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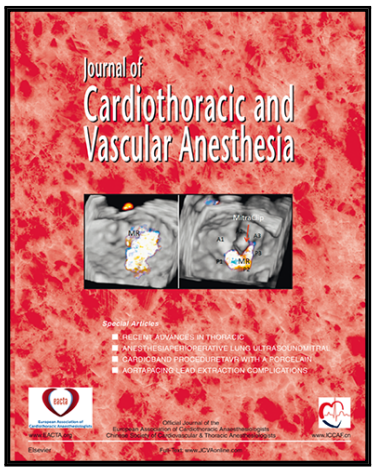

Rationale and study design for an Individualized PeriopeRative Open lung Ventilatory stratEgy in patients on One Lung Ventilation (iPROVE-OLV). A study protocol for an international, multicenter randomized controlled trial.

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A study protocol for an international, multicenter randomized controlled trial.

Running Title: iPROVE-OLV

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ABSTRACT

Objective: The aim of this clinical trial is to examine whether it is possible to reduce postoperative complications when using an individualized perioperative ventilatory strategy versus using a standard lung-protective ventilation strategy in patients scheduled for thoracic surgery requiring one-lung ventilation.

Design: International, multicenter, prospective, randomized, controlled clinical trial.

Setting: A network of university hospitals

Participants: A total of 1,380 patients scheduled for thoracic surgery.

Interventions: The individualized group will receive intraoperative recruitment maneuvers followed by an individualized positive end-expiratory pressure (PEEP) [open lung approach, OLA] during the intraoperative period plus postoperative ventilatory support with high-flow nasal cannula (HFNC), whereas the control group will be managed with conventional lung-protective ventilation.

Measurements: In both groups, we will analyse individual and total number of postoperative complications (including atelectasis, pneumothorax, pleural effusion, pneumonia, acute lung injury), unplanned readmission and reintubation, length of stay and death in the critical care unit and in the hospital.

Expected Results: Our hypothesis is that the intraoperative application of OLA followed by an individual indication of HFNC in the post-operative period will reduce pulmonary complications and length of hospital stay in high-risk surgical patients.

Keywords: Mechanical Ventilation, Postoperative Pulmonary Complications, One-Lung Ventilation, Positive end-expiratory pressure, Recruitment Maneuvers.

INTRODUCTION

Lung resection surgery is associated with a high risk of postoperative pulmonary complications (PPCs) [1,2,43], including the development of atelectasis, pneumonia and the acute respiratory distress syndrome. Ventilator induced lung injury (VILI) and acute respiratory distress syndrome are the main causes of morbidity and mortality after surgical lung resection [4]. These complications have a significant impact on health care costs in surgical patients [3]. PPCs increase the need for and the duration of mechanical ventilation (MV) in the postoperative period, increase the unscheduled readmissions in the intensive care unit (ICU), and lengthen the stay in the ICU and hospital [10 -14].

In patients with healthy lungs, MV can promote PPCs [5-7]. The main mechanisms of lung injury during MV are volutrauma (tissue damage caused by the excessive stretching of tissues that occurs when the lung is over-inflated) and atelectrauma (injury caused by the repetitive re-opening of closed lung units) [5, 47], causing an inflammatory response that favours the development of VILI [6,8] and extrapulmonary organ dysfunction [9]. Lung-protective ventilation with low tidal volume (VT) and moderate-to-high levels of positive end-expiratory pressure (PEEP) has shown to reduce PPCs [15,16]. Driving pressure, calculated as the difference between the plateau pressure (Pplat) minus PEEP, has been recently considered an independent risk factor for the development of PPCs [18], Although it is well accepted that low-VT MV decreases PPCs [17,18], there is some controversy about the benefits of PEEP in reducing PPCs [19]. During one-lung-ventilation (OLV), PEEP improves oxygenation, mitigates atelectrauma and attenuates lung injury, [20-24]. However, the level of adequate PEEP during OLV is questionable [25, 26].

There are no reports describing the optimal PEEP levels during OLV for preventing PPCs. Recent evidence suggests that an adequate lung-protective strategy is a judicious combination of low VT and PEEP [18]. We have recently reported our experience with an individualized ventilatory approach [27,28,40,41], achieving the lowest value of driving pressure. During the immediate postoperative period, there is an increased risk of respiratory dysfunction due to different factors related to the patient, the type of surgery and the general anesthesia. Since oxygenation through a high-flow nasal cannula (HFNC) decreases the respiratory work, maintains functional residual capacity and washes carbon dioxide [29,45], the use of HFNC during the initial postoperative phase could be beneficial.

Rationale

We assume that a pragmatic and standardized adjustment of PEEP, which is currently the common clinical practice, is erroneous since a PEEP lower or equal to the alveolar closing pressure will favour the reappearance of alveolar collapse after a recruitment maneuver (RM). On the contrary, if it is higher than what it is needed, it will increase the risk of overdistention. Both factors are recognized as determinants of deterioration of lung function during the intraoperative period, and will increase the risk of postoperative lung injury.

