Elec**T**rical **I**mpedance **T**omog**R**aphy vs dynamic compli**AN**ce guided positive end-expiratory pressure **T**itration during laparoscopic gynaecological surgery: A multi-centre, prospective randomized trial – **TITRANT Trial**

STUDY PROTOCOL WITH SAP

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STUDY PROTOCOL

Title of the Study

Elec**T**rical **I**mpedance **T**omog**R**aphy vs dynamic compli**AN**ce guided positive end-expiratory pressure **T**itration during laparoscopic gynaecological surgery: A multi-centre, prospective randomized trial – **TITRANT Trial**

PICO

P	Titrating PEEP - in order to determine individually optimal PEEP levels to reduce the mechanical power responsible for lung injury is one of the main targets of personalised mechanical ventilation, however there is no recommendation about best practice
I	EIT-guided decremental PEEP titration during laparoscopic gynaecological surgery
C	Cdyn-guided decremental PEEP titration during laparoscopic gynaecological surgery
O	Mechanical Power (MP), Postoperative Pulmonary Complications (PPCs), intra- and postoperative oxygenation indicated by PaO_2/FiO_2, driving pressure (dP), Positive End-Expiratory Pressure (PEEP), dynamic compliance (Cdyn), Global Inhomogeneity Index (GI), Overdistension/Collapse (ODCL)

Background

Despite both surgical and anaesthesia related risk factors of postoperative pulmonary complications (PPCs) are well known, PPCs occur frequently with an incidence of 5% to 33%, resulting in a 30-day mortality of about 20% in the affected patient population.[1-3]

Mechanical ventilation as a major risk factor plays a pivotal role in the development of PPCs, however, it is mandatory during laparoscopic surgeries under general anaesthesia. Mechanical ventilation alone alters the excursion of the diaphragm resulting a ventral redistribution of ventilation, additionally, the increased intraabdominal pressure due to the pneumoperitoneum and Trendelenburg position during laparoscopy leads to a cephalad shift

of the diaphragm decreasing the functional residual capacity and elevating the transpulmonary pressure (P_{TP}). Moreover, evidence exist, that inappropriate ventilatory parameters may lead to physical (volu-, baro- and atelectrauma) and biological damage of the lungs (summarized as ventilator-induced lung injury, VILI) causing PPCs accounting for substantial morbidity and mortality.[4] Recent research have suggested the importance of individual lung protective ventilation (LPV) applying low tidal volumes (VT), optimal positive end-expiratory pressure (PEEPopt), alveolar recruitment manoeuvres (ARMs) and limited plateau (Pplat < 25 cmH_2O), driving (dP < 15 cmH_2O) and transpulmonary pressures (P_{TP} < 20 cmH_2O) in order to reduce the risk of VILI, even in patients with healthy lungs, however, results remained controversial, and the incidence of PPCs has not decreased significantly.[5-11]

Respiratory system is complex, its reactions and tolerance to the effects of positive pressure mechanical ventilation are extremely individual, therefore focusing on separated ventilatory parameters does not lead to favourable clinical improvement and outcomes.

Low VT (4-6 mL/kg Ideal Body Weight, IBW) is a useful tool to prevent volutrauma but may result in increased dead space, atelectasis and hypercapnia. In this scenario increasing respiratory rate (RR) can reduce arterial carbon-dioxide tension ($PaCO_2$), however, too short expiratory time may increase intrinsic PEEP resulting air trapping, and hyperinflation of the lungs may occur. Estimating the end-inspiratory P_{TP} by measuring oesophageal pressure thus determining individually appropriate VT can eliminate these obstacles, however it is too expensive for everyday use.

