Effects of Intraoperative PEEP on Postoperative Pulmonary Complications in Patients Undergoing Robot-assisted Laparoscopic Radical Resection for Bladder Cancer or Prostate Cancer: Study Protocol for a Randomized Controlled Trial

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Method Article

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Abstract

Background: There are increasing studies shown that the use of a lung-protective ventilation strategy has a lung protection effect in patients undergoing abdominal surgery, however, the appropriate PEEP has not yet defined. Adopting a suitable PEEP may prevent PPCs. Robot-assisted laparoscopic surgery is the newest and most minimally invasive care for bladder cancer or prostate cancer. It is also necessary to consider the effects of trendelenburg position with pneumoperitoneum (PnP) on airway pressure and pulmonary function. The role of PEEP during the intraoperative period in preventing PCC for robot-assisted laparoscopic surgery is not clearly defined.

Methods/design: A total number of 208 patients undergoing robot-assisted laparoscopic radical resection for bladder cancer or prostate cancer will be enrolled and randomized into a standard PEEP (6-8 cmH2O) group and a low PEEP (≤ 2 cm H2O) group. Both groups will receive an inspired oxygen fraction (FiO2) of 0.50 and a tidal volume of 8 ml/kg ideal body weight (IBW). Standard perioperative fluid management standardization and analgesic treatments will be applied in both groups. The primary endpoint was postoperative pulmonary complications within 7 days after surgery. Secondary endpoints will be: the modified clinical pulmonary infection score (mCPIS), postoperative extrapulmonary complications, postoperative surgical complications, intensive care unit (ICU) length of stay, hospital length of stay, thirty-day mortality.

Discussion: This trial is aimed to assess the effects of low tidal volumes combined a intraoperative PEEP ventilation strategy on postoperative pulmonary complications in patients undergoing robot-assisted laparoscopic radical resection for bladder cancer or prostate cancer.

Background

Robot-assisted laparoscopic surgeries including Robot-assisted laparoscopic radical prostatectomy (RALP) and Robot-assisted laparoscopic radical cystectomy (RARC) are the newest and most minimally invasive care for bladder cancer or prostate cancer [1]. The advantages of robot-assisted surgery are nerve sparing, decreased blood loss, less pain, and the short hospital stays [2]. The incidence of postoperative pulmonary complications (PPCs) in patients undergoing general surgery is approximately 5%, and approximately 20% of patients experience PPCs will die within 30 days after surgery [3]. Furthermore,12% to 58% of patients undergoing abdominal surgery will develop a PPC [3, 4].PPCs are strongly associated with prolonged postoperative hospital stays and a higher risk of mortality [5-7].

Nearly 30% of surgery patients undergoing general anesthesia and mechanical ventilation are at intermediate to high risk for PPCs according to large cohort studies [4, 8].Both alveolar overstretching and atelectasis induce the release of nflammatory mediators, leading to lung and systemic organ damage [9]. Lung-protective ventilation including the use of low tidal volumes and positive endexpiratory pressure (PEEP), aims to prevent atelectasis and improve gas exchange [10, 11]. Furthermore, PEEP has

been found to reduce mortality in patients with the acute respiratory distress syndrome and in critically ill patients.[12]