Although it has been reported that driving pressure is the most important independent risk factor for PPCs, there are no prospective, randomized controlled studies supporting that statement. Results of different studies performed by our group suggest that an individualized OLA strategy decreases driving pressure for a given VT, potentially increasing the protective effect of this strategy. Finally, we propose that HFNC could reduce PPCs during the immediate postoperative period. In postoperative patients, this strategy has never been applied individually or in combination with an intraoperative OLA.

Hypothesis and Objectives

The primary hypothesis of the study is that an individualized perioperative OLA ventilatory strategy (including low VT, alveolar RM, individualized adjustment of PEEP, and individualization of ventilatory support in the immediate postoperative period) will reduce postoperative pulmonary complications in patients undergoing thoracic surgery requiring one-lung ventilation. It has been formulated as a null hypothesis of no differences in postoperative pulmonary complications between individualized and standardized ventilatory management in moderate-to-high risk patients.

Primary objective: To examine the efficacy of the experimental ventilatory strategy in reducing PPCs during the first 7 days after surgery, when compared to conventional ventilatory management.

Secondary objectives: To examine the efficacy of the experimental ventilatory strategy in reducing postoperative pulmonary and systemic complications, unscheduled ICU and hospital admissions, ICU and hospital length of stay during the first 30 days after surgery, when compared to conventional ventilatory management.

METHODS

Study design

This trial has been designed in accordance with the fundamental principles established in the Declaration of Helsinki, the Convention of the European Council relating to human rights and biomedicine, and the Universal Declaration of UNESCO on the human genome and human rights, and with the requirements established by Spanish legislation in the field of biomedical research, the protection of personal data, and bioethics, which was classified by the Spanish Agency of Drugs and Medical Devices as a clinical randomized study without drugs on September 7th, 2017. It was registered on 2017 at http://www.clinicaltrials.gov (NCT03182062). Approval of the final protocol by the local committee at each participation center will be required before patient enrolment.

The Individualized Perioperative Open-lung Ventilatory Strategy in patients submitted to one lung ventilation (IPROVE-OLV) trial is an International multicenter, controlled, not masked, clinical trial with random assignment of patients to two parallel groups of ventilatory management (Figure 1).

1. **Group STD-O2:**

After initiating selective pulmonary ventilation, all patients will receive lung-protective ventilation with a VT of 5-6 ml/kg of ideal body weight, 4 cmH_2O of PEEP and an FIO_2 of 0.8. During the first 6 postoperative hours, patients will be oxygenated with the minimum FIO_2 to maintain a SpO_2 ≥92%.

2. **Group iOLA-iHFNC:**

After initiating selective pulmonary ventilation, an alveolar RM followed by a PEEP titration trial will be performed to all patients. Patients included in this group will be ventilated intraoperatively with a VT of 5-6 ml/kg of ideal body weight, open-lung PEEP and with an FIO_2 of 0.8. After extubation, approximately 15 minutes after entering into the post-anesthesia care unit (PACU), an air-test (which consists in breathing at FIO_2 0.21 for 5 minutes) will be performed [30]. During the first 6 postoperative hours [in case of negative Air-Test (SpO2 ≥97%)], the patient will be oxygenated with the minimum FIO_2 to maintain an SpO_2 ≥92%. In case of positive air-test (SpO_2 ≤96%), oxygen therapy with HFNC at 50L/min flow will be indicated with the minimum FIO_2 to maintain a SpO_2 ≥92%.

In both groups, a new RM will be performed at the end of one-lung ventilation (OLV). After the RM in the STD-O2 group, a protocolized PEEP of 4 cmH_2O will be set. In the iOLA-iHFNC group, the last OLA-PEEP will be adjusted. Also, once extubation has been performed in the operating room, all patients will be oxygenated with 0.5 FIO_2 through a Venturi mask during the first 30 min until the air-test is done.

Study population

The study population is comprised of adult male and female ≥18 years old, scheduled for an open or video-assisted thoracic surgery with selective pulmonary ventilation and an expected operating time of ≥2 hours. Patients who meet all of the following inclusion criteria and none of the exclusion criteria will be consecutively included:

Exclusion criteria: 1) Pregnancy or breast-feeding, 2) moderate or severe acute respiratory distress syndrome defined as PaO_2/FiO_2 <200 mmHg, 3) diagnosis of heart failure defined as: IC <2.5 ml/min/m^2 and/or inotropic support before surgery and/or or suspicion of heart failure according to clinical signs (hypotension, oliguria, pulmonary oedema) together with NT-proBNP >13 pg/ml, 4) diagnosis or suspicion of intracranial hypertension (>15 mmHg), 5) MV in the last 15 days (including CPAP), 6) presence of pneumothorax or giant bullae on a chest radiograph or computed tomography (CT), 7) patients with chronic obstructive pulmonary disease requiring oxygen or CPAP, and patients participating in another interventional study with similar primary outcomes, 8) Previous lung resection.

Method of randomization and bias minimization

Informed consent will be obtained from each participant before enrolment in the study. Patients who meet all the inclusion criteria and none of the exclusion criteria will be consecutively included and randomized into one of the two study arms (Figure 1). Patients will be randomized, by the first investigator, online via the *website http://iprove.incliva.es* using the Mersenne Twister algorithm with an allocation rate of 1:1.

