Protocol title: Pilot Comparative Study on the Efficacy of Multimodal Management with Peritoneal Lavage Using Saline Solution versus Saline Solution with Ondansetron in laparoscopic Cholecystectomy (PLUSO study)

Acronym: Pluso Study (Peritoneal Lavage Using Saline and Ondansetron Study)

Date: November 13, 2025

Ethics Approval: This study protocol was approved by the **National Scientific Research Committee (Comité Nacional de Investigación Científica)** of the Mexican Social Security Institute (IMSS) on November 13, 2025

Clinical Trials.gov identifier: NCT06632184

Local Registration Numbers:

- Folio Number: F-CNIC-2025-082
- Registry Number: R-2025-785-080

Sponsor and Collaborators:

- Sponsor: Centro de Investigación y Asistencia en Tecnología y Diseño del Estado de Jalisco, A.C (CIATEJ)
- Colllaborating Institution: Instituto Mexicano del Seguro Social (IMSS), Delegación Jalisco
- Primary Study Site: Hospital General de Zona No. 89, Guadalajara, jalisco. Coordinación Clínica de Educación e Investigación en Salud.

Investigators:

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- **Thesis Director:** D.C. Tanya Camacho Villegas (Researcher in Medical and Pharmaceutical Biotechnology, CIATEJ)
- **Thesis Co-Director:** Dra. Martha Irazema Cárdenas Rojo (IMSS Associate Researcher)
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1. SUMMARY

1.1. Background

Postoperative pain and Postoperative Nausea and Vomiting (PONV) following laparoscopic cholecystectomy represent a significant burden, affecting patient recovery and quality of care. While standardized multimodal regimens (e.g., PROSPECT guidelines) are effective for pain, the incidence of PONV remains high.

Preliminary evidence suggests that intraperitoneal ondansetron, in addition to its antiemetic effect, may exert a local analgesic effect by blocking peripheral 5-HT3 receptors. However, no controlled studies have evaluated its combination with standard saline lavage within a standardized multimodal scheme while comprehensively measuring the total pain burden. This pilot study aims to generate preliminary evidence in this area.

1.2. Objective

To evaluate the efficacy of peritoneal lavage with 0.9% saline solution + intraperitoneal ondansetron (8mg) compared to lavage with 0.9% saline solution alone, in reducing the total postoperative pain burden (measured as the Area Under the Curve of the Visual Analog Scale over the first 24 hours – AUC-VAS/24h) in patients undergoing elective laparoscopic cholecystectomy within a standardized multimodal management protocol.

1.3. Study Design

A randomized, controlled, triple-blind, Phase IV pilot clinical trial, conducted according to CONSORT guidelines.

1.4. Participants

40 adult patients (ASA I-II) with symptomatic cholelithiasis and Nassar Grade I-II surgical difficulty will be recruited.

1.5. Intervention

Patients will be randomly assigned (1:1) to:

- Experimental Group: Peritoneal lavage with 500ml of 0.9% saline solution + 8mg ondansetron.
- Control Group: Peritoneal lavage with 500ml of 0.9% saline solution + placebo (saline only).

1.6. Main Outcome Measures

- Primary Outcome: Difference in the AUC-VAS/24h between groups.
- Secondary Outcomes: Incidence of PONV, duration of analgesia, consumption of rescue analgesics, sleep quality (Richards-Campbell Sleep Questionnaire), and procedure safety.

2. INTRODUCTION AND RATIONALE

Symptomatic cholelithiasis is a prevalent condition in Mexico. Laparoscopic cholecystectomy (LC) is the gold standard treatment, recognized for allowing faster recovery and shorter hospital stays compared to open surgery.

Despite advances in multimodal protocols, postoperative pain and PONV persist as relevant and frequent problems. PONV affects between 52% and 80% of post-LC patients and, together with poorly controlled pain, is a leading cause of unplanned hospital readmission. This morbidity burden not only impairs the patient experience but also increases the risk of serious complications.