Adopting an appropriate PEEP may prevent PPCs. When high PEEP is applied, alveolar may overinflated and pulmonary vascular resistance is likely to increase; however, use of low PEEP may not prevent atelectasis [9]. Compared with nonprotective mechanical ventilation without PEEP, a number of studies have shown that the use of a lung-protective ventilation strategy has a lung-protective effect in patients with healthy lungs who are undergoing abdominal surgery, reducing the incidence of PPC [13, 14]. Despite all these studies recommending the use of low tidal volume [9, 13-17], the appropriate PEEP has not yet been defined. A multicenter observational study showed that approximately 20% of patients did not receive PEEP during routine anesthetic practice [16]. In the Intraoperative Protective Ventilation (IMPROVE) trial that included patients undergoing major abdominal surgery with intermediate-risk and high-risk of PPCs, compared to a practice of nonprotective mechanical ventilation including higher tidal volumes without PEEP, a lung-protective ventilation strategy with lower tidal volumes and PEEP of 6 cm H2O was associated with improved clinical outcomes [13]. Furthermore, in another study including patients undergoing abdominal nonlaparoscopic surgery lasting more than 2 h, compared to a standard ventilation strategy, a protective ventilation strategy with 10 cm H2O PEEP improved respiratory function and reduced the modified clinical pulmonary infection score (mCPIS) [14]. However, another study showed that low tidal volume combined low PEEP (3 cm H2O) ventilation may induce postoperative inflammation and may increase the risk of PCC during major surgery such as hepatectomy [17]. In an international multicenter trial, Protective Ventilation using high vs. low PEEP (PROVHILO), including patients undergoing open abdominal surgery with high risk for PPCs, compared with low PEEP (≤ 2 cm H2O), a ventilation strategy of high PEEP (12 cm H2O) did not reduce the incidence of PPCs, but more likely caused haemodynamic instability [15]. Therefore, the authors suggested a ventilation strategy of low tidal volume combined with low PEEP (≤ 2 cm H2O) [15].

It should also be noted that all these studies included only open surgeries or various types of abdominal surgery; they did not include patients planning to undergo robot-assisted laparoscopic surgery. Furthermore, it is also necessary to consider the effects of steep Trendelenburg (sT) positioning and pneumoperitoneum (PnP) on airway pressure and pulmonary function [18], of which can increase intra-abdominal pressure and enhance the cranial displacement of the diaphragm. This displacement will decrease lung compliance, lung volumes and increase lung resistance. It has been recommended to addopting a PEEP of 7 cmH2O during RALP, which could improve arterial oxygenation without causing excessive peak airway pressure [19]. Also an another recent study found that as compared to a practice of nonprotective mechanical ventilation including higher tidal volumes (VT of 10 mL/kg) without PEEP, a lung-protective ventilation strategy with a lower tidal volume (VT) of 6 mL/kg and 8 cm H2O PEEP was associated with less impaired postoperative pulmonary functions in patients undergoing RALP[20].

The role of PEEP during the intraoperative period in preventing PCC for robot-assisted laparoscopic surgery has not been clearly defined. We hypothesize that, when compared to low PEEP, standard PEEP may prevent the incidence of PCC and may reduce the occurrence of organ dysfunction. These

anticipated results may further improve our knowledge regarding the effects of intraoperative PEEP on postoperative pulmonary complications, survival rates and in-hospital stays in patients undergoing robot-assisted laparoscopic radical resection for bladder cancer or prostate cancer.

Methods And Design

Objectives of the study:

This trial aimed to compare the effects of low tidal volumes combined with standard PEEP (6-8 cmH2O) to those of low PEEP (≤ 2 cm H2O) in patients at risk for complications undergoing robot-assisted laparoscopic radical resection for bladder cancer or prostate cancer during general anesthesia in terms of: (1) PPCs, (2) mCPIS score, postoperative extrapulmonary complications, changes in chest X-ray findings and oxygenation; (3) intraoperative complications including hypoxemia, hypotension and massive transfusion; and (4) postoperative surgical complications, intensive care unit (ICU) lengths of stay, hospital lengths of stay and thirty-day mortality.

Study endpoints

Primary outcome measure

The primary endpoint was PPCs including new atelectasis or infiltrates on a chest X-ray, respiratory failure defined as the need for noninvasive or invasive ventilation or partial pressure of arterial oxygen/fraction of inspired oxygen (PaO2/FiO2) < 300 within 7 days after surgery [21].

Secondary outcome measures

Secondary outcome variables were any pulmonary complications and extrapulmonary complications as follows:

1. Postoperative pulmonary complications (PPCs) within 30 days after surgery. Those PPCs are scored according to a grading scale ranging from 0 to 4 [22] (grade 0 representing no PPCs and grades 1 to 4 representing gradually worse forms of PPCs) within 7 and 30 days after surgery (Table 1).

