STUDY PROTOCOL

Comparison of Protective versus Conventional Ventilation Strategies on Lung Ultrasound Score in Patients Undergoing Laparoscopic Cholecystectomy: A Prospective Randomized Controlled Trial

Protocol Version: 1.0
Date: 28.03.2025
IRB Approval Number: 2025-KAEK-43

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1. BACKGROUND AND RATIONALE

Laparoscopic cholecystectomy is one of the most commonly performed surgical procedures worldwide. While laparoscopy offers numerous advantages over open surgery, the pneumoperitoneum and Trendelenburg positioning required during the procedure can lead to significant pulmonary complications, particularly atelectasis.

Pneumoperitoneum increases intra-abdominal pressure, which can cause cephalad displacement of the diaphragm, reduced functional residual capacity, and subsequent ventilation-perfusion mismatch. These physiological changes frequently result in intraoperative and postoperative atelectasis, which can manifest as hypoxemia, increased risk of pulmonary infections, and prolonged hospital stay.

Protective ventilation strategies, including the use of low tidal volumes, positive end-expiratory pressure (PEEP), and alveolar recruitment maneuvers, have been shown to improve pulmonary outcomes in various surgical settings. However, the optimal ventilation strategy during laparoscopic cholecystectomy remains a subject of ongoing investigation.

Lung ultrasound has emerged as a valuable, non-invasive tool for real-time assessment of lung aeration and detection of atelectasis. The lung ultrasound score (LUS) provides a quantitative measure of pulmonary aeration status and has been validated for detecting perioperative pulmonary complications.

This study aims to compare the effects of protective versus conventional ventilation strategies on lung aeration, as measured by LUS, in patients undergoing laparoscopic cholecystectomy.

2. STUDY OBJECTIVES

2.1 Primary Objective
To compare the change in lung ultrasound score (LUS) between protective and conventional ventilation strategies in patients undergoing laparoscopic cholecystectomy.

2.2 Secondary Objectives
- To compare the PaO_2/FiO_2 ratio between groups at different time points
- To assess the incidence of postoperative respiratory complications

- To evaluate intraoperative hemodynamic stability
- To compare recovery profiles between groups

3. STUDY DESIGN

3.1 Study Type
Prospective, randomized, controlled trial

3.2 Study Setting
Department of Anesthesiology and Reanimation, Fatih Sultan Mehmet Training and Research Hospital, Istanbul, Turkey

3.3 Study Duration
Approximately 12-18 months from study initiation to completion

4. STUDY POPULATION

4.1 Inclusion Criteria
- Age 18-65 years
- ASA physical status I-III
- Body Mass Index (BMI) < 30 kg/m²
- Scheduled for elective laparoscopic cholecystectomy under general anesthesia

4.2 Exclusion Criteria
- Emergency surgery
- BMI ≥ 30 kg/m²
- ASA physical status IV or higher
- Pre-existing pulmonary disease (COPD, asthma, interstitial lung disease)
- Cardiac failure (NYHA class III-IV)
- Neuromuscular disorders
- Contraindications to pneumoperitoneum
- Conversion to open cholecystectomy
- Patient refusal

4.3 Sample Size
Based on power analysis with $\alpha=0.05$, $\beta=0.20$ (power 80%), and expected difference in LUS of 2 points with SD of 2.5, the required sample size is 40 patients per group (total N=80).

5. RANDOMIZATION AND BLINDING

5.1 Randomization
Patients will be randomized to either the protective ventilation group or conventional ventilation group using computer-generated random numbers in sealed envelopes. Randomization will occur after induction of anesthesia.

5.2 Blinding
Due to the nature of the intervention, anesthesiologists cannot be blinded to group allocation. However, lung ultrasound assessments will be performed by investigators blinded to group assignment. Postoperative outcome assessors will also be blinded to group allocation.

6. INTERVENTION

6.1 Standard Anesthesia Protocol (Both Groups)
All patients will receive standardized anesthetic management:

Preoperative Assessment:
- Baseline lung ultrasound examination (8 zones)
- Baseline LUS calculation

Monitoring:

- Standard ASA monitoring (ECG, non-invasive blood pressure, SpO2, temperature)
- Bispectral index (BIS)
- End-tidal CO2 (EtCO2)
- Airway pressures (peak, plateau)
- Dynamic compliance

Induction:
- Preoxygenation with 100% O2 for 2 minutes
- Propofol 2 mg/kg IV
- Fentanyl 2 mcg/kg IV
- Rocuronium 0.6 mg/kg IV
- Orotracheal intubation after adequate muscle relaxation

Maintenance:
- Sevoflurane 1.5-2% in 50% O2/air mixture (2 L/min)
- Remifentanil infusion 0.05-0.5 mcg/kg/min
- BIS target: 40-60
- Normothermia maintained with forced-air warming

