Effect of post-extubation high-flow nasal cannula combined with respiratory training versus conventional oxygen therapy on postoperative pulmonary complications in patients after major abdominal surgery: Protocol for a single-centre randomised controlled trial

Mengjing Yao (yaomengjing@sysush.com)
The Seventh Affiliated Hospital Sun Yat-sen University

Biao Jin
The Seventh Affiliated Hospital Sun Yat-sen University

Wenjuan Shen
The Seventh Affiliated Hospital Sun Yat-sen University

Le Fu
The Seventh Affiliated Hospital Sun Yat-sen University

Xu Zheng
The Seventh Affiliated Hospital Sun Yat-sen University

Tiexiang Zhan
The Seventh Affiliated Hospital Sun Yat-sen University

Liang Luo
The Seventh Affiliated Hospital Sun Yat-sen University

Research Article

Keywords: Postoperative pulmonary complications, High-flow nasal cannula, Conventional oxygen therapy, Major surgery

Posted Date: November 7th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-2056994/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Abstract

Background

Nearly 234 million patients undergo surgery each year, and 1.3 million develop complications. The risk of postoperative pulmonary complications (PPCs) remains high, especially in major upper abdominal surgery. The occurrence of PPCs seriously affects the outcomes of surgical patients, and the risk of death is significantly increased. This could have a serious impact on the prognosis of patients if no effective prevention or timely intervention is carried out. High-flow nasal cannula (HFNC) is increasingly used in postoperative patients and is confirmed to be as effective as noninvasive ventilation (NIV) in preventing postoperative hypoxaemia and respiratory failure. In our clinical study, we observed faster recovery with combined HFNC and respiratory training (using PEP Acapella Choice) in patients with postoperative atelectasis. These two interventions have a theoretical benefit in the prevention of PPCs, but no relevant prospective randomised controlled studies have been conducted. Could HFNC combined with respiratory training reduce the incidence of PPCs compared to conventional oxygen therapy (COT) in postoperative patients? Could these combined interventions reduce mortality or improve the long-term prognosis? The answers to these questions remain unknown. In this randomised controlled trial, we hypothesise that HFNC combined with respiratory training will reduce the incidence of PPCs and mortality and improve the long-term prognosis in this cohort.

Methods

This is a randomised controlled single-centre trial. A total of 328 patients who undergo major abdominal surgeries will be included. Subjects will be randomised to receive HFNC combined with Acapella or COT alone immediately after extubation. Our primary endpoint is the incidence of PPCs within 7 days, and the secondary outcome measures include 28-day mortality, reintubation, length of hospital stay, and all-cause mortality within 1 year.

Discussion

This trial would help provide evidence of the preferred effect of HFNC combined with Acapella on COT in patients after major abdominal surgery. The objective of this study is to determine the optimal choice for improving the prognosis of patients undergoing surgery.

Trial registration: ChiCTR2100047146. Registered on 8 June 2021. Retrospectively registered.

Background

Nearly 234 million patients undergo surgery every year, among whom 1.3 million experience complications, while 315 000 die in hospital\(^1\). Postoperative pulmonary complications (PPCs) are a general term for multiple clinical outcomes, including the presence of respiratory infection, respiratory failure, pleural exudation, atelectasis, pneumothorax, bronchospasm, aspiration pneumonia, pneumonia, acute respiratory distress syndrome (ARDS), and tracheobronchitis, according to the definition of PPCs issued by EPCO in 2015\(^2\). However, most studies on PPCs have observed pneumonia and respiratory failure as the outcomes. PPCs are more common than cardiovascular complications after surgery\(^3,4\). The incidence of PPCs varies widely, ranging from 6 to 80%. This is related to the definition and severity of PPCs, which seriously affect the outcome of surgical patients and significantly increase the risk of death\(^5\). Studies estimate that there are nearly one million PPCs in the United States each year, resulting in 46,200 patient deaths and 480,000 additional hospital days\(^6\). Ana et al.\(^7\) found that in non-cardiothoracic surgery patients with American Society of Anesthesiologists (ASA) grade III who underwent surgery for more than 2 h, the incidence of PPCs was still high (approximately 33%), even with the intraoperative use of protective pulmonary ventilation. Most will significantly affect postoperative mortality within 7 days after surgery, even mild PPCs, such as atelectasis and prolonged oxygen demand. Therefore, PPCs deserve close attention in clinical practice.