2. Postoperative pulmonary complications will also be analyzed separately.

Pneumonia is defined according to Centers for Disease Control (CDC) criteria [23] as follows: patients with altered or new pulmonary opacities on chest X-ray; patients should also meet at least two of the following criteria: (1) temperature ≥ 38.5°C or < 36°C, (2) white blood cell (WBC) count > 12 x109/L or < 4 x109/L; (3) purulent sputum: new cough or difficulty breathing or previous coughing or difficulty breathing is further aggravated.

Postoperative hypoxemia and severe hypoxemia [24], hypoxemia is defined as PaO2 < 60 mmHg or oxygen saturation (SpO2) < 90% on room air but responding to oxygen treatment (hypoventilation should

be excluded). Severe hypoxemia is recorded in cases where the patient requires non–invasive or invasive mechanical ventilation.

Suspected pulmonary infection is described in a previous study [15]: the patient takes antibiotics and should meet at least one of the following criteria: (1) changed or new sputum, (2) changed or new pulmonary opacities on chest X–ray, (3) temperature greater than 38.3°C, and (4) WBC count > 12 x109/L.

Pulmonary infiltrate is defined according to consensus guidelines: unilateral or bilateral infiltrate with development of ALI (acute lung injury)/ARDS (acute respiratory distress syndrome) on chest X-ray [25].

Atelectasis, pleural effusion or pneumothorax are identified by chest X-ray.

The modified clinical pulmonary infection score (mCPIS) is calculated as previously described [26] (Table 2).

Suspected pulmonary complications[14] are defined in cases where patients display at least three of the following new findings: (1) cough, (2) increased secretions, (3) dyspnea, (4) chest pain, (5) temperature> 38°C, and (6) pulse rate> 100 beats per minute.

Requirement for postoperative ventilation (respiratory failure that requires noninvasive and/or invasive ventilation) for at any time after surgery according to standard criteria and clinical practice guidelines[22].

3. Postoperative extrapulmonary complications within 30 days after surgery:

Systemic inflammatory response syndrome (SIRS) criteria are defined when meeting the following four criteria by the most deranged value recorded after surgery[12]: (1) rectal or tympanic temperature > 38°C or <36°C (0.5°C will be added to the measured value when oral or other temperatures are used); (2) ventricular rate > 90 beats/min (excluding those who have a known medical condition or are receiving treatment that would prevent tachycardia); (3) respiratory rate> 20 breaths/min or a $PaCO_2$< 32 mmHg or requiring mechanical ventilation; (4) WBC count >12 x 109/L or < 4 x 109/L.

Sepsis and severe sepsis [12]: sepsis is recorded when meeting at least two SIRS criteria with a defined focus of infection. Defined infection is indicated in patients when they meet at least one of the following criteria: (1) an organism grown in blood or sterile site, (2) an abscess, (3) infected tissue (e.g., pneumonia, urinary tract, peritonitis, soft tissue, vascular infection, etc.) Severe sepsis is recorded in a patient with sepsis who has at least one organ failure, hypotension or hypoperfusion.

Septic shock [12]: regardless of how adequate fluid resuscitation has been administered, the patient remains with sepsis-induced hypotension with the presence of perfusion abnormalities.

Other extrapulmonary infection including surgical site infection (SSI) and intraabdominal abscess: SSI [27] defined as surgical site infection within 30 days after surgery; at least the incision has a purulent

effluent; the incision drainage fluid or tissue culture results are positive, with pain or tenderness, local swelling, redness or fever.

Need for postoperative blood transfusion.

Postoperative surgical complications: anastomotic leakage and need for surgical reintervention, defined according to consensus criteria [28].

Unexpected intensive care unit (ICU) admission or readmission.

ICU length of stay and hospital length of stay.

Hospital free-days at follow-up day 30.

In-hospital mortality and thirty-day mortality (all-cause mortality 30 days after randomization).

Intraoperative complications: pneumothorax confirmed by chest X-ray and any other complications.

Study design: This is an unfunded, parallel-group, double-blinded, prospective, randomized controlled clinical trial was registered at http://www.chictr.org.cn (ChiCTR1800019867) and was conducted at the Department of Anesthesiology and Intensive Care of P Zhejiang Provincial People's Hospital. The first patient will be randomized in January 2019. This trail protocol is conducted according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines (Figure 1). The SPIRIT 2013 Checklist is given in Additional file 1.

