Recruitment manoeuvres during mechanical ventilation with sequential high-flow nasal oxygen after extubation to prevent postoperative pulmonary complications in patients undergone thoracic surgery: a protocol, prospective randomised controlled trial

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ABSTRACT

Introduction The incidence of postoperative pulmonary complications (PPCs) following thoracic surgery is high, which increases the mortality rate, prolongs the length of hospital stay and increases medical costs. Some studies have confirmed that preoperative risk assessment, intraoperative anaesthesia methods and intraoperative mechanical ventilation strategies, including recruitment manoeuvres (RMs), can reduce the incidence of PPCs. Despite these improved strategies, the incidence of PPCs remains high. However, mechanical ventilation strategies have not been studied in the postoperative period.

Methods and analysis We assume that RM during mechanical ventilation with sequential high-flow nasal oxygen therapy (HFNO) after extubation can maintain the opening of the postoperative alveoli and ultimately reduce the incidence of PPCs after thoracic surgery. We will include thoracic surgery patients and divide them into the RM with sequential HFNO group and the control group. They will be given RMs and sequential HFNO or be given conventional treatment. The sample size is 654 adult patients (327 per group) undergone thoracic surgery and presenting to the intensive care unit.

Ethics and dissemination This study was approved by the Biomedical Research Ethics Committee of West China Hospital of Sichuan University (REC2019-730). It is expected that this study will lead to a randomised controlled trial. We assume that the findings will provide more evidence about PPCs and improve the management of patients undergone thoracic surgery.

Trial registration number ChiCTR2100046356.

INTRODUCTION

Every year, approximately 300 million people undergo surgery around the world. At least 30% of patients undergoing surgery lasting at least 2 hours with general anaesthesia and mechanical ventilation may suffer from postoperative pulmonary complications (PPCs). PPC is associated with significantly increased early postoperative mortality, intensive care unit (ICU) admission and prolonged length of stay in the ICU and hospital. For patients undergone thoracic surgery, mechanical ventilation strategies, analgesia and sedation, the use of muscle relaxants and mechanical ventilation—positive pressure postoperatively may cause or exacerbate the occurrence of PPCs. Numerous clinical studies have examined preoperative risk assessment and prevention strategies and the impact of intraoperative muscle relaxants and mechanical ventilation strategies on PPCs.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ In this study, the prospective design of a randomised controlled trial ensures the reliability of the results.
⇒ The study included well-defined patients who will receive mechanical ventilation after surgery; therefore, a recruitment manoeuvre could be implemented for every eligible participant.
⇒ The 72-hour high-flow nasal oxygen therapy following the recruitment manoeuvre enhanced the persistent effect of opening the lung with positive pressure.
⇒ A limitation is that this study is unblinded.

To cite: Wang Z, Wang B, Xia W, et al. Recruitment manoeuvres during mechanical ventilation with sequential high-flow nasal oxygen after extubation to prevent postoperative pulmonary complications in patients undergone thoracic surgery: a protocol, prospective randomised controlled trial. BMJ Open 2022;12:e056438. doi:10.1136/bmjopen-2021-056438.
pressure (PEEP) or other reasons, restricted breathing and decreased cough ability after surgery, small airway obstruction generated by reduced airway cilia movement, blocking secretions caused by analgesia and sedative drugs, and the inhalation of pure oxygen. Corresponding preventative and curative strategies, such as using intermittent lung recruitment manoeuvre (RM) intraoperatively and pharmacological reversal, have also been proposed. Despite this evidence and improved strategies, the incidence of PPCs remains very high.

RMs open the collapsed alveoli by mechanically increasing airway pressure in a short time, and this strategy has been widely used in patients with moderate to severe acute respiratory distress syndrome and has been approved to improve oxygenation and prognosis. Intraoperative RMs have been confirmed to decrease respiratory resistance and increase lung compliance, but the intraoperative ventilation strategy for RMs remains to be elucidated. In thoracic surgery, one-lung ventilation is sometimes used to ensure good vision during the operation. The operative-side lung is in a state of atelectasis for a long time, but sustained inflation is only performed in a short time at the end of the operation. The existing strategies to prevent atelectasis by repeated recruitment during surgery are clearly not feasible for thoracic surgery, and the incidence of atelectasis on the operating side increases greatly after surgery. RMs during postoperative mechanical ventilation may be more suitable and effective in preventing PPCs. However, the impact of postoperative mechanical ventilation strategies on PPCs has not been studied, and whether intermittent RMs before ventilator withdrawal can reduce the risk of PPCs is currently unclear.