Applying PEEPopt may prevent atelectasis and cyclic lung collapse (cyclic opening and closing of alveoli). On the other hand, high PEEP may lead to barotrauma, ventilation-perfusion mismatch and haemodynamic compromise can develop due to a high intrathoracic pressure.[12]

Several methods exist to determine PEEPopt. It can be titrated applying respiratory mechanics parameters (static or dynamic pulmonary compliance, Cstat / Cdyn; dead space fraction; end-expiratory P_{TP}; dP) or bedside visualization of the lungs using ultrasound (US) or electrical impedance tomography (EIT) can be another option. Main concerns about the use of basic respiratory mechanics parameters are that neither overdistension of the lungs, nor distribution of ventilation cannot be measured. However, dP – calculated as the difference between Pplat and PEEP (dP = Pplat - PEEP) – seems to be an important safety parameter to determine appropriate PEEP and VT, and may decrease the incidence of PPCs as compared to conventional LPV.[13]

Bedside visualization of the lungs by US is useful, however appropriate practice and experience are required for proper assessment. Moreover, it only provides intermittent evaluation, while performing US imaging during surgery may be cumbersome and time consuming.

EIT provides a non-invasive, radiation-free, real time, continuous monitoring, that identifies changes in lung impedance which corresponds to lung volume. Besides these advantages, EIT imaging gives the opportunity to optimize PEEP by visualizing the distribution of ventilation, and to distinguish recruitment from overdistension. The global inhomogeneity index (GI) quantifies the homogeneity of the tidal volume distribution. It correlates with lung recruitability and may guide ventilatory settings in order to optimise alveolar homogeneity.[14,15] During an EIT-guided titration procedure, regional overdistension (OD) and alveolar collapse (CL) can be quantified (ODCL), and PEEPopt is considered as the intersection between the lower percentage of overdistension and collapse.[16-18] Optimizing PEEP using EIT to counterbalance the effects of laparoscopic procedures has some rational as indicated in a previous trial.[19]

ARMs are the most controversial components of the LPV concept, as it is obvious that not all lungs are recruitable, while ARMs can cause severe haemodynamic instability especially in hypovolaemic patients. Despite they may improve oxygenation and reverse atelectasis by opening collapsed alveoli, there is no recommendation about their exact role and use.[1]

Recognizing these issues, a new conceptional direction emerged in the last few years by evaluating the potential role of the amount of energy transferred to the lung parenchyma per unit of time (J/min) during mechanical ventilation.[20,21] This energy is called mechanical power of ventilation (MP), and recent trials found correlation between high MP values (MP > 12 J/min) and the severity of VILI both in critically ill patients with ARDS and patients with non-injured lungs as well.[22-26] MP integrates the major components of positive pressure ventilation that drive VILI (static, dynamic and resistive, related to PEEP, dP, flow and airway resistance respectively; and respiratory rate), thus gives the opportunity to balance the effects of each respiratory parameters. Theoretically, reducing MP below the safety threshold may be the main goal of the LPV strategy. Due to the original equation is very sophisticated and difficult to calculate, a surrogate formula was established including RR, VT, peak inspiratory pressure, PEEP and Pplat: MP = 0.098 x RR x TV (L) x [Ppeak – ½ x (Pplat – PEEP)]. These parameters can be acquired from the ventilators of all anaesthesia machines, thus MP can be easily calculated

during surgery.[27] It is important to notice, that VT is a predominant parameter in the formula, while PEEP is a double-edged sword. Inappropriate PEEP may increase MP, whereas optimal PEEP can decrease it by improving pulmonary compliance. Neglecting the role of respiratory rate is common in terms of the genesis of VILI, however it is obvious that it has a linear correlation with MP, that should be taken in account. Despite the robust pathophysiological rational of implementing MP as a goal of LPV, some limits must be emphasized. First, validation of its use in the surgical population is still lacking. Second, due to the complexity of the interaction between the respiratory parameters and inhomogeneities in the distribution of ventilation (atelectasis and hyperinflation may be present at the same time in different lung areas), local lung tissue injury may still develop.[28]

The aim of our study is to compare the effects of two different PEEP titrating methods (EIT-guided vs Cdyn-guided) on mechanical power of ventilation, oxygenation, respiratory mechanics parameters, global inhomogeneity index, overdistension/collapse and postoperative pulmonary complications in patients with non-injured lungs undergoing laparoscopic gynaecological surgery. Despite Cdyn-directed LPV has several proven advantages, we hypothesize that optimizing intraoperative mechanical ventilation using EIT-guided PEEP titration may further improve patient outcomes by reducing mechanical power responsible for VILI and consequent PPCs. These anticipated advantages may improve our knowledge about individualized protective ventilation, enhance postoperative recovery, shorten in-hospital stay and reduce healthcare related costs.