Blinding, data collection, randomization and recordkeeping

Selection of the participants

Researchers will be trained prior to investigation. Study data including patient clinical characteristics, intraoperative respiratory parameters, postoperative outcomes, and laboratory test will be collected onto case report forms (CRF) (Additional file 2).

An independent researcher will randomize the participants into the study group (standard group PEEP) and control group (low PEEP group) in a ratio of 1:1. The random sequence will be computer-generated and participants will be allocated in numerical order with sealed opaque envelopes. The attending anesthesiologist will perform anesthesia strictly according to the research protocol, and will be responsible for data during the preoperative, intraoperative and PACU period. The chief surgeon performs the postoperative laboratory testing. An independent researcher will be involved in postoperative follow-up and data collection. Statistical analysis will be performed by a statistician who does not participate in the data collection. Patients, research staff, surgeons, intensive care physicians and the statistician will be unaware of the group allocation. Some preoperative characteristics and laboratory results will automatically derived from a computer data base.

The original data (CRF and relevant records) will be maintained for 10 years and then destroyed according to hospital standards.

Selection of the participants

Patients scheduled for elective robot-assisted laparoscopic radical resection for bladder cancer or prostate cancer under general anesthesia will be screened and recruited during preoperative assessment. Patients meeting inclusion criteria will be required to provide their written informed consent. The participant can withdraw from the trial at any time.

Inclusion criteria are patients older than 18 y, American Society of Anesthesiologists (ASA) physical status I - III, body mass index (BMI) between 18-35 kg/m2.

Exclusion criteria are emergency surgery or history of previous lung surgery, history of mechanical ventilation within the 2 weeks before recruitment, non–invasive ventilation or oxygen therapy at home, acute respiratory failure (pneumonia, acute lung injury or acute respiratory distress syndrome), history of chronic obstructive pulmonary disease (COPD), persistent hemodynamic instability or severe cardiac disease (New York Heart Association class III or IV, or persistent ventricular tachyarrhythmia's, or acute coronary syndrome), sepsis or septic shock, need renal replacement therapy (CRRT), progressive neuromuscular illness, pregnancy, participation in another study or refusal to participate.

Time course of the study

Preoperative admission

Medical history, ASA physical status, BMI, 12-lead ECG, laboratory results, chest X-ray or computed tomography (CT) scan, ARISCAT score (the Assess Respiratory Risk in Surgical Patients in Catalonia study, the Additional file 3) and nutritional risk screening (NRS 2002 tool), the results of echocardiography and spirometry (in cases of history of coronary artery disease or smoking) will be recorded.

Intraoperative care

A central venous catheter and an arterial cannula will be placed before induction of anesthesia. Peripheral oxygen saturation (SpO2), arterial blood pressure, heart rate (HR), ECG, end-tidal carbon dioxide tension (EtCO2) and bispectral index (BIS) will be monitored continuously. Pneumoperitoneum (PnP), tidal volume, PEEP, airway pressures including peak pressure and plateau pressure, airway resistance (Raw), Vds/Vt, core temperature, and arterial blood gas analysis data will be recorded.

Crystalloid (12-15ml/kg/h) was infused to maintain hemodynamic stability and central venous pressure 5-12 cm H2O. Blood loss and vasodilation was supplemented by colloidal fluid.

Routine anesthesia was induced with intravenous dexmedetomidine(1 ug/kg) or midazolam (0.05-0.075mg/kg), cisatracurium (2 mg/kg), propofol (2-3 mg/kg) and fentanyl (1-3 μ/kg) for tracheal intubation. Anesthesia was maintained with propofol, sevoflurane and remifentanil infusion to maintain

the BIS 40-50 until skin suturing was completed. Cisatracurium (1.0-1.5 mg/kg) was administered every hour and the last dose was at least 1 hour before the end of operation.

Ropivacaine was administrated as local anesthetic before and at the end of operation respectively. Fentanyl (1-3 μg/kg) and flurbiprofenaxetil 50 mg was required before remifentanil was stop.

Postoperative care

Patients will be transferred to the post anesthesia care unit (PACU) after surgery regardless of whether they are still intubated.