High-flow nasal oxygen therapy (HFNO) can comfortably deliver warmed humidified gas at a flow rate of 20–70 L/min and a fraction of inspired oxygen (FiO₂) ranging from 0.21 to 1.0. The high flow of HFNO provides stable airway pressure and increases end-expiratory lung volume, causing an appropriate positive end expiratory pressure. HFNO has a good heating and humidification function, which can improve airway secretion and maintain ciliary function. Thus, HFNC therapy helps the removal of airway secretions. The use of HFNC has been confirmed to be effective and safe in patients with acute respiratory failure, and it can prevent intubation or reintubation. Furthermore, prophylactic HFNC in the immediate postoperative period reduces reintubation and the escalation of respiratory support.

Based on the previous evidence, we hypothesise that RMs during postoperative mechanical ventilation combined with sequential HFNO after the extubation of thoracic surgery patients could reduce alveolar collapse and improve the drainage of secretions to increase airway patency and alveolar ventilation, thus reducing the incidence of PPCs.

METHODS AND ANALYSIS

Study design
This work is a prospective, single-centre, randomised controlled clinical study. This study will be carried out in a single-tertiary academic hospital.

Eligibility criteria
The inclusion criteria are patients aged 18–80 years, who are undergoing elective pulmonary and mediastinal operations, patients receiving mechanical ventilation after surgery and patients and/or next-of-kin who are informed about the study and have consented to participate in the study.

The exclusion criteria are severe obesity (body mass index ≥35 kg/m²), postoperative shock due to various causes; history of surgery within 1 month before the operation; pregnant women; patients with mental disorders, Parkinson’s disease or neuromuscular disease; patients whose invasive mechanical ventilation cannot be withdrawn within 24 hours after surgery; tracheoesophageal fistula caused by the surgery; patients who did not receive RM after anaesthesia emergence, extubation and transferring to the ICU; and patients unable to tolerate HFNC.

Patient and public involvement
No patient was involved.

Intervention
After study inclusion, patients will be randomly allocated to the experimental group or control group (figure 1).

Setting of mechanical ventilation parameters
Before the spontaneous breathing trial (SBT), patients in both groups will be given volume control ventilation mode, with PEEP at 5 cmH₂O, respiratory rate at 12
breaths/min and tidal volume at 6–8 mL/kg. During mechanical ventilation, the oxygen fraction (FiO₂) in both groups will be set according to the target of SpO₂ 92%–96% or oxygen partial pressure 60–80 mm Hg, and if patients had chronic obstructive pulmonary disease before the surgery, the oxyg enation target will be to maintain SpO₂ at 89%–92%. We will use pressure support ventilation for SBT and observe patients for 30 min, with PEEP at 5 cm H₂O and PS at 8 cm H₂O. The ventilator will be withdrawn if the SBT is successful.

**RMs with sequential HFNO**

Before SBT, the patient will be treated with RM every 2 hours. Alveolar RMs will be standardised and will consist of a stepwise increase in PEEP until an airway plateau pressure of 40 H₂O is achieved. During this period, if patients have adverse events, such as hypotension or obvious dyspnoea, RMs will be terminated immediately and recorded. In the PEEP decremental process, PEEP will be reduced every 40 s by 5 cm H₂O until it returns to the prime setting.

After weaning, we will sequentially use HFNO for oxygen treatment. The FiO₂ setting target will be to maintain SpO₂ between 92% and 96%; the flow will initially be set to 30 L/min and titrated upwards based on patient comfort. The temperature will initially be set to 34°C, unless reported to be too hot by patients. After returning to the specialist ward, the patient will continue to receive HFNO for 72 hours.

**Conventional treatment group**

During mechanical ventilation, RMs will not be used, and ordinary therapeutic oxygen will be given after extubation. Patients will use a nasal cannula for oxygen, with an FiO₂ to ensure SpO₂ between 92% and 96%.