The standard multimodal management of post-LC pain, as synthesized by the PROSPECT guidelines, effectively controls pain. However, a critical gap remains: even with the best strategies, the incidence of PONV stays unacceptably high, affecting between 27% and 43% of patients. This underscores the need for complementary interventions specifically targeting this problem.

Preliminary evidence from Abdelaziz et al. (2021) suggests that intraperitoneal ondansetron (4mg) at the end of LC results in a clinically relevant reduction in pain and a drastic decrease in the incidence of severe PONV. However, this study had limitations, including a small sample size and the use of a 4mg dose.

Therefore, this study proposes to evaluate the addition of 8mg of intraperitoneal ondansetron to the standard saline lavage. This strategy aims to simultaneously target two pathophysiological mechanisms: visceral pain (via saline irrigation that dilutes irritants) and PONV (via the potential local analgesic and antiemetic effect of ondansetron), with the goal of improving the overall quality of postoperative recovery. The safety of the intervention is supported by evidence demonstrating the stability of ondansetron in saline solution and the favorable risk profile of intraperitoneal lavage.

3. STUDY OBJECTIVES

3.1. Primary Objective

To determine whether peritoneal lavage with saline solution plus intraperitoneal ondansetron (8mg) reduces the global intensity of postoperative pain by at least 13 points in the AUC-VAS/24h, compared to lavage with saline solution alone, in patients undergoing elective laparoscopic cholecystectomy.

3.2. Secondary Objectives (Exploratory)

To evaluate, in an exploratory manner, the effect of the intervention on the following secondary variables:

- To quantify the effect of the intervention on the incidence of PONV, defined as a minimum absolute reduction of 20% in the proportion of patients experiencing at least one episode of PONV within the first 24 hours, compared to the control group.
- To evaluate the impact on the need for rescue analgesia, measuring whether the intervention prolongs the time to the first request for analgesia (duration of analgesia) by at least 2 hours and reduces the mean consumption of buprenorphine by at least 30% compared to the control group.
- To determine whether the intervention improves postoperative sleep quality by at least 10 points in the total score of the Richards-Campbell Sleep Questionnaire (RCSQ) at 24 hours, compared to the control group.

3. To document the safety of intraperitoneal ondansetron, defining it as non-inferior to the control group if the difference in the incidence of related adverse events does not exceed 5%.

4. METHODS

4.1. Study Design

This is a randomized, controlled, triple-blind, Phase IV pilot clinical trial designed to compare the efficacy of two multimodal pain management strategies in patients undergoing elective laparoscopic cholecystectomy. The trial is structured in accordance with the CONSORT (Consolidated Standards of Reporting Trials) guidelines to ensure transparency, internal validity, and reproducibility of results.

- Type of Study: Phase IV pilot clinical trial, evaluating an approved drug (ondansetron) for a non-conventional route of administration (intraperitoneal).
- Allocation: Participants will be randomly assigned in a 1:1 ratio to one of two treatment groups.
- Blinding: The study will be conducted under a triple-blind scheme:
    - Patients are blinded to group assignments.
    - The attending and research team (surgeons, anesthesiologists, outcome assessors, nursing staff) are blinded to group assignment.
    - The data analyst is blinded to group assignment until the primary analysis is complete.
- Primary Purpose: Treatment (efficacy and safety).

4.2. Study Setting

The study will be conducted exclusively at the Hospital General de Zona No. 89 of the Mexican Institute of Social Security (IMSS), located in Guadalajara, Jalisco, Mexico.

4.3. Study Duration

The study is designed to complete patient recruitment, data analysis, and presentation of results within an estimated period of twelve months, following approval by the National Research and Ethics Committee.

4.4. Participants (Eligibility Criteria)

Eligible participants will be adult patients scheduled for elective laparoscopic cholecystectomy at the study site. To ensure a homogeneous sample appropriate for this pilot trial, strict inclusion and exclusion criteria have been defined.