High-flow nasal cannula (HFNC) is increasingly used in postoperative patients, particularly after extubation. It has been confirmed that HFNC is similar to noninvasive ventilation (NIV) in preventing hypoxaemia and respiratory failure\(^8\). The Acapella-vibrating positive pressure ventilation therapy system produces a positive pressure at the end of the expiratory period to maintain lung expansion. It can promote sputum excretion, strengthen respiratory muscle, and reduce the incidence of pneumonia. However, the use of HFNC after extubation in patients undergoing major surgery does not reduce the rate of hypoxaemia and reintubation compared with conventional oxygen therapy (COT)\(^9\), and routine respiratory training (such as incentive spirometry) is generally not recommended for patients after
major surgery. In our clinical practice, we observed that patients at high risk for PPCs recovered faster using HFNC combined with respiratory training (PEP Acapella Choice). Therefore, a pilot trial of 12 cases of the combined use of HFNC and Acapella breathing training was conducted. The incidence rate of PPCs was 50% (3/6) in the conventional treatment group and 16.7% (1/6) in the combined treatment group, and the diaphragm function recovered faster, showing a preventive effect. To date, no randomised controlled trials have verified the role of HFNC combined with respiratory training in preventing PPCs.

In this randomised controlled study, we hypothesise that the combination of HFNC and respiratory training could reduce the incidence of PPCs in patients who undergo major abdominal surgery compared to conventional oxygen therapy, which could be applied for the prevention of PPCs.

Methods

Design

The study is a parallel, randomised, controlled, single-blind clinical trial.

Study Aim

This project intends to apply HFNC combined with respiratory training to patients who undergo major abdominal surgery (operation time > 2 h) after extubation, using a single-centre prospective randomised controlled clinical study to achieve the following objectives:

Primary objective: To reduce the incidence of PPCs within 7 days after surgery compared to with COT and to guide clinical practice.

Secondary objective: To investigate whether HFNC combined with respiratory training can improve major abdominal surgical patient outcomes, such as reducing 28-day mortality, 1-year all-cause mortality, reintubation rates, and length of hospital stay.

Study population

Patients who undergo elective abdominal surgery (operation time > 2h) at the Seventh Affiliated Hospital of Sun Yat-sen University will be recruited.

The inclusion criteria are as follows: (1) age ≥ 18 years, (2) surgery time ≥ 2 h, (3) abdominal surgical site, and (4) BMI ≤ 35 kg/m² (normal, mild obesity, excluding moderate to severe obesity).

The exclusion criteria are:

1. Endotracheal intubation not successfully removed within 24 h after surgery;
2. Obstructive sleep apnea syndrome (OSAHS);
3. Patients with haemodynamic instability (defined as the need for a norepinephrine dose > 0.5 ug/kg/min or dopamine > 10ug/kg/min to maintain mean arterial pressure [MAP] ≥ 65 mmHg);
4. Contraindications for the use of the PEP Acapella Choice;
5. Significant abnormal preoperative chest radiograph or chest CT affecting the identification of PPCs;
6. PPCs, such as pneumothorax, pneumonia, and pleural effusion, appearing before randomisation.
7. Preoperative impaired consciousness or mental illness (Glasgow score ≤ 14);
8. Emergency operation;
9. Participation in other clinical studies;
10. Pregnant woman;
11. Informed consent not obtained.

Consent And Ethical Consideration

The study protocol and information forms have been approved by the Ethics Committee of the Seventh Affiliated Hospital of Sun Yat-sen University (registration number: KY-2021-017-01; date of approval: 18 March 2021). Important protocol modifications will be
communicated to the ethics committees. The patients will be verbally informed and provided with written documents. Patients will be informed about the trial and their right to refuse participation at any time during the study. All participants will sign an informed consent form.

**Randomization**

A random number table has been generated using SAS software and assigned according to a random number in a 1:1 ratio. Opaque envelopes have been created, and the random grouping results (Group A or Group B) corresponding to the enrolment number of the study participants will be placed inside the envelopes and sealed. After the eligibility of the participants is confirmed and informed consent is obtained, a trial number will be assigned only after all inclusion and exclusion criteria have been met. Participants may be randomly assigned to the trial. See flowchart in Fig. 1.

**Interventions Of The Trial**

Implementation of the intervention will start within 30 min of extubation. See in Additional file 1.