**Outcomes**

This study takes the incidence and grade of PPCs as the primary outcomes and the length of stay in the ICU, the rate of non-invasive ventilation (NIV) use after endotracheal extubation, the rate of endotracheal reintubation, the rate of readmission to the ICU, the length of hospital stay and the 28-day mortality rate as secondary outcomes. We defined another composite outcome to capture clinical failure of our intervention that includes the use of NIV after endotracheal extubation, endotracheal reintubation and death.

PPCs include seven types of events: respiratory failure, lung infection, pleural effusion, atelectasis, pneumonia, bronchospasm and aspiration pneumonia. PPC will be diagnosed if any of the previous conditions occur within 7 days after surgery.

- Respiratory failure is defined as one of the following situations: the arterial partial pressure of oxygen is lower than 60 mm Hg, PaO₂/FiO₂<300, SpO₂ is lower than 90% with ambient air and oxygen therapy is needed.

**Table 1** Severity of PPC listed as degree 0–4 defined by PaO₂/FiO₂

| PPC score | PaO₂/FiO₂ |
|-----------|-----------|
| 0         | PaO₂/FiO₂>400 |
| 1         | PaO₂/FiO₂<400 |
| 2         | PaO₂/FiO₂<300 |
| 3         | PaO₂/FiO₂<200 |
| 4         | PaO₂/FiO₂<100 |

FiO₂, fraction of inspired oxygen; PPC, postoperative pulmonary complication.

- Pulmonary infection is defined as using antibiotics and having at least one of the following conditions: increased sputum volume or deterioration of sputum properties, body temperature ≥38.3°C, WBC ≥12000/mm³ and new or worsening chest X-rays with decreasing light transmittance.
- Atelectasis: radiograph transmittance decreasing with movement of the mediastinum, hilum or diaphragm to the affected area and compensatory hyperaeration of adjacent lung areas.
- Pneumothorax: local lung texture disappeared on chest radiograph.
- Bronchospasm: expiratory wheezing and requiring bronchodilator treatment.
- Aspiration pneumonia: respiratory failure after aspiration of stomach contents.

The severity of PPCs is rated according to the PaO₂/FiO₂ value listed in table 1.

**Sample size and recruitment**

We used the incidence of PPCs after thoracic surgery as the primary endpoint. According to the latest study, 22% of PPCs occur after thoracic surgery. We assume that RMs during mechanical ventilation with sequential HFNO can reduce the incidence of PPCs by 10% compared with conventional treatment and calculated the sample size according to the sample size calculation formula for comparing two rates: N=4[(Zα/2+Zβ)/δ]²π(1-π), with α=0.05 and β=0.1, π1=0.5, π2=0.35; Zα/2=Z0.05/2=1.96, Zβ=Z0.10=1.282. The contents of the two samples are equal, and n1=n2=N/2=297. Because a small number of patients may give up treatment or be lost to follow-up in clinical practice after being included in the trial, the sample size was increased by 10% to 654.

Patients will be recruited by the main researchers when they are transferred to the ICU after thoracic surgery. Each patient will provide written informed consent prior to enrolment, and the study physician is responsible for obtaining informed consent prior to each patient being enrolled in the study.

**Allocation sequence**

Permuted block randomisation using computer-generated random numbers will be used to produce the randomisation sequence, and the treatment arm will be decided
by opening the randomisation envelope at the time of care. The randomisation process will be performed by someone who is not part of the research team.

Due to the nature of the intervention, participants and clinicians could not be blinded. The results will be analysed by statisticians independent of the research team.

**Data collection**

The patient’s preoperative information will be collected through the electronic medical record system. Data about anaesthesia and surgery will be collected through the surgical observation sheet and surgical record sheet. Mechanical ventilation and RM data in the ICU will be recorded by the respiratory therapist in charge of the patient’s treatment, and the daily PPC assessment will be evaluated and recorded by the main research assistants. The information transferred out of the ICU will be evaluated and recorded by the main research assistants.

The data collection process will be supervised by the Biomedical Research Ethics Committee of West China Hospital of Sichuan University every 2 months.

Data will be collected in a hard copy and then collected as an Electronic Data Capture System. The hard copy will be saved by the main research assistants.