Analgesia and Antiemetic Prophylaxis (20 minutes before end of surgery):
- Paracetamol 1 g IV
- Tramadol 1 mg/kg IV
- Ondansetron 4 mg IV

Reversal:
- Sugammadex 2 mg/kg IV at end of surgery
- Extubation criteria: spontaneous breathing, BIS ≥85, adequate muscle strength

6.2 Group-Specific Ventilation Protocols

Group 1: Protective Ventilation Strategy
- Tidal volume: 6-8 mL/kg predicted body weight
- PEEP: 8 cmH2O
- Recruitment maneuver before extubation:
  * Driving pressure: 15 cmH2O
  * Stepwise PEEP increase: 5 → 10 → 15 cmH2O
  * Each step held for 10-15 seconds
  * PEEP maintained at 6-8 cmH2O until extubation
  * Maneuver stopped if PIP >35 cmH2O
- Respiratory rate adjusted to maintain EtCO2 35-40 mmHg
- Volume control mode

Group 2: Conventional Ventilation Strategy
- Tidal volume: 8-10 mL/kg predicted body weight
- PEEP: 0-5 cmH2O
- No recruitment maneuver
- Respiratory rate adjusted to maintain EtCO2 35-40 mmHg
- Volume control mode

7. OUTCOME MEASURES

7.1 Primary Outcome
Change in Lung Ultrasound Score (LUS) from baseline to:
- 30 minutes after pneumoperitoneum (T1)
- 30 minutes after desufflation (T2)

LUS Assessment Method:
- 12-zone lung ultrasound examination
- Scoring: 0 (normal aeration, A-lines) to 3 (consolidation) per zone
- Total score range: 0-36 (higher scores indicate worse lung aeration)

7.2 Secondary Outcomes
- PaO2/FiO2 ratio at T0, T1, T2
- Incidence of desaturation (SpO2 <90%)
- Postoperative pulmonary complications (atelectasis, pneumonia)
- Intraoperative hemodynamic parameters (MAP, HR)
- Dynamic compliance (Cdyn)
- Peak inspiratory pressure (PIP)
- Plateau pressure (Pplat)
- Duration of surgery and anesthesia
- Time to extubation
- Length of hospital stay

8. DATA COLLECTION AND MANAGEMENT

8.1 Time Points for Data Collection
- T0: After induction, before pneumoperitoneum
- T1: 30 minutes after pneumoperitoneum
- T2: 30 minutes after desufflation
- Postoperative: During hospital stay until discharge

8.2 Data Recording
All data will be recorded on standardized case report forms and entered into a secure electronic database. Patient confidentiality will be maintained using study identification numbers.

8.3 Data Quality Assurance
- Regular monitoring of data completeness
- Source data verification for key variables
- Query resolution process for discrepancies

9. STATISTICAL ANALYSIS PLAN

9.1 Statistical Methods

Primary Outcome Analysis:
- Independent samples t-test will be used to compare the change in LUS between groups at T1 and T2
- Repeated measures ANOVA for within-group comparisons across time points
- Significance level: $\alpha = 0.05$ (two-sided)

Secondary Outcome Analysis:
- Continuous variables: Independent samples t-test or Mann-Whitney U test (depending on distribution)
- Categorical variables: Chi-square test or Fisher's exact test
- Repeated measures: Mixed-effects models

Subgroup Analyses:
- Analysis by ASA status
- Analysis by BMI categories
- Analysis by surgery duration

9.2 Handling of Missing Data
- Primary analysis: complete case analysis
- Sensitivity analysis: multiple imputation if missing data >5%

9.3 Interim Analysis
No interim analysis is planned due to the short study duration and low risk of intervention.

9.4 Statistical Software
SPSS version 25.0 or later will be used for all statistical analyses.

9.5 Sample Size Justification

Based on pilot data and previous studies, we anticipate:
- Mean LUS change in conventional group: 7.0 ± 2.5
- Mean LUS change in protective group: 4.5 ± 2.5
- Clinically significant difference: 2.0 points

Power calculation:
- Alpha: 0.05 (two-sided)
- Power: 80% (beta = 0.20)
- Effect size: 2.0 points
- Pooled SD: 2.5
- Required sample size: 40 per group
- Total: 80 patients

10. ETHICAL CONSIDERATIONS

10.1 Ethical Approval
This study has been approved by the Institutional Review Board/Ethics Committee of
Istanbul Provıncıal Dırectorate Of Health Koşuyolu Hıgh Specıalızatıon Educatıon And Research Hospıtal
IRB Approval Number: 2025-KAEK-43
Approval Date: 28.03.2025