Inclusion criteria

Patients meeting all the following criteria will be considered for enrollment:

1. Aged between 18 and 60 years.

2. American Society of Anesthesiologist (ASA) physical status classification I or II.

3. Scheduled for elective laparoscopic cholecystectomy due to symptomatic cholelithiasis, resolved choledocholithiasis post-endoscopic retrograde cholangiopancreatography (ERCP), or gallbladder polyp.

4. Placement of a ¾-inch Penrose drain in the subhepatic cavity as part of the standardized surgical technique, to allow evacuation of residual CO2, residual lavage fluid, and close monitoring for possible postoperative bleeding or bile leakage.

5. Intraoperative surgical difficulty assessed as Grade I, II or III according to the Nassar scale.

6. Ability to provide written, informed consent

Exclusion Criteria

Patients presenting with any of the following will be excluded:

1. Confirmed pregnancy or lactation

2. Intraoperative findings of Nassar Grade IV, suspected gallbladder cancer, scleroatrophic gallbladder, or cirrhosis

5. Use of NSAIDs within 24 hours prior to surgery, or chronic use of NSAIDs, opioids, immunosuppressants, chemotherapy, or anticoagulants.

6. Known allergies to ondansetron, acetaminophen, diclofenac sodium, buprenorphine or tramadol

7. Significant cardiac disease (e.g., heart failure, arrhythmias, pacemaker dependency)

8. Obesity Grade IV (Body Mass Index ≥ 50 kg/m2)

9. History of recurrent vertigo or motion sickness

Elimination Criteria

Patients who meet inclusion criteria but experience the following intraoperative events will be eliminated from the final per-protocol analysis: significant bleeding or bile duct injury requiring re-intervention, conversion to open surgery, or a total operative time exceeding 80 minutes.

4.5. Interventions

All participants, in both groups, will receive a standardized multimodal management protocol based on PROSPECT guidelines throughout the pre-, intra-, and postoperative phases. The only difference between the groups will be the solution used for the peritoneal lavage and aspiration.

Standardized Protocol for All Patients:

- Preoperative (Anesthesia Holding Area):
    - Dexamethasone 8mg IV (single dose, as part of the multimodal antiemetic scheme).
    - Antibiotic prophylaxis according to clinical history and allergies.
    - Peripheral venous cannulation and initiation of IV fluids.
- Intraoperative (Anesthesia and Surgery):

    - Anesthesia: Standardized general anesthesia with midazolam, fentanyl, propofol, and cisatracurium. Maintenance with sevoflurano.
    - Multimodal Analgesia: Acetaminophen 1g IV + Diclofenac 75mg IV.
    - Surgical Technique:
        - Low-pressure pneumoperitoneum (10-12 mmHg).
        - Infiltration of trocar sites with 20 ml of bupivacaine 0.75%.
        - Standardized four-port laparoscopic cholecystectomy.
        - Active aspiration of pneumoperitoneum at the end of surgery.
    - Antiemetic Protocol:
        - Dexamethasone 8mg IV is the only permitted prophylactic antiemetic.
        - The use of intravenous ondansetron is not permitted in any perioperative phase to avoid confounding the intervention's effects. Metoclopramide 10mg IV is the only authorized rescue antiemetic postoperatively.
- Postoperative:
    - Basal Analgesia: Acetaminophen 1g every 8 hours + Diclofenac 75mg every 12 hours.
    - Rescue Analgesia: Buprenorphine 75mcg subcutaneously, administered if pain intensity is ≥ 50mm on the VAS or ≥4 on the Faces Pain Scale-Revised (FPS-R) and the patient explicitly requests additional analgesia.
    - Rescue Antiemetic: Metoclopramide 10mg IV every 8 hours as needed for PONV.

Study Interventions (Applied at the end of surgery, after gallbladder extraction):

- Experimental Group:
    - Peritoneal Lavage: Instillation of 500 ml of 0.9% saline solution + 8 mg of ondansetron into the peritoneal cavity.
    - The solution will remain in contact for 5 minutes, with the patient in a 20° Trendelenburg position.
    - Complete aspiration of the solution is performed thereafter.
- Control Group:
    - Peritoneal Lavage: Instillation of 500 ml of 0.9% saline solution (without ondansetron) into the peritoneal cavity.
    - The solution will remain in contact for 5 minutes, with the patient in a 20° Trendelenburg position.
    - Complete aspiration of the solution is performed thereafter.