Blinding: At least two investigators are required in each participating center, because the study characteristics do not allow the blinding of investigators in the operating and postoperative room, so data acquired in these sites will not be blinded. After 24 h, all data will be acquired by the second investigator who will be blinded to the randomization arm.

Study variables and definitions

The primary outcome of the iPROVE trial is a composite of pulmonary complications, following standard definitions [31] experienced by the study population in the first 7 days after surgery as discussed below.

1. Atelectasis requiring bronchoscopy. Atelectasis is defined as chest X-ray images suggesting lung opacities with a shift in the mediastinum, hilum, or hemi-diaphragm toward the affected area and compensatory over-inflation in the adjacent non-atelectatic lung.

2. Severe respiratory failure: Hypoxemia (defined as SpO_2 of 92% or less with 0.21 FIO_2 or SpO_2 of 95% or less with 0.5 FIO_2) requiring ventilatory support.

3. Contralateral pneumothorax: air in the pleural space and the mediastinum is shifted to the opposite side (a chest radiography will be performed in suspected cases of auscultation hoarseness).

4. Early extubation failure or requirements of reintubation: If the patient has mild (PaO2 < 60 mmHg, PaO2/FiO2 <300 mmHg, SpO2 <90% and requiring oxygen therapy) or severe acute respiratory failure (PaO2 <60 mmHg, PaO2/FiO2 <300 mmHg, SpO2 <90% and requiring non-invasive ventilation (including CPAP) or invasive ventilation.

5. Acute respiratory distress syndrome. Berlin definition:

- Timing: Within one week of a known clinical insult or new or worsening respiratory symptoms and

- Chest imaging: Bilateral opacities not fully explained by effusions, lobar/lung collapse or nodules and

- Origin of oedema: Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. echocardiography) to exclude hydrostatic oedema if no risk factor present and

- Oxygenation. *Mild: PaO2/FIO2 between 26.7 and 40.0kPa (200–300mmHg) with PEEP or CPAP ≥5 cmH2O *Moderate: PaO2/FIO2 between 13.3 and 26.6 kPa (100–200mmHg) with PEEP ≥5 cmH2O. *Severe: PaO2/FIO2 13.3 kPa (100mmHg) with PEEP ≥ 5 cmH2O

6. Suspicion of pulmonary infection or pneumonia: Treatment with antibiotics or/and the presence of a new pulmonary infiltrate and/or progression of previous pulmonary infiltrates on a chest radiograph plus at least two of the following criteria: (a) leucocytosis with >12,000 WBC/mm3 or leukopenia with <4000 WBC/mm3, (b) fever >38.5° C or hypothermia <36°C, and (c) increased secretions with purulent sputum and a positive bronchial aspirate.

7. Bronchopleural fistula: Presence of continuous air leak through the bronchial stump and diagnosed with fiberbronchoscopy.

8. Pleural empyema with or without surgical reintervention: Collection of pus in the pleural cavity, confirmed by thoracentesis and positive bacterial culture.

The secondary outcomes are the composite of postoperative pulmonary complications over the first 30 post-surgical days. These are [31, 46, appendix 1]:

1. Atelectasis without bronchoscopy: Positive air-test (SpO2 ≤96% when removing the oxygen mask and leaving the patients breathing room air for at least 5 min).

2. Hypoxemia without requirements of supplementary oxygen or ventilator support [44]: Peripheral capillary oxygen saturation <90%.

3. Contralateral pleural effusion: chest x-ray with the presence of costophrenic angle blunting, displacement of adjacent anatomical structures, and blunting of the hemidiaphragmatic silhouette in the supine position

4. Bronchospasm: presence of expiratory wheezing treated with bronchodilators.

5. Aspiration pneumonitis: respiratory failure after the inhalation of regurgitated contents.

6. Pulmonary thromboembolism: A new blood clot or thrombus within the pulmonary arterial system.

7. Chronic obstructive pulmonary disease exacerbation: sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variations that is acute in onset and may warrant additional treatment

8. Hemothorax with or without surgical reintervention or transfusion: presence of blood in the pleural space, specifically when the hematocrit of the pleural fluid is greater than or equal to 50% of that of the peripheral blood

9. Claven-Dildo classification

10. ICU and hospital length of stay

11. ICU and hospital readmission in the first 30 days after surgery

12. Mortality within the first 30 days

Secondary outcomes that are systemic complications following standard definitions [31, appendix 1]:

1. Cardiac ischemia

2. New atrial fibrillation

3. Sepsis or septic shock

4. Acute kidney failure

5. Surgical site infection

6. Other infections (catheter, urinary tract…)

The primary and secondary outcome variables will be recorded at 1, 2, 5, 7, and 30 days after surgery. Plasma samples will be taken preoperatively and at 2 days after surgery. If the patient is not extubated in the operating room, the first four data time points will be taken from the time of extubation.

Other follow-up variables

Baseline variables will be recorded preoperatively: age, sex, height, weight, body mass index, American Society of Anesthesiologists (ASA) physical status [32], Charlson comorbidity index [33], preoperative pulmonary function test, sequential organ failure assessment (SOFA) score [34], ARISCAT risk score [35], type of intervention, and medical history.

