients taken to cholecystectomy with mild, moderate, and severe pancreatitis was published. Complication rates in all three groups did not present statistically significant differences, however, in patients with severe pancreatitis there was a statistically significant difference when considering the time interval between pancreatitis diagnosis and performing cholecystectomy. This study's conclusions were that laparoscopic cholecystectomy could be performed safely in pancreatitis regardless of its severity. Limitations of this study were the sample size and its retrospective nature.[8]

A systematic review of the literature which hoped to review the optimal time of cholecystectomy in patients with moderate-to-severe acute biliary pancreatitis concluded that there is currently a marked variation between guidelines about definitive treatment of moderate and severe pancreatitis and a disparity for defining moment of cholecystectomy. A small number of guidelines proposed a specific time period for performing cholecystectomy with low-quality evidence, however, deferring the procedure was associated to a decrease in morbimortality rates and as a result this must be the optimal treatment route until level I evidence is available in current literature.[17]

Traditionally, interval cholecystectomy has been considered the ideal surgical choice in cases of pancreatitis because it is thought that early cholecystectomy is potentially more demanding due to poorer patient condition and local inflammation, however, data supporting this statement is lacking and in cases of mild pancreatitis, this procedure holds evidence in being technically less demanding and reduces the incidence of recurrent gallbladder disease and as a result diminishes the risk of further episodes of acute biliary pancreatitis.[18 19] In severe pancreatitis, the presence of peripancreatic collections may difficult cholecystectomy and as a result a deferred procedure after resolution of pancreatitis and stabilization of present collection(s) is the preferred recommendation in most guidelines with low grades of evidence.[7]

The lack of evidence in a moment of cholecystectomy calls to provide convincing level I evidence to support this decision in habitual clinical practice, and as a result a randomized controlled trial is the preferred option. A double-blinded controlled trial would be optimal. However, because of the difference in timing of controlled cholecystectomy, blinding is not possible.

To compensate for the impossibility of a blinded assessment, early cholecystectomy will be performed in a semiurgent setting by an experienced surgeon that is not part of the research team in the following 72 hours after the patient is admitted into the study. Interval cholecystectomy will be scheduled 4 weeks after the clinical resolution of pancreatitis considering most guidelines and recent studies looking to evaluate interval cholecystectomy uses this measure of time when comparing it to early cholecystectomy.

For the proper time of randomization, the patient must have a resolution of the pancreatitis episode consisting of two criteria: 24-hour oral tolerance defined by food consumption without vomiting and controlled pain (<4 on the pain Visual Analog Scale). This is considering that patients with severe pancreatitis may not recover quickly and as a result there is a variation between onset of pancreatitis and resolution and between resolution and performing the procedure. This variation depends on the patient's individual clinical evolution. Due to randomization, there should not be a significant difference between both study arms.

The primary endpoint seeks to evaluate morbidity in severe pancreatitis. This endpoint was chosen because the study aims to present strong evidence that interval cholecystectomy reduces the rate of complications considering other studies that have yielded similar results with lower grades of evidence.

The CHISPA trial is a randomized controlled trial designed to show a reduction in the primary endpoint of incidence of major complications following interval cholecystectomy compared with early cholecystectomy in patients with a first episode of moderately severe and severe biliary acute pancreatitis.

Trial status

This trial was registered in ClinicalTrials.gov on October 2023. Data collection is expected to start in April 2024.

Contributors CR-G: Study conception and design, drafting of manuscript, critical revision of manuscript. DCM: Study conception and design, drafting of manuscript, critical revision of manuscript. AI-R: Study conception and design, drafting of manuscript. JAD-V: Study conception and design, drafting of manuscript. IV-L: Drafting of manuscript, critical revision of manuscript. LT-G: Study conception and design, drafting of manuscript.

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Patient consent for publication Not applicable.

Ethics approval The trial has been approved by our institution Hospital Universitario Mayor Méderi's CIMED research committee (Protocol nr. 2022-26-02B) and the Universidad del Rosario's Ethics Committee CEI-UR (DVO005 2456-CV1683). Participants gave informed consent to participate in the study before taking part.

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