**Statistical analysis**

Continuous variables in the study will be analysed with the t-test, multiple ordinal categorical variables will be analysed with the Wilcoxon rank-sum test and Kruskal-Wallis H test and binomial classification variables will be analysed with Fisher’s exact probability method.

**Subgroup analysis**

We will divide patients into two groups according to whether the patients are known to have high-risk factors (operation time greater than 2 hours, preoperative airway problems, smoking 8 weeks before surgery, ASA score 3–5 points by American Society of Anesthesiologists) and whether the patients used intraoperative one-lung ventilation during the operation. The incidence of seven types of PPCs will also be counted separately.

**ETHICS AND DISSEMINATION**

**Ethics**

This research complies with the Pharmaceutical Administration Law of the People’s Republic of China, Pharmaceutical Clinical Trial Quality Management Regulations, Medical Device Clinical Trial Regulations, World Medical Congress Helsinki Declaration, Ethical Review Measures for Biomedical Research Involving People (Trial) and other ethical guidelines, as well as the WHO’s guidelines on ethical reviews. Clinical trial research programmes were strictly reviewed from the perspective of protecting the rights and safety of subjects.

**Disseminations**

This protocol will lead a randomised controlled trial to identify the strategy of PPC management after surgery. All trial results will be sent to investigators as EDCs, and every patient enrolled in this trial will receive their own data in paper format. Trial results will only be used to write articles about this trial. The findings will be published in high-quality, open access journals.

**Protocol amendments**

When the patients are observed to have severe adverse events during RM, such as hypotension or hypoxaemia, the protocol will be discussed by the research team. Anytime the protocol is changed, the Biomedical Research Ethics Committee of West China Hospital of Sichuan University will be informed.

**DISCUSSION**

The use of RMs during postoperative mechanical ventilation to prevent PPCs in patients undergone thoracic surgery has not been studied. Existing evidence about mechanical ventilation strategies focuses on the intraoperative period, during which patients are under general anaesthesia combined with muscle relaxation and ventilated with pure oxygen at low tidal volume and low PEEP, leading to alveolar collapse. For a patient undergoing thoracic surgery, PEEP may be set to 0, and RM may not be performed during thoracic surgery due to the high risk of lung injury. Furthermore, RM can only be employed once in the operating room, which cannot significantly open the collapsed alveoli.

This research will ensure the safety and feasibility of RM during postoperative mechanical ventilation. The RM will be performed in a standard manner every 2 hours, and airway plateau pressure will be to a maximum of 40 cm H₂O to ensure safety and tolerance. In the PEEP decremental process, PEEP will be reduced by 5 cm H₂O every 40 s. After endotracheal extubation, patients in the experimental group will receive HFNC sequentially to maintain the opening of alveoli at low CPAP. Moreover, HFNC can guarantee airway humidification and ultimately help secretion clearance. Thus, the collapsed alveoli will reopen, and the obstructed airway will be cleared.

This randomised controlled clinical study will be the first to focus on postoperative mechanical ventilation combined with RM and sequential HFNC to prevent PPCs. We will perform this study at a single centre to ensure rigorous education and consistent protocol implementation, but this design may decrease the applicability of the results to other medical centres. The unblinded nature of the study, coupled with different types of surgery options and procedures, may confound our results. Some patients may not receive any RM due to early anaesthesia emergence after transfer to the ICU and extubation, and some patients may be unable to tolerate HFNC.

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Acknowledgements

We would like to express our gratitude to Dr Ni Yue Nan, who helped us during the writing of this protocol.

Contributors

ZW and BW had full access to all the data and take responsibility for the integrity of the data and accuracy of data analysis. Concept and design: ZW, BW, Y-GZ, KY and JDM; acquisition, analysis or interpretation of data: all authors; drafting of the manuscript: ZW, BW and WK; critical revision of the manuscript for important intellectual content: ZW, BW, FW and GL; obtained funding: BW.

Funding

This work is supported by Science & Technology Department of Sichuan Province grant number 2020YS0093.

Competing interests

None declared.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication

Consent obtained from parent(s)/guardian(s)

Ethics approval

This study involves human participants and was approved by Biomedical Research Ethics Committee of West China Hospital of Sichuan University, REC2019-730. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

Data are available on reasonable request.

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