Methods and design

Objectives of the study

The aim of the study is to compare the effects of two different PEEP titrating methods on mechanical power of ventilation, oxygenation, respiratory mechanics parameters and postoperative pulmonary complications in patients with non-injured lungs undergoing laparoscopic gynaecological surgery.

Study endpoints

Primary endpoints:

- Mechanical power of ventilation (MP; J/min)
    - MP will be calculated using a comprehensive formula for volume-controlled ventilator mode
        - MP = 0.098 x RR x TV (L) x [Ppeak – ½ x (Pplat – PEEP)]

Secondary endpoints:

- Oxygenation (PaO_2 / FiO_2)
- PEEP
- Cdyn
- Driving pressure
- PPCs within 48 hours after surgery
    - atelectasis detected on computed tomography or chest radiograph,
    - pneumonia,
    - Acute Respiratory Distress Syndrome,
    - pulmonary aspiration (clear clinical history AND radiological evidence)

Tertiary endpoints:

- length of hospital stay (days)
- in-hospital mortality
- 28-day mortality
- adverse events related to the PEEP titrating procedure

Study design

Multi-centric, double-arm, parallel-group, single-blinded (subject), interventional, prospective, randomized controlled trial.

Participating Centres

Number	Centre Data
1	Flór Ferenc Hospital Kistarcsa, Hungary
2	Semmelweis University, Hungary
3	Semmelweis Hospital Kiskunhalas, Hungary

SPIRIT

	STUDY PERIOD						
	Enrolment		Allocation	Post-allocation			Follow up
TIMEPOINT**	***-2/1 week***	***-t_1***	**0**	***DOS***	***POD1***	***POD2***	***POD3-28***
ENROLMENT:							
Preoperative assessment (pre-screening)	X						
Eligibility screen		X					
Informed consent		X					
Allocation			X				
INTERVENTIONS:							
PEEP-EIT				X			
PEEP-Cdyn				X			
ASSESSMENTS:							
Mechanical power				X			
Oxygenation (PaO_2/FiO_2)				X	◆—	—◆	
PEEP				X			
Cdyn				X			
Driving pressure				X			
EIT parameters (TV_{ROI3-4}, EELV, GI, ODCL)				X	◆—	—◆	
Postoperative pulmonary complications				X	◆—	—◆	◆—◆
SOFA Score				X	◆—	—◆	
In-hospital stay					◆—	—◆	◆—◆
In-hospital mortality				X	◆—	—◆	◆—◆
28-day mortality				X	◆—	—◆	◆—◆
Adverse events				X			

Blinding, data collection, randomization and record-keeping

Patient data, intra- and postoperative measurements, respiratory parameters, laboratory results, and clinical status (SOFA Score) will be collected onto Case Report Forms (CRF). CRF and patient evaluation chart will not be assessed in front of the patient.

Participants will be randomized to two interventional groups in a ratio of 1:1. Randomization will be carried out by a computer-generated blocked randomization list with 20 blocks of 10 patients per block. Allocation will be stored in sealed opaque and numbered envelopes. Participants will be included and allocated in numerical order.

Selection of the participants

Inclusion criteria:

- Patient scheduled for elective laparoscopic gynaecological surgery
- Age > 18 years
- Signed consent to participate in the trial

Exclusion criteria:

- Age < 18 years
- ASA physical status IV
- History of severe restrictive or chronic obstructive pulmonary disease (COPD, GOLD grades III or IV)
- Uncontrolled bronchial asthma
- Pulmonary metastases
- History of any thoracic surgery
- Need for thoracic drainage before surgery
- Congestive heart failure (NYHA grades III or IV)
- Extreme obesity (BMI>35 kg m^{-2})
- Lack of patient's consent.