Both solutions are transparent and colorless, ensuring visual indistinguishability. The preparation and coding of the solutions are managed by a blinding coordinator nurse not involved in patient care or outcome assessment.

4.6. Outcomes

4.6.1 Primary Outcome

Total Postoperative Pain Burden: Quantified as the Area Under the Curve of the Visual analog Scale (VAS) over the first 24 hours (AUC-VAS/24h). the VAS (0-100mm) will be serially measured at 0, 2, 6, 12 and 24 hours postoperatively. The AUC will be calculated using the trapezoidal rule, integrating both the intensity and duration of pain.

4.6.2 Secondary Outcomes (Exploratory)

Pain intensity: measured at specific time points using:

- Visual Analog Scale (VAS) at 0, 2, 6, 12 and 24 hours postoperatively
- Faces Pain Scale-Revised (FPS-R) at 0, 2, 6, 12 and 24 hours postoperatively

Pain Characteristics:

- Anatomic location of the most intense pain (assessed at the same time points)
- Predominant type of pain (parietal, visceral, or referred; assessed at the same time pints).

Postoperative Morbidity

- Incidence of Postoperative Nausea and Vomiting (PONV) within the first 24 hours.
- Duration of analgesia (time in minutes from the end of the surgery until the first request for rescue analgesia).
- Total consumption of rescue analgesia (number of buprenorphine doses in 24 hours).
- Total dose of metoclopramide administered (mg)

Functional Recovery:

Time to unassisted ambulation (hours postoperatively)

Postoperative sleep quality, measured with the Richards-Campbell Sleep Questionnaire (RCSQ) at 24 hours.

Safety and Resource Utilization:

- Incidence and type of adverse events associated with ondansetron
- Incidence and type of postoperative complications.
- Duration of hospital stay (days)

4.7. Sample size

This is a pilot study. Therefore, the sample size calculation is not designed for high statistical power to detect significant differences, but to assess feasibility and obtain preliminary estimates for designing a future definitive study.

The sample size was calculated for the primary outcome variable (AUC-VAS/24h). Parameters were based on the study by Kim et al. (2022), which reported a clinically relevant difference of 13 points in the AUC-VAS/24h between multimodal management groups, with a combined standard deviation (SD) of approximately 18 points.

Using the formula for comparing two independent means ($\alpha = 0.05$, power = 80%), a definitive study would require 31 patients per group (62 total). Adjusting for a 10% anticipated loss rate, the necessary size would be 70 participants (35 per group).

However, following methodological recommendations for pilot studies, a sample size of **20 participants per group (40 in total)** was selected. This size is adequate to:

Evaluate the feasibility of recruitment, randomization, blinding, and protocol adherence.

Estimate the standard deviation (σ) of the primary variable (AUC-VAS/24h (in our specific population more precisely.

Obtain a preliminary estimate of the effect size (mean difference, Δ) of the intervention.

Evaluate the safety and adverse event profiles of intraperitoneal ondansetron.

Test and optimize all operation processes of the study.

Analyses of secondary outcomes are exploratory in nature. This sample size is not calculated to have sufficient power to detect differences in these variables.

4.8. Randomization

- Sequence Generation: A computer-generated randomization sequence will be created using Random Allocation Software Version 1.0.0. The sequence will use permuted blocks of sizes 4 and 6 (randomized) and will be stratified by Sex and ASA Classification (I/II) to ensure balance between groups for these prognostic factors.
- Allocation Concealment: The allocation sequence will be concealed using sequentially numbered, opaque, sealed envelopes. The envelopes will be made of thick paper to prevent transparency.
- Implementation: In the preoperative area, before anesthetic induction, the patient will randomly select one envelope from an opaque bag. A designated blinding coordinator nurse (not involved in patient care or outcome assessment) will open the envelope in private, prepare the assigned solution, and label it only with a code (A or B).