Intraoperative parameters recorded at three different time-points (post-induction, 60 min after induction, and pre-extubation) are: arterial blood gases, SpO_2, FIO_2, respiratory variables [VT, PEEP, Paw, Pplat, Crs, respiratory system resistance (Raw), hemodynamics (cardiac index, PAM, and stroke volume variation (SVV) and/or pulse pressure variation (PPV)], diuresis, and body temperature. Other relevant data that include the types of anesthetic drugs used, type and volume of fluids, blood loss and transfusion requirements, need of vasoactive drugs, diuresis, nasogastric tube insertion, duration of surgery, mechanical ventilation time, number of recruitment maneuvers performed, and the need for rescue therapy will also be recorded.

General procedures

All participating patients, regardless of the study arm into which they are randomized, will be monitored and managed following general standard of care practices aimed at maintaining optimal conditions. Both intraoperative and immediate-postoperative (6h) anesthetic management (unrelated to ventilatory management) will be decided by the attending physician as they see fit, following the established protocols at each center. However, in order to ensure a high standard of anesthetic management, a number of common strategies have been established: halogenated agents will be given to maintain anesthesia, intra- and postoperative pain will be controlled with neuraxial anesthetics, fluids will be administered following goal-directed therapy principles. Appropriate antibiotic prophylaxis will be administered, and pharmacological prevention of postoperative nausea and vomiting will be adopted. Finally, when nasogastric tube insertion is required, it should be withdrawn prior to extubation when possible. All these data will be collected and analyzed.

Monitoring

Intraoperative monitoring will include an electrocardiogram (ECG), pulse oximetry, capnography, bladder or esophageal temperature, anesthetic depth analysis (bispectral analysis, BIS) and a neuromuscular blockade (with train of four), invasive blood pressure measurements, and advanced

hemodynamic monitoring with minimally invasive monitoring (optional depending on the standard clinical practice and availability of equipment at each hospital). Ventilatory parameters will be monitored by the anesthesia machine: VT, PEEP, FIO_2, peak airway pressure (Paw), plateau pressure (Pplat), driving pressure (DP) and dynamic compliance of the respiratory system (Cdyn). Postoperative monitoring will include at least an ECG, pulse oximetry, and invasive arterial pressure measurements.

General intraoperative ventilator management

Pre-oxygenation will be performed for 5 min at FIO_2 1.0 with a tightly sealed face mask before induction. Patients will be ventilated in volume control mode (VCV) with squared flow, a VT of 8 ml/kg of the predicted body weight (PBW) during two lung ventilation and 5-6 ml/kg of the predicted body weight (PBW) during one-lung ventilation, PEEP of 4 cmH_2O and a Pplat of ≤25 cmH_2O. If the Pplat reaches or exceeds 25 cmH_2O, VT will be decreased in 1 ml/kg steps until the Pplat drops to ≤25 cmH_2O. The respiratory rate (RR) will be set to maintain an end-tidal carbon dioxide partial pressure ($EtCO_2$) between 35-45 mmHg, with an inspiratory to expiratory ratio (I:E) of 1:2 (it could be modified under the criteria of the attending physician) and a inspiratory pause time of 5-10% of the inspiratory time. FIO_2 will be set at 0.8 throughout the whole procedure. During the awakening period from general anesthesia (patients with spontaneous ventilation), a FIO_2 of 1.0 will be applied at the same end-expiratory pressure used, using either PEEP or CPAP.

In all the study patients, adequate selective ventilation must be corroborated with the fiberoptic bronchoscope. Extubation will not be allowed by applying a positive pressure above the previously set PEEP or CPAP or while suctioning through the tracheal device. If necessary, aspiration can be performed at least 10 min before extubation. After suction, the patient will be switched back to mechanical ventilation. If the patient is randomized into the iOLA-iHFNC group, a new alveolar recruitment maneuver will be performed. Once extubation has been performed, all the study patients will be oxygenated with 0.5 FIO_2 through a Venturi mask during the first 30 minutes.

Specific intraoperative ventilatory management

STD-O2 group: The patients will be ventilated as previously described in the general intraoperative ventilator management section.

iOLA-iHFNC: a RM will be performed immediately after selective ventilation is initiated followed by a PEEP titration trial. Before the RM is performed, the clinician must ensure that there is hemodynamic stability [mean arterial pressure (MAP) of more than 70 mmHg and/or a cardiac index of more than 2.5 ml/min/m^2] for

at least 5 min, a stroke volume variation (SVV) of less than 10%, and an adequate neuromuscular blockade (0 of 4 by train of four). The ARM is performed as described in the following section.