Study Protocol

Time course of the study

Preoperative assessment and admission

During standard institutional preoperative assessment patient's eligibility for laparoscopic gynaecological surgery will be evaluated. Medical history, laboratory and chest X-ray or CT scan, 12-lead ECG, ASA physical status, BMI, postoperative respiratory failure risk assessment (RFRI and ARISCAT), nutritional risk screening (NRS 2002 tool) and if required (in case of history of smoking or coronary artery disease) results of spirometry, echocardiography and ergometry will be recorded. Participants fulfilling the inclusion criteria will be asked for their signed informed consent.

After admission to the Department of Gynaecology (on the day before surgery) patient will be randomized into one of the study groups.

Intraoperative care

Before induction of anaesthesia an arterial cannula will be inserted for invasive arterial blood pressure monitoring and blood gas sampling while an EIT belt (Dräger PulmoVista 500) will be placed between the 4^{th} and 6^{th} intercostal space according to the manufacturer's recommendation.

Immediately after induction of anaesthesia and orotracheal intubation, once a steady state has been reached (Table 2), all patients will be submitted to an ARM using the sustained airway pressure by the CPAP method, applying 30 cmH_2O PEEP for 30 seconds. After ARM, PEEP will be set to 6 cmH_2O in both groups and LPV (TV = 6 mL/Kg IBW, FiO_2 = 0.4) will be performed.

After pneumoperitoneum (maximal intraabdominal pressure = 12 cmH_2O) and Trendelenburg position (35°) optimal PEEP (PEEP-EIT) will be determined during a decremental PEEP titration procedure using the PEEP Trial Diagnostic Tool of the EIT device in the PEEP-EIT group. During the procedure Cdyn values and belonging PEEP levels will also be recorded. In the PEEP-C group, optimal PEEP will be determined using Cdyn values: the highest achievable Cdyn will determine the optimal level of PEEP (PEEP-C). EIT parameters will also be recorded. During surgery ARM will be repeated and arterial blood gas samples (ABGs) will be evaluated every

30 minutes. In case of decreasing oxygen saturation (SpO_2 < 92%) a rescue ARM will be performed using FiO_2 of 1.0.

To maintain anaesthesia, in both groups a target-controlled infusion regimen (propofol – remifentanil) will be performed during surgery. Depth of anaesthesia will also be monitored.