10.2 Informed Consent
Written informed consent will be obtained from all participants before enrollment. The informed consent form (see Section 11) explains:
- Study purpose and procedures
- Potential risks and benefits
- Right to withdraw at any time without affecting medical care
- Confidentiality protections

10.3 Patient Safety
- All interventions are within accepted clinical practice
- Continuous monitoring during anesthesia
- Immediate management of any adverse events
- Stopping criteria clearly defined (e.g., PIP >35 cmH2O during recruitment)

10.4 Data Protection
- Patient data will be anonymized using study ID numbers
- Electronic data stored in password-protected databases
- Access limited to study personnel
- Data retention as per institutional policy

10.5 Adverse Event Reporting
All adverse events will be documented and reported to the IRB according to institutional guidelines.

11. INFORMED CONSENT FORM

Study Title: Comparison of Protective versus Conventional Ventilation Strategies on Lung Ultrasound Score in Patients Undergoing Laparoscopic Cholecystectomy

Principal Investigator: Cansu Ofluoglu, MD
Institution: Fatih Sultan Mehmet Training and Research Hospital
IRB Approval Number: 2025-KAEK-43

INTRODUCTION
You are being invited to participate in a research study. Before you decide to participate, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully.

PURPOSE OF THE STUDY

This study aims to compare two different breathing strategies during your laparoscopic gallbladder surgery to determine which provides better lung function. During laparoscopic surgery, carbon dioxide gas is used to inflate your abdomen, which can sometimes affect your lungs. We want to find the best way to support your breathing during this procedure.

STUDY PROCEDURES
If you agree to participate:

1. Before Surgery:
   - We will perform a lung ultrasound examination (painless, similar to pregnancy ultrasound)
   - This takes about 5-10 minutes

2. During Surgery:
   - You will receive standard anesthesia care
   - You will be randomly assigned (like flipping a coin) to one of two groups:
     * Group 1: Protective breathing strategy with gentle lung inflation at the end of surgery
     * Group 2: Standard breathing strategy currently used in our hospital
   - We will monitor your breathing and vital signs continuously (standard practice)

3. After Surgery:
   - Another lung ultrasound examination 30 minutes after surgery
   - Standard recovery room care
   - We will monitor for any breathing problems during your hospital stay

Total additional time for study procedures: approximately 15-20 minutes

RISKS AND DISCOMFORTS
The risks of participating in this study are minimal:
- Lung ultrasound: No known risks (uses sound waves, no radiation)
- Breathing strategies: Both are commonly used in anesthesia practice
- Possible temporary discomfort during lung inflation maneuver (you will be asleep)
- All procedures will be stopped immediately if any problems occur

BENEFITS
Potential benefits:
- You may have better lung function after surgery
- The information gained may help improve care for future patients undergoing similar surgery

There is no guarantee that you will personally benefit from participation.

ALTERNATIVES TO PARTICIPATION
Your alternative is to receive standard anesthesia care without the research procedures (lung ultrasound and specific breathing strategy assignment). This will not affect the quality of your surgical or anesthesia care.

CONFIDENTIALITY
Your personal information will be kept strictly confidential:
- You will be assigned a study identification number
- Your name will not appear in any reports or publications
- Only the research team will have access to identifiable information
- Study data will be stored securely for [INSERT PERIOD] years

VOLUNTARY PARTICIPATION
- Your participation is completely voluntary
- You may refuse to participate or withdraw at any time
- Your decision will not affect your medical care in any way
- You do not need to provide a reason for withdrawal

COMPENSATION
There is no financial compensation for participation. You will not incur any additional costs.

CONTACT INFORMATION
If you have questions about the study, please contact:
Cansu Ofluoğlu, +905358640564

If you have questions about your rights as a research participant, contact:
Istanbul Provincial Directorate of Health Koşuyolu High Specialization Education and Research Hospital Clinical Research Ethics Committee
Phone: +90 216 459 4440
Email: kosuyolu.kek@saglik.gov.tr

CONSENT
I have read and understood the information provided above. I have had the opportunity to ask questions and all my questions have been answered satisfactorily. I understand that my participation is voluntary and that I am free to withdraw at any time without giving a reason and without affecting my medical care.

12. TIMELINE AND MILESTONES

Month 1-2:
- IRB approval finalization
- Staff training on lung ultrasound technique
- Case report form development

Month 3-14:
- Patient recruitment and enrollment
- Data collection

Month 15-16:
- Data cleaning and analysis
- Manuscript preparation

Month 17-18:
- Results dissemination
- Study completion report

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APPENDICES

Appendix A: Lung Ultrasound Scoring Protocol
Appendix B: Case Report Forms
Appendix C: Data Collection Sheets
Appendix D: IRB Approval Letter