Alveolar recruitment maneuver (RM)

Recruitment will be performed as previously described [42]. The ventilator will be changed from VCV to pressure-controlled ventilation with a 20-cmH_2O driving pressure and RR of 15 breaths per minute (rpm), I:E of 1:1, 0.8 FIO_2, and PEEP of 5 cmH_2O. For the recruitment phase, the PEEP level will be increased in 5 cmH_2O steps every five respiratory cycles, up to 20 cmH_2O of PEEP to produce an airway opening pressure of 40 cmH_2O and maintained for 10 respiratory cycles in the opening pressure (total maneuver time: 100 s). If hemodynamic instability appears during the recruitment phase (a >50% decrease in the cardiac index or MAP), the RM will be interrupted and 5-15 mg ephedrine or 0.05-0.15 mg phenylephrine given; after hemodynamic stabilization, a new RM will be performed. After lung recruitment is accomplished, optimal PEEP is titrated through a decremental PEEP trial, as described in the next section. (Figure 2).

Titration of the optimal individual positive end-expiratory pressure: Decremental PEEP trial.

At the end of the last step of the PCV recruitment phase when the PEEP is 20 cmH_2O, the mode will be switched to VCV with a VT of 5-6 ml/kg, RR of 15 rpm, and I:E of 1:2, 0.8 FIO_2. After this, PEEP is decreased 2 cmH_2O steps every 15 s until the highest Cdyn observed on the ventilator's monitor (until Cdyn starts decreasing or does not increase). In case that highest Cdyn appears with several PEEP values, the PEEP with lowest driving pressure (Pplat – PEEP) will be seleted. Once the best Cdyn is known, a new recruitment maneuver is performed and the PEEP for the best Crs is adjusted. In the case of accidental airway depressurization, a new ARM is performed while an identical PEEP is set (Figure 2).

The need of new RMs and a PEEP trial will be evaluated every 40 min by measuring the Cdyn. If there is a drop of more than 20% of the Cdyn, a new recruitment and PEEP trial will be performed.

Intraoperative rescue maneuvers

In the case of arterial hypoxemia (SpO_2 of ≤92% with FIO_2 0.8), after excluding endobronchial tube displacement, bronchospasm, pneumothorax, or a hemodynamic cause, a protocol for rescue therapy has been devised for each specific group.

STD-O2 group: The 0.1 FIO_2 is increased until SpO_2 is more than 95%. If arterial hypoxemia persists with 1.0 FIO_2, the PEEP is increased in steps of 2 cmH_2O (until a maximum of 10 cmH_2O). If hypoxemia persists, a CPAP in the non-dependent lung is allowed.

iOLA-iHFNC: A new RM and PEEP trial will be performed. If SpO_2 is less than 92% (0.8 FIO_2), FIO_2 is increased in 0.1 steps. If hypoxemia persists, a CPAP in the non-dependent lung is allowed.

Lung RM in the non-dependent lung

If it is necessary to perform a lung RM for a leak test or as a rescue maneuver for hypoxemia, this will be done by connecting a CPAP system with adequate oxygen flow, increasing the level of CPAP in 5 cmH_2O steps from 5 to 10 cmH_2O every 5 seconds.

For leak tests, the lung will be thereafter depressurized again. If the RM is performed as a rescue maneuver the minimum level of CPAP that maintains an SpO_2 ≥92% will be adjusted.

General postoperative management in the postoperative care unit

General postoperative management in the PACU or ICU, not related to ventilator management will be decided by the attending physician following the established protocols at each center. Patients will be oxygenated with FIO_2 0.5 through a Venturi mask for the first 15 – 30 min.

In all the study patients the arterial oxygenation will be evaluated 15 to 30 min later when patients are awake and collaborative [Glasgow coma score (GCS) higher than 13] without any residual anesthetic effect (Richmond scale -1 to +1) and under pain control [verbal analog pain scale (echelle visuelle analogique; EVA) score <4] by decreasing the FIO_2 to 0.21 for at least 5 min (air-test). The air-test will not be performed if the patient already has an SpO_2 below 96% with FIO_2 0.5. When the patient arrives in the PACU or ICU with invasive MV, the above-mentioned management will be applied after extubation.

Specific postoperative ventilatory management

STD-O2 group: Patients will be oxygenated through a Venturi mask with the minimum FIO_2 that maintains a SpO_2 ≥92%.

iOLA-iHFNC group: Supplemental oxygen at FIO_2 0.5 will be delivered through a Venturi mask. During the first 6 postoperative hours [in case of negative air-test (SpO_2 ≥97%)] the patient will be oxygenated with the minimum FIO_2 to maintain an SpO_2 ≥92%. In case of positive Air-Test (SpO_2 ≤96%), high-flow oxygen therapy (HFNC) will be indicated with with 50L/min flow and the minimum FIO2 to maintain a SpO2 ≥92%.

Postoperative rescue maneuver

In patients with persistent hypoxemia and/or hypercapnia [$PaCO_2$ >50 mmHg with a pH <7.30], tachypnea (RR >25 rpm), or increased activity of accessory respiratory muscles are present, inspiratory support with non-invasive ventilation (NIV) will be started.

Non-invasive ventilation (NIV)

The ventilator (specific for NIV or with software for NIV) and interface for NIV will be chosen by the attending physician and based on hospital availability. Positive pressure will start with an inspiratory positive airway pressure of 5 cmH_2O higher than the expiratory positive airway pressure and will be increased in steps of 5 cmH_2O up to 15 cmH2O. The expiratory positive airway pressure will be increased to a maximum of 10 cmH_2O (15 cmH_2O if the BMI exceeds 30).