4.9. Blinding (Masking)

This study will employ a triple-blind design:

- Patients: Will not know their group assignment.
- Care Providers and Outcome Assessors: Surgeons, anesthesiologists, residents, intern physicians, research passers, and nursing staff in the operating room and recovery area will remain blinded to the assigned intervention.
- Data Analyst: The statistician responsible for the initial data cleaning and analysis will receive a coded database (Group A vs. Group B) without access to the randomization key until the primary analysis is complete.

Methods for Maintaining Blinding:

- The experimental and control solutions (saline + ondansetron vs. saline alone) are both transparent and colorless, making them visually identical.
- The randomization list and the key linking codes A/B to the intervention groups will be kept under the exclusive custody of the Head of Education of the hospital, who has no contact with patients or participation in the study's execution or outcome evaluation.
- The sealed allocation cards will be stored securely after each procedure.

The blinding will only be broken after the data collection for all 40 patients is complete and the database is locked, prior to the final statistical analysis and interpretation of results.

5. STATISTICAL METHODS

5.1. Data Analysis Plan

Data analysis will be performed using IBM SPSS Statistics software, version 30.0.0.0. A p-value ≤ 0.05 will be considered statistically significant for two-tailed tests. Where appropriate, 95% confidence intervals (95% CI) will be reported.

6.2. Descriptive Analysis

The study population will initially be characterized through descriptive analysis of all variables:

- Categorical variables (nominal or ordinal): Expressed as absolute (n) and relative frequencies (%).
- Quantitative variables (continuous and discrete): described according to their contribution. If they follow a normal distribution, they will be reported as mean ± standard deviation (SD). In case of a non- normal distribution, they will be presented as median an interquartile range (IQR), specifying minimum and maximum values.

6.3. Verification of Assumptions and Selection of Inferential Tests

The choice of inferential statistical tests will be based on the nature of the variables and the fulfillment of normality assumptions.

- Normality testing: the distribution of all quantitative variables will be assessed using:
- Shapiro-Wilk test (suitable for sample sizes n ≤ 50)
- Complementary graphical analysis (histograms and Q-Q plots)

A normal distribution is considered with a p-value ≥ 0.05 in the Shapiro-Wilk test, supported by a symmetrical appearance in the graphs.

Statistical Tests for Group Comparisons:

- Quantitative variables with normal distribution: Comparison between intervention and control groups will be performed using the Student´s t-test for independent samples.
- Quantitative variables with non-normal distribution: The Mann-Whitney U test will be used.
- Categorical variables: Associations will be analyzed with the Chi-Square test. For 2x2 tables or when more than 20% of cells have an expected frequency ≤5, Fisher´s exact test will be employed.
- Survival analysis: The duration of analgesia will be analyzed using Kaplan-Meier curves, and the comparison between groups will be performed with the log-rank test.

Correlation Analysis:

Linear associations between quantitative variables will be explored using Pearson´s coefficient (for normal data) or Spearman´s coefficient (for non-normal data). For example, the relationship between postoperative sleep quality (RCSQ) and pain intensity (AUC-VAS/24h) will be evaluated.

6.4. Strategy for the Analysis of Multiple Outcomes

To control de risk of Type I error due to multiple comparisons, the following strategy will be implemented:

- Primary Outcome (Confirmatory Analysis): the analysis of the Area Under the Curve of the VAS at 24 hours (AUC-VAS/24h) is the primary and confirmatory
- comparison. It will be interpreted using alpha level of 0.05 without adjustment.
- Secondary Outcomes (Exploratory Analysis): All other outcomes (e.g., PONV incidence, duration of analgesia, sleep quality, analgesic consumption) are considered exploratory or hypothesis-generating.
    - Their raw p-values (unadjusted) will be reported.
    - Their interpretation will be performed with extreme caution. Any significant finding ($p \leq 0.05$) will be considered a preliminary signal justifying investigation in future studies, but not as conclusive evidence of efficacy.
    - Publications and reports will clearly distinguish between confirmatory (primary) and exploratory (secondary evidence).
- Correction for intravariable Multiple Comparisons: For repeated comparisons of the same variable at different time points (e.g., VAS at 0, 2, 6, 12, and 24 h), the Bonferroni correction will be applied, adjusting the alpha level by dividing 0.05 by the number of planned comparisons.