Postoperative pain management will be suggested to achieve a visual analogue scale (VAS) pain score of < 3/10 using a patient-controlled intravenous analgesia pump including fentanyl (0.3-0.5 μg/kg), flurbiprofenaxetil (100 mg) and palonosetron hydrochloride (0.25 mg) palazidine.

The ICU physician and surgeon will independently monitor clinical progress and all endpoints by daily physical examinations. Appropriate prophylactic antibiotics and antithrombotic treatments will be administered as required during the postoperative period. A chest X-ray will be performed by an independent, trained radiologist on POD 5. Arterial blood gas analysis will be performed on POD 1 and POD 3 and other laboratory tests will performed on POD 1, POD 3, POD 5 and POD 7. The examinations will be repeated and microbiology tests will be performed when the development of pulmonary complications are suspected.

Study arms and intraoperative ventilation protocol

Patients will be randomly assigned to with the low PEEP ventilation group (PEEP ≤ 2 cm H2O) or the standard PEEP group (PEEP = 6-8 cm H2O) using a volume-controlled ventilation strategy (Datex Ohmeda S/5 Avance; GE Healthcare, Helsinki, Finland) with a tidal volume of 8 ml/kg ideal body weight (IBW), an inspired oxygen fraction (FiO2) of 0.50 and inspiratory to expiratory ratio of 1:2. Respiratory rate should be adjusted to maintain ETCO2 between 35 and 45 mmHg) and plateau pressure should be no more than 30 cmH2O. IBW is calculated with formulas as follows [13]: 45.5 + 0.91 x (centimeters of height -152.4) for females and 50 + 0.91 x (centimeters of height - 152.4) for males. Recruitment maneuvers (RMs)[21] will be performed immediately after tracheal intubation and every time ventilator is interrupted until the end of surgery in each group. The compliance of the respiratory system will be calculated with the formulas of VT/ (plateau pressure of the respiratory system - PEEP).

Recruitment maneuvers will be performed as follows:

(1). Pressure support ventilation (PSV) mode

(2). Positive end-expiratory pressure (PEEP) set to 30 cm of water

(3). Inspiratory gas flow set to the highest value

(4). Duration of the maneuver = 30 sec

A rescue therapy will be applied in case of desaturation (defined as a peripheral SpO2 of less than 92%), consisting of increased FiO2 to 100% in each group and increasing PEEP in the low PEEP group (Additional file 4).

From postoperative day 7 (POD 7 to POD 30, follow-up)

Secondary endpoints and any mortality will also be evaluated during the follow-up period. The CONSORT flowchart of the trial is shown in Figure 2.

Data monitoring and Handling of implausible values or missing values: A clinical investigator will identify implausible values. Missing continuous variables should be less than 10% and will be replaced by median. Data monitoring is managed by an independent investigator who is not involved in the study. The progress of the study will be evaluated and the completeness and accuracy of the data (Informed Consent Forms, source data, CRF and outcome variables) will be verified.

Statistics:

Normally distributed variables will be expressed as the mean ± standard deviation (SD) and will be compared with the Student's t-test. Categorical variables will be compared using the chi-square test or the Fisher's exact test. Abnormal continuous variables will be expressed as median (interquartile range (IQR)) and evaluated with the Mann-Whitney U-test. Analysis will be by intention-to-treat comparing the composite outcome measure at 7 days in the two groups by the chi-squared test (or Fisher's exact test as appropriate) and multiple logistic regression analysis adjusting will be performed to identify various risk factors (for the primary outcome and the pulmonary complications at postoperative Day 30). $P<0.05$ will be considered statistically significant and all reported p values will be 2-sided. Interim analysis of safety will be conducted after enrolment of the first 200 patients. All analyses will be conducted using the SPSS Version 18.0 (SPSS, Chicago, IL, USA) software.

Sample size calculation

The incidence rate of postoperative pulmonary complications was 0.39 in the low PEEP group [15]. Two tailed chi-squared test was performed and we estimated that 188 patients were required to provide 90% power to detect a 50% relative difference between the two groups, with a type I error probability of 0.05. Assuming that follow-up lost rate was 10 %, then a total of 208 cases are needed. Analysis was computed using G-Power (version 3.1; Informer Technologies, Inc.).