Invasive ventilation

Direct tracheal intubation (without NIV trial) will be indicated if the patients also meet at least one of the following criteria:

1. Hemodynamic instability [a systolic blood pressure (SBP) <80 mmHg or <40% of the basal or vasoactive drug requirements for more than 2 h is required to maintain the SBP >80 mmHg].
2. Ventricular arrhythmias with hemodynamic instability or ECG signs of myocardial ischemia.
3. GCS of less than 9.
4. Sedation requirement due to agitation.

Tracheal intubation after 1 h of NIV will be indicated in patients meeting at least one of the following criteria:

1. Severe hypoxemia (SpO_2 <92%).
2. Respiratory acidosis (pH <7.30 with a $PaCO_2$ > 50 mmHg)
3. Signs of distress with increased use of accessory respiratory muscles or paradoxical thoracic-abdominal respiratory movements.

Sample Size

Assuming a confidence level of 95%, a percentage of pulmonary complications of 18% at 7 days post-intervention [18], a total of 655 patients per group (intervention and control groups) are required to detect with a power of 80%, an absolute reduction of 5% in the prevalence of pulmonary complications. Assuming 5% of possible losses, the final sample size is 1380 patients (690 per group).

Statistical analysis

The characteristics of patients will be described by frequencies and percentages, in the case of categorical variables, and using mean and standard deviation or median and interquartile range in the continuous variables, depending on normality. The categorical variables will be compared using Chi-square test or Fisher's test, and the magnitude of the association with relative risks or odds ratios will be established. Continuous variables will be compared using the Student's t test or the Mann-Whitney U test,

depending on normality. The baseline characteristics of the control group and the intervention group will be compared, and in the case of finding any difference in potentially confounding variables, they will be included as adjustment variables in the corresponding multivariate models. The main outcome variable will be expressed as a proportion of complications together with a 95% confidence interval. A difference of proportions test will be done, or multivariate logistic regression -including potentially confounders- will be applied, to compare intervention group and control group. Time-to-event variables such as time to primary or secondary outcome will be analysed using Kaplan-Meier curves and univariate or multivariate, as appropriate, Cox proportional hazards models. Variables with different measures over time will be analysed using mixed linear models. All analyses will be done by intention to treat and the missing data will be imputed using multiple imputation methods when more than 5% appear in the primary or secondary outcome variables. A level of significance of $\alpha = 0.05$ will be considered.

Data Safety Monitoring Board - Stopping Rules

The stopping rule is based on the modification of the limits of Haybittle-Peto. The analysis of the main outcome variable will be presented to the Data and Safety Management Board (DSMB) blindly to the study groups. The intermediate analysis will be done once the efficacy variables of the first 655 patients are obtained. If the analysis is significant ($P<0.001$) both positively and negatively for the intervention group, the safety committee will be able to paralyze the inclusion of new patients. Given this blinded monitory strategy, we will not assume any alpha spending function approach and subsequent analyses will follow the level of predetermined level of significance ($\alpha = 0.05$)

DISCUSSION

MV in healthy lungs can promote the development of PPCs. Contemporary reports have shown that ventilation with high VT and low PEEP favours the appearance of PPCs. The use of lung-protective ventilation with low VT and adequate PEEP could reduce PPCs, the need for postoperative ventilator support, unplanned ICU and hospital readmissions and ICU and hospital length of stay [15,19]. Likewise, during the immediate postoperative period there is an increased risk of developing pulmonary dysfunction due to different causes, both anesthetic and surgical. Some studies have shown that the ventilatory support during this phase could reduce postoperative complications [36,37].

Although lung-protective MV has decreased the prevalence of PPCs, its prevalence in patients undergoing thoracic surgery is around 20-30% [1,2,18]. The appearance of complications worsens the patient's prognosis and increases the consumption of health resources.

Different ventilatory strategies such as the use of a physiological low-VT, RMs, individualized PEEP and HFNC in the postoperative period, which are not widely used in routine clinical practice [38,39], have been shown to reduce the incidence of postoperative pulmonary complications. However, there is no prospective, controlled and randomized clinical studies demonstrating that the use of a perioperative OLA strategy consisting of performing RMs plus individualized PEEP adjustment during the intraoperative period along with the postoperative individualized indication of HFNC decreases PPCs with respect to a standardized ventilation strategy in patients undergoing lung resection.

In this study, the effectiveness of the application of a perioperative open lung strategy will be evaluated. If it were shown that it reduces PPCs, it would represent a notable advance in the clinical management of these patients. In addition, a reduction in these complications would reduce the use of healthcare resources.

Trial status

The iPROVE-OLV screening for patients begins in October 2018. Local ethics approval at each participation center is required.