6.5. Intention-to-Treat (ITT) Principle and Handling of Missing Data

The primary analysis will be performed according to the intention-to Treat (ITT) principle, including all participants in the group to which they were originally randomized, regardless of protocol compliance or study withdrawal. This preserves the benefits of randomization and provides a more realistic estimate of effectiveness.

Handling of Missing Data:

- Prevention: Prospective data collection with real-time verification and scheduled follow-up will be implemented to minimize losses.
- Imputation strategy: the primary method will be multiple imputation (MI), generating 20 datasets. Alla baseline and outcome variables will be included in the imputation model. As a sensitivity analysis, a complete case analysis will be performed.

Application Criteria:

- If missing data is 5%, multiple imputation will be the primary method.
- If between 5% and 20%, an extensive sensitivity analysis will be performed.
- If they exceed 20%, a qualitative analysis of the missing patterns will be conducted.

6.6. Sensitivity and Robustness Analysis

To evaluate the robustness of the findings, the following sensitivity analyses will be carried out:

- Per-Protocol (PP) analysis: The results of the ITT analysis will be compared with an analysis that includes only participants who strictly complied with all phases of the protocol.
- Comparison of Imputation Methods: Results from multiple imputation will be contrasted with complete case analyses.

- Adjustment for Covariates: An ANCOVA will be used for the primary outcome, adjusting for any baseline variable that shows a clinically relevant imbalance between groups.
- Analysis of Outliers: Robust non-parametric tests and resampling analysis (bootstrapping) with 1000 replications will be used to verify that the results are not biased by outliers.

6.7. Strategies to Ensure Baseline Homogeneity and Analysis of Comparability

- Design: To minimize baseline imbalances, randomization was performed using permuted blocks (sizes 4 and 6) and was stratified by sex and ASA classification (I/II).
- Verification of Baseline Homogeneity: After recruitment, a comparability analysis between groups will be performed for the following pre-specified variables: age, sex, body mass index (BMI), ASA classification, duration of cholelithiasis pain, number of previous emergency admissions, and presence of relevant comorbidities.
    - Continuous variables will be compared with the Student's t-test or Mann-Whitney U test, and categorical variables with Chi-square or Fisher's exact test.
    - A p-value ≤ 0.05 will be considered indicative of a potential imbalance.
- Handling of Imbalances: If clinically relevant imbalances in prognostic variables are identified, an ANCOVA for the primary outcome will be performed, adjusting for these variables. The impact of any imbalance will be explicitly reported in the interpretation of the results.

6.8. Quality Control and Data Monitoring Plan
To ensure data integrity, accuracy, and consistency throughout the study, the following quality control scheme will be implemented:

- Database Quality Monitoring:
    - Weekly Audit: The principal investigator will perform a weekly review of the electronic database to identify inconsistencies, out-of-range extreme values, and missing data.
    - Double Data Entry Verification: A random subset of 10% of the Case Report Forms (CRFs) will undergo double data entry by a different research passer to calculate a concordance index (target Kappa ≥ 0.9).
- Procedural Compliance Monitoring:
    - Weekly Protocol Review: Surgical and anesthetic records will be reviewed weekly against a standardized checklist to confirm compliance with key procedures (pneumoperitoneum pressure, lavage volume, administration of protocol drugs).
    - Corrective Action: Any deviation will be documented and immediately communicated to the surgical team and the tutorial committee for resolution and to implement corrective actions to prevent recurrence.
- Interim Analysis and Stopping Rules:
    - A single interim analysis will be performed when 50% of recruitment is reached (n=20 patients).