Adverse events and interruption of the trial:

All patients will be continuously monitored during the study including daily visits during in-hospital and daily phone-call visits during the out of hospital follow-up period (until POD 30). All serious adverse, unexpected or possibly related events will be recorded in the CRF and will be reported to the data

monitoring and safety committee (DMSC). DMSC will recommend that the study must to be stopped if it is found that the continued conduct of the study compromises patient safety (a between-group difference in serious adverse events or in 30- day mortality is found).

Discussion

In this pragmatic, prospective, randomized controlled trial of patients undergoing robot-assisted laparoscopic radical resection for bladder cancer or prostate cancer, our aim will not be only to assess possible single effects of PEEP levels on major PPCs from those of lower tidal volumes and RM, but also to assess relevant clinical parameters associated with alterations in pulmonary function such as chest X-ray, abnormalities, mCPIS, arterial oxygenation/peripheral oxygen saturation in air and changes in dyspnea/cough/secretions. Our findings might change current practice of mechanical ventilation in patients undergoing robot-assisted laparoscopic radical resection for bladder cancer or prostate cancer.

Notably, mechanical ventilation itself is one of major contributors to PPCs [29]. Also sT positioning together with pneumoperitoneum is also an important risk factor for PPCs [30]. Intraabdominal pressure is frequently higher than airway pressure during PnP with carbon dioxide (CO_2) for laparoscopic surgery. This pressure gradient usually causes cephalad displacement of the diaphragm and collapses adjacent pulmonary tissues. PnP also decreases respiratory compliance and arterial oxygenation [31] .All these influences on PnP lead finally to atelectasis [32]. The major difference between robot-assisted surgeries and other laparoscopic surgeries is the sT positioning, which will further decrease respiratory compliance and vital capacity.

On the other hand, PEEP is thought to prevent the development of atelectasis by keeping the airways open and maintaining adequate gas exchange at the end of the expiratory period during PnP [9]. Certainly, the level of PEEP should be adopted according to the patient's and surgical characteristics, as well as to the patient's positioning.

The optimal PEEP has not yet been defined in patients undergoing robot-assisted laparoscopic surgery even though it is recommended to adopting PEEP of over 5 cm H_2O in patients undergoing laparoscopic surgery [11]. One study recommended to addopting a PEEP of 7 cmH_2O during RALP[19], another recent study found that 8 cm H_2O PEEP was the optimal level of PEEP in patients undergoing RALP[20]. As we know that very low levels of PEEP are potentially associated with atelectasis by promoting repeated opening and closing of small airways [33]. However, higher levels of PEEP may increase mean airway pressure of the respiratory system and likely even impair hemodynamics.

There is an increasing number of highly qualitative Randomized Controlled Trials (RCTs) regarding intraoperative mechanical ventilation and PPCs both in abdominal surgeries [10, 11] and laparoscopic surgeries[32], whereas direct assessment of the effect in patients undergoing robot-assisted laparoscopic radical resection for bladder cancer or prostate cancer remains lacking. The potential significance of this trail is that it may provide evidence of the effects of intraoperative PEEP on postoperative pulmonary

complications in patients undergoing robot-assisted laparoscopic radical resection for bladder cancer or prostate cancer.

There are some potential strengths of the present trial protocol. First, the included patients will undergo elective robot-assisted laparoscopic radical resection for bladder cancer or prostate cancer with longer anesthesia duration, which is potential risk factor of PPCs [7]. Second, this trial design includes instructions for fluid management standardization and analgesic treatments during the perioperative period. Third, the adopting ARISCAT score is considered to be the most valuable tool for predicting PPCs, although various scores have been developed for predicting PPCs incidence based on various countries and surgical populations, [9].

Trial status

The study protocol version number was (V1.0, September 10, 2018). It was first submitted to the Ethics Committee of Zhejiang Provincial People,s Hospital (People,s Hospital of Hangzhou Medicine College) on 10 September 2018 and finally approved on 22 October 2018. The first participant is expected to be recruited before March 2019 and the estimated completion date of recruitment will be October 2021.