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ABBREVIATIONS

ARM, Alveolar recruitment maneuvers; ASA, American Society of Anesthesiologists; BIS, Bispectral analysis; BMI, Body mass index; Bpm, Breaths per minute; CI, Confidence interval; CPAP, Continuous positive airway pressure; Cdyn, Dynamic compliance of the respiratory system; CT, Computed tomography; DP: driving pressure; ECG, Electrocardiogram; $EtCO_2$, End-tidal carbon dioxide partial pressure; EVA, Visual analog pain scale (echelle visuelle analogique EVA); FIO_2, Inspiratory oxygen fraction; GCS, Glasgow Coma Score; HFNC: high-flow nasal cannula; HR, Heart rate; ICU, Intensive care unit; I:E, Inspiratory-to-expiratory ratio; iPROVE, Individualized perioperative open lung ventilatory strategy; LPV: lung protective ventilation; MAP, Mean arterial pressure; MV, Mechanical ventilation; NIV, Noninvasive ventilation; OLA: open-lung approach; OLV: one-lung ventilation; $PaCO_2$, Partial pressure of carbon dioxide; PACU, Postoperative care unit; Paw, Peak airway pressure; PBW, Predicted body weight; PCV, Pressure control ventilation; PEEP, Positive end-expiratory pressure; PPCs, Postoperative pulmonary complications; Pplat, Plateau pressure; PPV, Pulse pressure variation; Raw, Respiratory system resistance; RR, Respiratory rate; SBP, Systolic blood pressure; SOFA, Sequential Organ Failure Assessment; SpO_2, Peripheral capillary oxygen saturation; SSI, Surgical site infection; STD: standard; SVV, Stroke volume variation; VCV, Volume control ventilation; VILI, Ventilator-induced lung injury; VT, Tidal volume.

APPENDIX 1

Systemic complications following standard definitions:

1. Cardiac ischemia: Increase in serum cardiac biomarker values (preferably cardiac troponin) with at least one value above the 99th percentile upper reference limit and at least one of the following criteria:10 symptoms of ischaemia; new or presumed new significant ST segment or T wave ECG changes or new left bundle branch block; development of pathological Q waves on ECG; radiological or echocardiographic evidence of new loss of viable myocardium or new regional wall motion abnormality; identification of an intracoronary thrombus at angiography or autopsy

2. New atrial fibrillation: ECG evidence of cardiac rhythm disturbance (atrial fibrillation)

3. Sepsis or septic shock. Sepsis: Infectious focus identified plus organ dysfunction (defined as an increase in SOFA ≥2). Septic shock: Severe sepsis with hypotension and hypoperfusion that is unresponsive to fluids.

4. Acute kidney failure: AKIN-scale

* Stage I: Diuresis <0,5 mg/Kg (6h) or increase in serum Cr >0,3 mg/dl.

* Stage II: Diuresis <0,5 mg/Kg (12h) or basal Cr x 2 mg/dL.

* Stage III: Diuresis <0,3 mg/Kg (24h) o anuria (12h) or basal Cr x3 mg/dL, or Cr >4 mg/dL or renal replacement therapy.

5. Surgical site infection:

The CDC defines a superficial incisional surgical site infection as one which meets the following criteria. (1) Infection occurs within 30 days after surgery and (2) Involves only skin and subcutaneous tissue of the incision and (3) The patient has at least one of the following: (a) purulent drainage from the superficial incision (b) organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision (c) at least one of the following symptoms or signs of infection: pain or tenderness, localised swelling, redness or heat, and superficial incision is deliberately opened by surgeon and is culture positive or not cultured. A culture negative finding does not meet this criterion. (d) diagnosis of an incisional surgical site infection by a surgeon or attending physician.

6. Other infections (catheter, urinary tract…)

Other secondary outcomes are:

1. Claven-Dildo classification

- Grade I: Any deviation from the expected postoperative course that does not require specific treatment.

- Grade II: Complications requiring drug therapy, blood transfusions or nutritional support.

- Grade III: Postoperative changes that require invasive treatment (puncture, drainage and re-operations) Grade IIIa: without general anesthesia Grade IIIb: with general anesthesia

- Grade IV: Complications with imminent risk of death and need for intensive care

Grade IVa: 1 organ dysfunction Grade IVb: 2 or more organs dysfunction

- Grade V: Postoperative death

2. ICU and hospital length of stay

3. ICU and hospital readmission in the first 30 days after surgery

4. Mortality within the first 30 days

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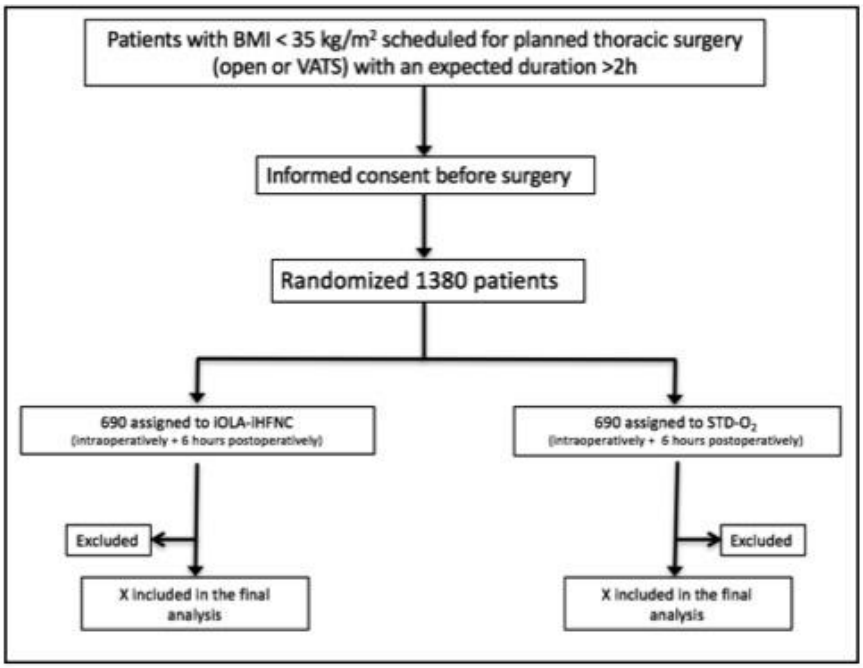