Steady state after induction of anaesthesia

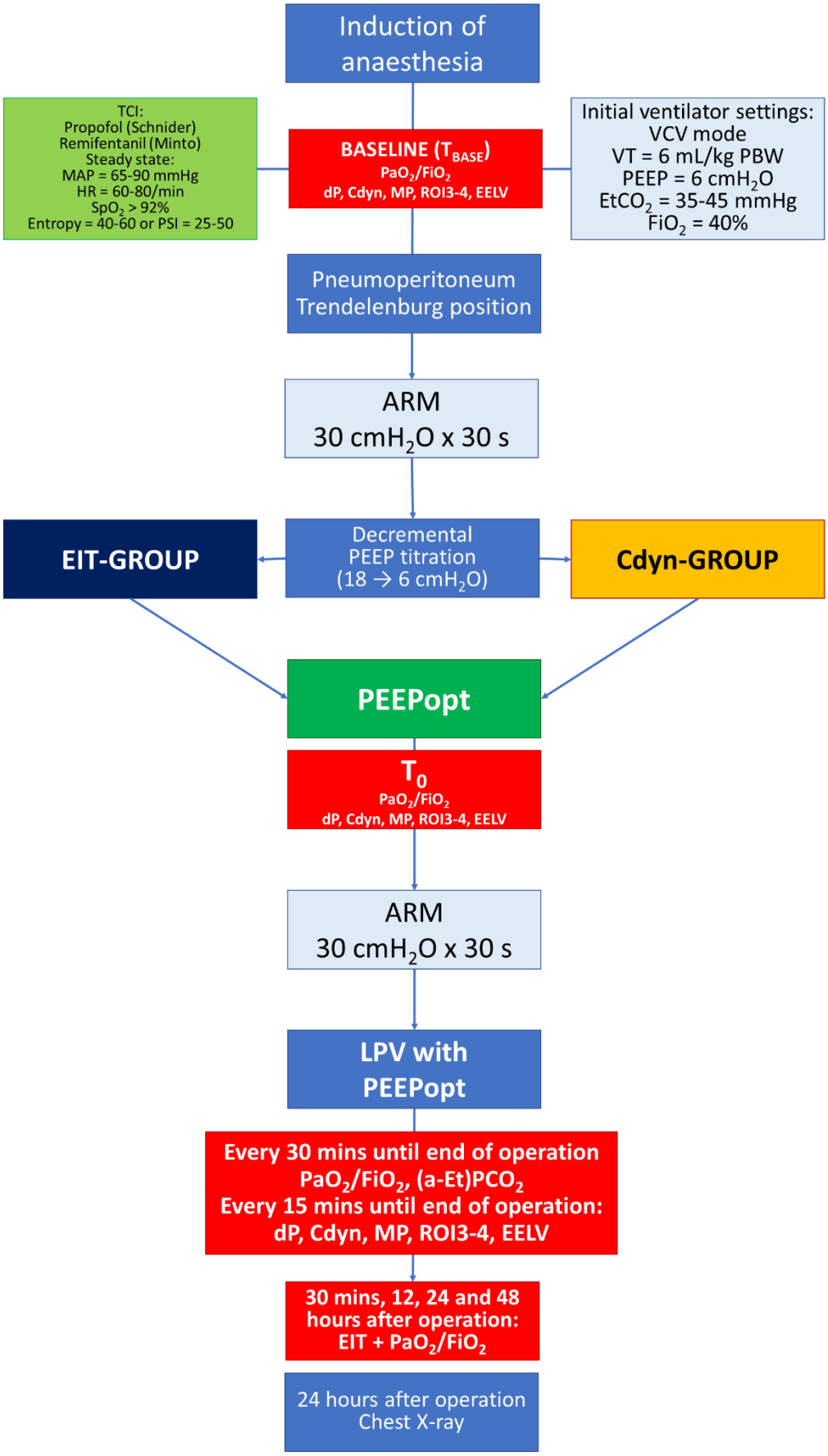
Haemodynamics	
Mean arterial pressure	65-90 mmHg
Heart Rate	50-100 min^{-1}
Ventilation	
SpO_2	≥ 96 %
$EtCO_2$	35-45 mmHg
Depth of anaesthesia	
Entropy	40-60
BIS	40-60
PSI	25-50

SpO_2, $EtCO_2$, BIS, PSI

Arterial blood pressure, heart rate (HR) and end-tidal carbon dioxide tension ($EtCO_2$) will be monitored continuously. Cdyn, core temperature and train-of-four relaxometry data will be recorded every 15 minutes.

During surgery, in cases of hypotension vasopressor treatment (ephedrine, phenylephrine, norepinephrine) will be started to maintain mean arterial pressure above 65 mmHg. For intraoperative fluid management patients will receive a 2 mL/Kg/h of balanced crystalloid solution until the end of surgery. In cases of bleeding crystalloid substitution will be given. Packed red blood cell (PRBC) transfusion will be given whenever the attending anaesthetist renders it necessary (Figure 2).

Protocol of intraoperative interventions



Postoperative care

After extubation, patients will be admitted to the Post-Anaesthesia Care Unit. ABGs will be collected and evaluated for PaO_2/FiO_2 30 minutes, 6, 12, 24 and 48 hours after surgery. At the same timepoints EIT measurements including mid-dorsal and dorsal and regions of interest (TV_{ROI3}, TV_{ROI4}) and end-expiratory lung volume (EELV) will also be performed and recorded. On the first postoperative day (24 hours after surgery), a chest X-ray will be performed and repeated on the following days if developing of pulmonary complications were suspected. Chest X-ray will be evaluated by an independent trained radiologist who will not be involved in the study. Postoperative analgesia will be based on institutional protocol.