Declarations

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This trial was conducted with no external or internal funding. These tests in this trial are performed as routine medical care in our institute.

Availability of data and materials

Not applicable.

Authors' contributions

ZHOU ZFand HU SFdesigned the study protocol and wrote the paper. WANG HF and ZHANG MZ designed the statistical method. The work of patient recruitment and data collecting will be done by FANG JB, YU YJ, WANG WY, Chen L and CHEN JB. HU SF is the study director and FANG JB is the principal investigator of this study. All authors have read the manuscript and approved to submitting the final paper.

Authors' information

Not applicable.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Zhejiang Provincial People,s Hospital (People,s Hospital of Hangzhou Medicine College) (registration number KY2018027) on 22 October 2018. Any subsequent protocol and informed consent document amendments must be approved by the responsible of Ethics Committee. All communications with the regulatory authorities and the Ethics Committee must be recorded.

All recruited patients will be informed of the trial purposes and their duties within the trial before randomization. Informed consent will be obtained from all study participants. Recruited patients can withdraw from the study at any time without providing any specific reason. The patient data will be stored in a separate, safe place but that it may be reviewed by the relevant investigator.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

1. Grade scale for postoperative pulmonary complications.

e	Detailed description
e	- Cough, dry - Microatelectasis: abnormal lung findings and temperature > 37.5°C without other documented cause; results of chest radiograph either normal - Dyspnea, not due to other documented cause
e	- Cough, productive, not due to other documented cause - Bronchospasm: new wheezing or pre-existent wheezing resulting in change therapy - Hypoxemia - Atelectasis: radiological confirmation plus either temperature > 37.5°C or abnormal lung findings - Hypercarbia, transient, requiring treatment, such as naloxone or increased manual or mechanical ventilation
e	- Pleural effusion, resulting in thoracentesis - Pneumonia, suspected: radiological evidence without bacteriological confirmation -Pneumonia, proved: radiological evidence and documentation of pathological organism by Gram stain or culture - Pneumothorax - Re-intubation postoperative or intubation, period of ventilator dependence (non-invasive or invasive ventilation) ≤ 48 hours
e	Ventilatory failure: postoperative non-invasive ventilation dependence ≥ 48 hours, or re-intubation with subsequent period of ventilator dependence ≥ 48 hours

Figures

Table 2. The definition of modified Clinical Pulmonary Infection Score (mCPIS).

Items	CPIS Points		
	0	1	2
Tracheal secretions	Rare	Abundant	Abundant + purulent
Chest X-ray infiltrates	No infiltrate	Diffused	Localized
Temperature (℃)	36.5- 38.4	38.5- 38.9	≤ 36.5 or ≥ 39.0
Leukocytes count (per mm^3)	4,000-11,000	<4,000 or >11,000	< 4,000 or > 11,000 + band forms ≥ 500
PaO_2/FiO_2,(mm Hg)	> 240 or ARDS		≤ 240 and no evidence of ARDS
Microbiology	Negative		Positive

PaO_2 =Partial pressure of arterial oxygen; FiO_2 =Fraction of inspired oxygen; ARDS =Acute respiratory distress syndrome

Standard Protocol Items

	Study period								
	Enrolment		Allocation		Post-allocation				
Timepoint	-1 week	-t1	0	DOS	POD1	POD3	POD5	POD7	POD8-30
Enrolment:									
Perioperative assessment	√								
Eligibility screen		√							
Informed consent		√							
Allocation			√						
Interventions:									
Study Group(Low PEEP)				√					
Control Group(Standard PEEP)				√					
Assessments:									
Intraoperative complications				√					
Postoperative pulmonary complications					√	√	√	√	√
Physical examinations					√	√	√	√	√
Blood gas analysis					√	√	√	√	√
chest X-ray							√		
Postoperative extra-pulmonary complications					√	√	√	√	√
Postoperative surgical complications					√	√	√	√	√
ICU length of stay									
Hospital length of stay									
In-hospital mortality									
Thirty-day mortality					◄———				———►

Standard Protocol Items: Recommendation for Interventional Trials (SPIRIT) schedule of enrollment, interventions and assessments. DOS: day of surgery; POD: postoperative day; ICU: Intensive care unit.