- Stopping rules will be based solely on safety criteria (serious related adverse events) and efficacy (an extremely large difference in AUC-VAS/24h with $p \leq 0.001$, according to the Haybittle-Peto criterion), to minimize Type I error.
- This interim analysis will be performed by an ad-hoc Data and Safety Monitoring Committee (DSMC), composed of two senior investigators not directly involved in recruitment or study execution. The committee will have the authority to recommend the continuation, modification, or suspension of the study based on safety and efficacy data.

Informed Consent Letter for Adults, accompanying research protocols submitted to the National Committee for Scientific Research

Place and Date: Guadalajara, Jalisco_____

Institutional Registration Number: R-2025-785-080, F-NIC-2025-083

NCT Number: NCT06632184

Justification and Research objective: after laparoscopic cholecystectomy, many people experience abdominal pain. This pain can interfere with recovery, rest, and general well-being. This study is seeking new ways to improve pain control after surgery. A medication called ondansetron, which is normally used to prevent nausea and vomiting, has shown in some studies that it might also help reduce pain if applied directly inside the abdomen during surgery. This study aims to evaluate whether the use of ondansetron in this way helps reduce pain after surgery, compared to using only saline solution, which is the standard practice. The objective of this study is to determine whether applying a solution with an anti-nausea medication (called ondansetron) inside the abdomen at the end of gallbladder surgery helps reduce pain and discomfort after the operation.

Procedures: If you decide to participate in this study, this is what will happen:

- Before Surgery: The study will be explained to you.
- You will randomly select an envelope. This envelope will indicate which type of lavage will be used during your surgery: Saline solution only or saline solution with a medication called ondansetron.
- You will not know which one you received, nor will the medical team caring for you, to make the study more reliable (Double-blind).
- During Surgery: The surgery will be performed in the usual manner to remove the gallbladder (laparoscopic cholecystectomy); at the end of the surgery, the surgeon will lavage your abdomen with the assigned solution (with or without ondansetron); after this lavage, the fluid will be completely aspirated (removed).
- After Surgery: You will receive the same pain treatment as all other surgical patients: paracetamol and diclofenac; only if you need it, a stronger analgesic may be administered. A member of the research team, who does not know which solution was used, will ask you at five different times (upon waking, and at 2, 6, 12, and 24

hours) how you feel and how much pain you have. You will also be asked if you have nausea, vomiting, and how you slept that night.

- Follow-up: Your follow-up will be the same as for any patient undergoing gallbladder surgery. All data collected will be confidential.

Possible benefits of participating in the study:

- You will receive the same high-quality surgical, anesthetic, and analgesic treatment as any other patient undergoing gallbladder surgery at this institution, regardless of your participation in the study.
- It is important to mention that no direct benefit to you can be guaranteed from your participation in this research. The main objective of this study is to generate scientific knowledge.
- If you are administered the solution with ondansetron, you might experience a reduction in postoperative pain, but this is a possibility under investigation and not a guaranteed outcome.
- The main benefit of your participation is the contribution to the advancement of medical knowledge, which could help improve care and pain management for future patients undergoing this type of surgery.

Possible Risks and Discomforts:

- No additional risks beyond those of conventional gallbladder surgery are expected.
- The medication ondansetron has been used safely for many years to prevent nausea and vomiting. In this study, it will be applied directly inside the abdomen, which is not its usual route of administration, but so far no serious adverse effects have been reported with this form of application in similar studies.
- Mild discomfort such as burning, bloating, or abdominal tenderness might occur, although it is unlikely.
- There is a minimal risk that you will not experience additional benefits, even if you receive the solution with ondansetron.
- If your pain does not improve with the established medications, a complete medical evaluation will be performed to rule out any postoperative complications.

Information about Results and Treatment Alternatives:

- If new relevant information related to your health, the treatment, or preliminary study results is obtained during the study, you will be informed directly by the principal investigator or the research team, during your hospital stay or in subsequent follow-up if necessary.
- If any significant clinical benefit of the ondansetron administered inside the abdomen (intraperitoneal route) is identified, this information will be communicated to you and your treating physician.
- The surgical and medical treatment you will receive corresponds to the current standard protocol of the Mexican Institute of Social Security (IMSS) for gallbladder surgery, which includes:
    - Laparoscopic cholecystectomy.