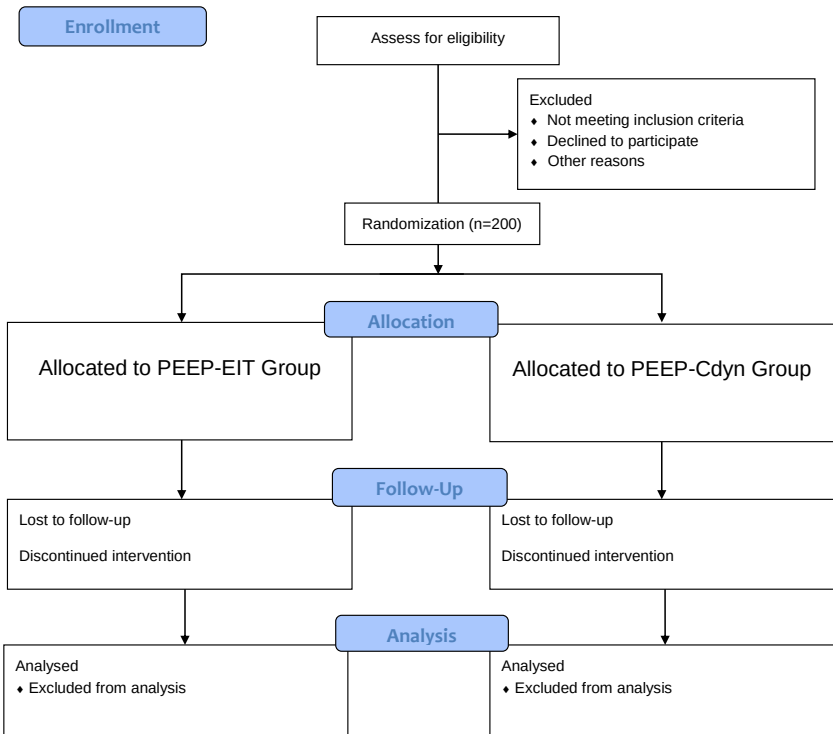
Patients' clinical progress will be monitored by daily SOFA Scores, laboratory and physical examinations.

From postoperative day 3 (POD 3 – POD 28, follow-up)

During follow-up period, secondary endpoints, in-hospital stay, 28-days and in-hospital mortality will also be evaluated.

Figure 3 shows the CONSORT flowchart of the trial.

CONSORT flowchart of the trial



Study arms and assigned intraoperative interventions

A total number of 200 patients scheduled for laparoscopic gynaecological surgery will be enrolled in this study. An equal number of patients will be randomized into the PEEP-EIT and PEEP-C groups.

Patients randomized into the PEEP-EIT group undergo an ARM using the sustained airway pressure by the CPAP method, applying 30 cmH_2O PEEP for 30 seconds followed by a decremental PEEP titration procedure directed by EIT PEEP Trial of the PulmoVista 500 device. During the PEEP titration procedure, PEEP will be decreased from 18 cmH_2O by 2 cmH_2O every 20 ventilatory cycles, until a final PEEP of 6 cmH_2O. On each level of PEEP Cdyn values will also be recorded. Optimal PEEP is considered as the intersect between the lower percentage of overdistension and collapse, based on the diagnostic tool of the EIT device. After PEEP titration procedure, a lung protective mechanical ventilation will be performed using PEEPopt (PEEP-EIT) and low tidal volumes.

Patients randomized into PEEP-C group will undergo the same ARM followed by a decremental PEEP titration procedure directed by Cdyn. During the PEEP titration procedure, PEEP will be decreased from 18 cmH_2O by 2 cmH_2O every 20 ventilatory cycles, until a final PEEP of 6 cmH_2O. On each level of PEEP EIT measurements will also be recorded. Optimal PEEP is considered as the PEEP value resulting the highest possible Cdyn measured by the ventilator. After PEEP titration procedure, a lung protective mechanical ventilation will be performed using optimal PEEP and low tidal volumes. ARMs will be performed every 30 minutes in both groups.