Figure 1

Standard Protocol Items

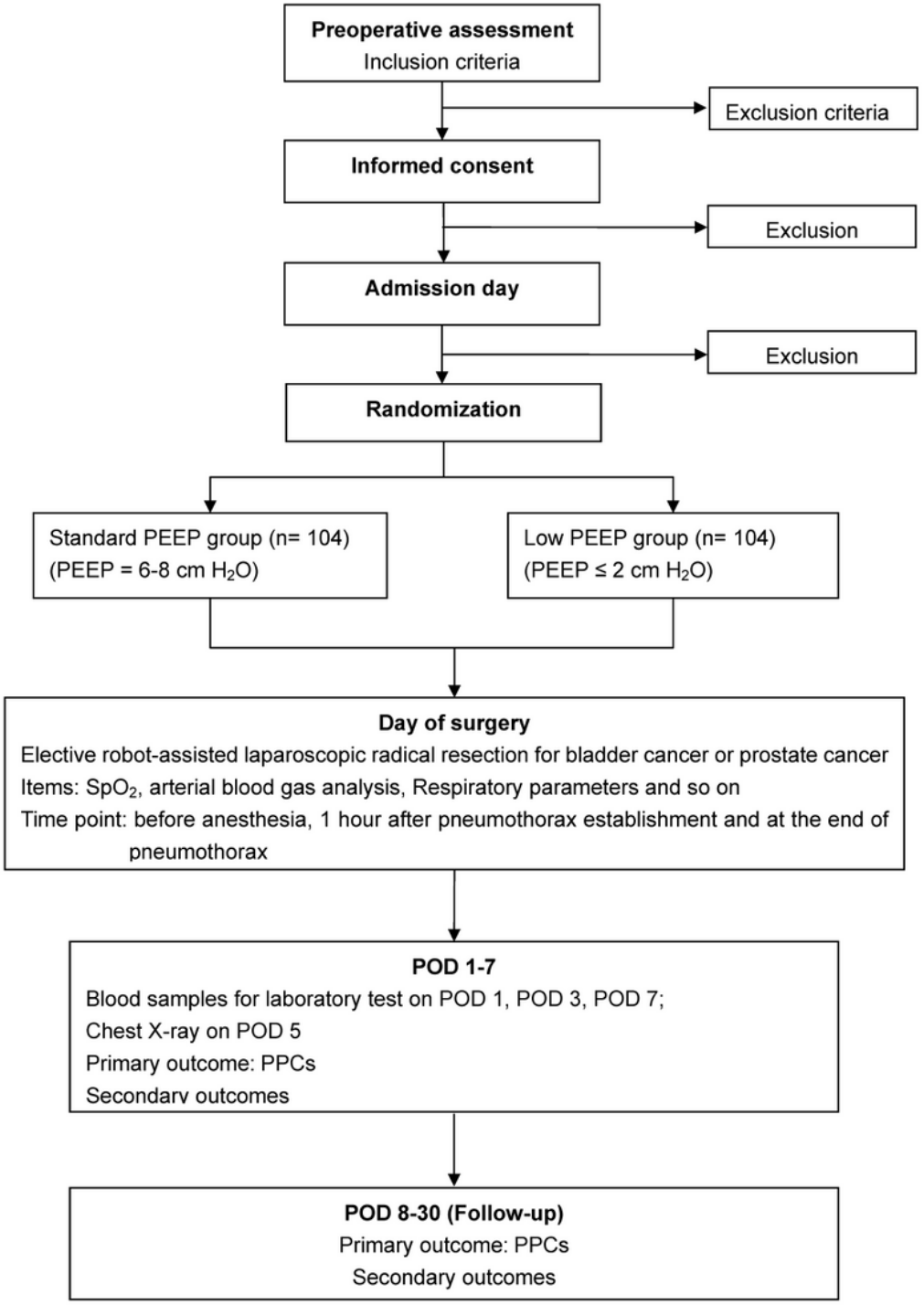

Figure 2

The CONSORT flowchart of the trial

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