Figure 1. Flow diagram of iPROVE-OLV. BMI: Body-mass index; VATS: Video-assisted thoracic surgery; iOLA: individualised open lung approach; HFNC: high-flow nasal cannula.

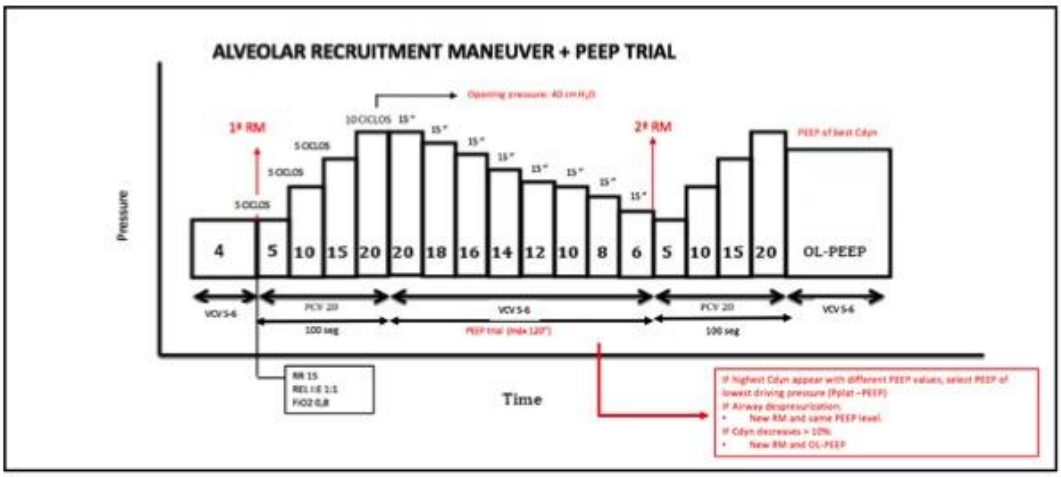

Figure 2. Recruitment maneuver plus PEEP trial.

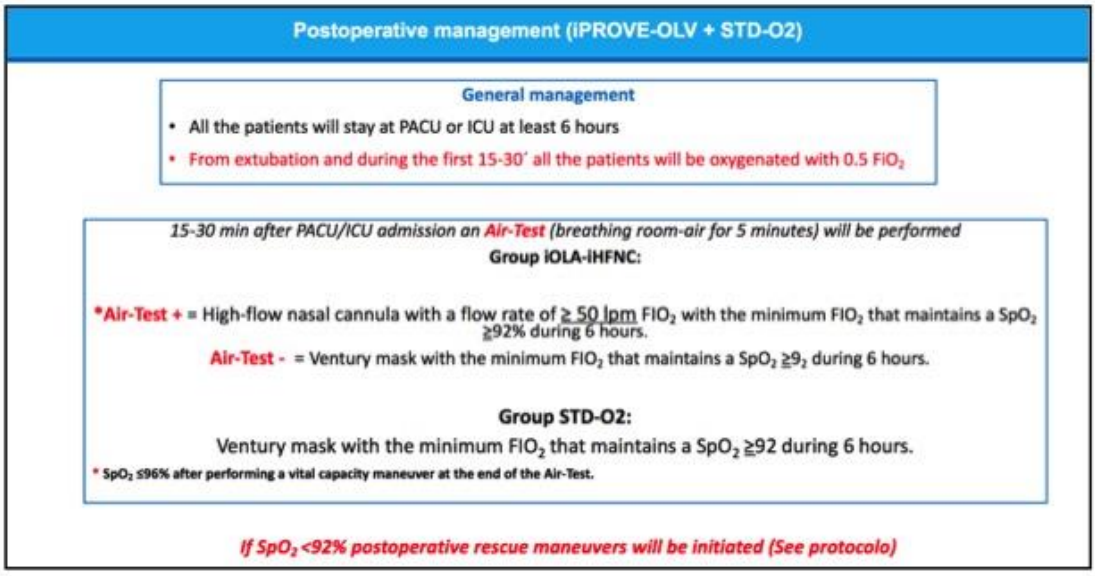

Figure 3. General and specific postoperative ventilatory management. PACU: Post-anesthesia care unit; ICU: Intensive Care Unit.