    - Pain management with medications such as paracetamol, diclofenac, and if necessary, buprenorphine.
    - Management of nausea and vomiting with metoclopramide if required.
- Participation in this study does not imply suspending or delaying your usual treatment.
- Ondansetron is approved by COFEPRIS and is available within the institutional basic formulary. However, its use via the intraperitoneal route is experimental, so its routine use after the study is not guaranteed.
- If this method is proven to offer clear advantages for patients, its adoption as part of standard management will be proposed, but this will depend on future clinical evaluations and institutional decisions. Currently, its systematic use after the study is not contemplated.

Participation and Withdrawal: Your participation in this study is completely voluntary. You have the right to decide whether you wish to participate or not, without this affecting the medical care you receive at the Mexican Institute of Social Security (IMSS). If you agree to participate, you may withdraw from the study at any time, without needing to give a reason and without this having negative consequences for your treatment, medical care, or relationship with the healthcare staff. You may also request that your data not be used in the study analyses if you decide to withdraw before your participation ends. If you experience an unexpected medical condition, complication, or if the investigators believe that continuing in the study could be risky for your health, you will be informed and may be withdrawn from the study for safety reasons, always ensuring your well-being.

Remember that your well-being and safety are the priority at all times.

Privacy and Confidentiality: The personal and clinical data obtained during your participation in this study will be treated confidentially and protected according to the law. Your information will be identified using a numerical code and your name will not be used in the study reports. Only the authorized research team will have access to the list linking your name to that code. All information will be stored in protected and locked files under the custody of the principal investigator, and will not be used for any other study or research different from the one described here. The data will be kept for a maximum period of five years after the study is completed, solely for analysis purposes or review by Ethics Committees, Research Committees, or institutional authorities. Subsequently, they will be securely deleted or destroyed. You have the right to access, correct, cancel, or object to the use of your data (ARCO rights) at any time, if you so wish. If you have questions or need to exercise these rights, you can contact the principal investigator through the contact details provided at the end of this document.

Extrainstitutional Agreements: This study does not have external financial sponsorship, nor is it funded by the pharmaceutical industry or private companies for commercial purposes. However, it is reported that there is an academic agreement with the Centro de Investigación y Asistencia en Tecnología y Diseño del Estado de Jalisco A.C (CIATEJ), as part of the Master's program in Clinical Research that the principal investigator is enrolled in. This agreement aims to provide methodological advice and academic supervision through a tutorial committee, without implying funding or interference in the study results. The conduct of the study, patient care, and data management are carried out autonomously by the medical team of Hospital General de Zona No. 89 of the IMSS.

Consent Declaration:

After having read and having had all my doubts about this study explained to me:

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text

I do NOT accept to participate in the study.

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text

I DO accept to participate and for the sample to be taken only for this study.

I DO accept to participate and for the sample to be taken for this and future studies, retaining my data for up to 5 years after which it will be destroyed.

Note: Biological samples will not be used for permanent or immortal cell lines, unless specific consent is requested within this same letter.

In case of questions or clarifications related to the study, you may contact:

Principal Investigator: Dr. Francisco Aguilar Espinosa, ID: 991443482, Affiliation: Clinical Coordination of Surgery, email: fraguilar_al@ciatej.edu.mx, work phone number: 3788853968

Note: In case of questions or clarifications about your rights as a participant, you may contact: Research Ethics Committee of the Centro Médico Nacional Siglo XXI (Coordination of Health Research): Avenida Cuauhtémoc 330, Colonia Doctores. CP 06720, Alcaldía Cuauhtémoc, Mexico City. Phone (55) 56 27 69 00 extension 21230, email: comiteeticainv.imss@gmail.com.

Participant's Name and Signature
Name and Signature of the Person Obtaining Consent

Witness 1 Name and Signature
Witness 2 Name and Signature

This form constitutes a guide that must be completed according to the specific characteristics of each health research protocol, without omitting relevant information about the study.