MP, dP, Cdyn, TV_{ROI3}, TV_{ROI4} and EELV will be recorded immediately after the PEEP titration trial and every 15 minutes during surgery in both groups.

Oxygenation and dead space fraction indicated by PaO_2/FiO_2 and (a-Et)PCO_2, respectively will recorded every 30 minutes during surgery in both groups. PaO_2/FiO_2 will be recorded immediately after extubation, 30 mins, 2, 6, 12, 24 and 48 hours after extubation also.

GI and ODCL will be evaluated retrospectively after surgery using the EIT Diag SW 1.6 diagnostic software for Dräger PulmoVista 500.

Data monitoring

Data monitoring will be performed centrally for quality control purposes by an external, independent doctor, who will not be involved in the study. Monitoring will evaluate the progress of the study, and verify the accuracy and completeness of data recording (eCRF, source data, informed consent forms and outcome variables).

Statistical analysis

The sample size was estimated for the secondary endpoint, the Cdyn. In a previous study conducted by Shu et al, a difference of 4.5% was found regarding the Cdyn (66.3 ± 10.66 mL/cmH_2O vs 61.8 ± 11.03 mL/cmH_2O) between the PEEP-Cdyn and PEEP-EIT groups.[29] A sample size of 200 patients (100 patients in each arm) will be needed to observe this difference, assuming $\alpha = 0.05$ and power of 80% and considering a data loss of 10%.

Data will be analysed by the research team in collaboration with a medically versed biostatistician after completion of the trial. There will be no interim analysis. Statistical analysis will be conducted on an intention-to-treat basis.

It is expected that the majority of source data will be recorded onto eCRFs, nonetheless before starting the data analysis, the missing-data mechanism and pattern will be evaluated and these findings will be used to determine whether they have impact on statistical analysis and results and how they can be managed.

Data distribution will be tested by the Kolmogorov-Smirnov analysis. Normally distributed data will be presented as mean and standard deviation (SD) and skewed data as median (interquartile range). Comparing related samples, the paired and unpaired Student t-test will be used for normally distributed data and the Wilcoxon signed rank test and Mann-Whitney U-test for skewed data. Differences in proportions will be evaluated using the Fisher's exact test, and risk ratio with associated 95% confidence interval (CI).

Two-way repeated-measures analysis of variance (2-way RM ANOVA) will be used to compare the groups MP levels. Relationship between MP levels and PPCs will be evaluated using the Pearson correlation. Statistical analysis of SOFA scores, in-hospital stay, readmission rate, in-hospital and 28-days mortality data of groups will be implemented by the chi-square test. P value of less than 0.05 will be considered significant.

Adverse events and interruption of the trial

Every patient included in the trial will receive daily visits from intensive care therapist and gynaecologist in charge from POD 1 until leaving the hospital. The study nurse will be responsible for collecting blood samples and record relevant required data onto eCRFs. During out-of-hospital follow-up period (until POD 28) patients' progress, respectively deterioration will be checked by daily phone call visits.

Investigators will monitor the patients for any adverse events (AEs), which are defined as severe or prolonged hypotension (systolic blood pressure < 90 mmHg) and significant cardiac arrhythmias associated with the PEEP titration procedure. AEs will be documented on the eCRF and the principal investigator will be informed.

Serious adverse events (SAEs) are defined as severe barotrauma leading to pneumothorax, significant prolongation of hospitalization, persistent or significant disability or incapacity, and severe deterioration (life-threatening state or even death) associated with the PEEP titration procedure. All treatment related SAEs will be recorded and reported to the Hungarian Scientific and Medical Research Council Ethics Committee and the local ethics committees. If any SAEs occur, the trial will be interrupted and an investigation will be performed.

Duration of the trial

The annual number of laparoscopic gynaecological surgery is around 1500 in the participating study centres. Recruitment of the participants is expected within 24 months. Final data collection and estimated completion date of the trial is 31 October, 2027.

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This is the latest version of the study protocol.

Date: 08/09/2025