**Combination treatment group**

After extubation, patients will receive HFNC therapy for at least 48h and 3 respiratory training sessions per day (using Acapella PEP Choice) for at least 3 days. After 48 h postoperatively, COT may be administered or stopped according to the patient's condition.

**Routine treatment group**

COT should be continued for at least 48h after extubation and may be continued or stopped after 48h.

**Standard procedure**

1. Preoperative respiratory training will be performed using incentive spirometry and recorded.
2. An intraoperative protective ventilation strategy will be applied (tidal volume set at 6–8 ml/kg).
3. Postoperative withdrawal and extubation procedures will be performed according to the ATS/ACPP clinical practice guidelines for mechanical ventilation withdrawal.
4. Postoperative pain management will be administered to maintain a VAS score of < 3.
5. Decisions regarding other therapeutic monitoring of the patient during the postoperative period will be made by the supervising physician based on professional knowledge and routine clinical practice.

Once acute hypoxic respiratory failure occurred, and HFNC or NIV could not improve within two hours, endotracheal intubation and invasive ventilation should be considered. Other rescue measures shall be treated according to the routine diagnosis and treatment.

**Organization Of The Trial**

**Funding and support**

The trial is supported by “The Seventh Affiliated Hospital, Sun Yat-sen University Clinical Research 735 Program”.

**Blinding**

Given the nature of the intervention, it is not possible to blind the physicians, nurses, and patients. Physicians who are not aware of the clinical research and intervention will collect data on clinical and vital signs. In addition, a team of experts, consisting of one ultrasonographer, one radiologist, and one intensivist, has been established to interpret the ultrasound and chest radiograph results; each member is at least an attending physician. The expert team is unaware of the patient information.

**Outcomes**

**Primary outcome**
The primary outcome is the incidence of PPCs within 7 days after surgery. This includes respiratory infections, bronchospasm, aspiration lung injury, pneumonia, atelectasis, pleural exudation, pneumothorax, and acute respiratory failure. Each diagnostic criteria see in Additional file 2.

**Secondary Outcome**

Incidence of PPCs during hospitalisation, length of hospital stay, 28-day mortality, NIV or reintubation rates, incidence of surgical complications (surgical site bleeding, infection, wound infection, anastomotic leakage, surgical reintervention), and all-cause mortality within 1 year.

**Sample Size**

Based on our previous clinical data and the latest sample size analysis in the literature, we predict that the incidence of PPCs will be approximately 15% lower in the combined treatment group than in the conventional treatment group. Assuming an α value of 0.025, a β value of 0.1, and a rate of loss to follow-up of approximately 5%, the final calculated single-group sample size is 157 patients, so the total sample size is 314 patients.

**Follow Up**

Patients will be visited daily for 1 week postoperatively and followed-up during hospitalisation, as appropriate. If patients are discharged within 7 days after surgery, chest ultrasound and radiography will be performed at the outpatient clinic on the seventh postoperative day. Patients will be followed-up on postoperative day 28, month 3, month 6, and month 12 for survival status, readmission, and reasons for readmission.

Duration of the clinical trial and reasons for determination: The duration of the original trial and follow-up was not long, and with reference to the case data, the trial is expected to last for 5 years, which would ensure sufficient trial cases. See in Table 1.
Table 1
Flowchart of patients follow-up.

<table>
<thead>
<tr>
<th>TIMEPOINT</th>
<th>Screening D-7 to D-1</th>
<th>Inclusion D-1 to D0</th>
<th>D1 to D7 After randomization</th>
<th>End of hospitalization</th>
<th>D28 after randomization</th>
<th>D90 after randomization</th>
<th>1Y after randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENROLLMENTS</td>
<td>×</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eligibility screen</td>
<td>×</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients information</td>
<td>×</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Informed consent</td>
<td>×</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomization</td>
<td>×</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INTERVENTIONS</td>
<td>×</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HFNC</td>
<td>×</td>
<td>×</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory training</td>
<td>×</td>
<td>×</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COT</td>
<td>×</td>
<td>×</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASSESSMENTS</td>
<td>×</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline variables</td>
<td>×</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory tests</td>
<td>×</td>
<td>×</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultrasound, chest radiography</td>
<td>×</td>
<td>×</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary outcomes</td>
<td>×</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>×</td>
<td>×</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complication / adverse events</td>
<td>×</td>
<td>×</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alive or dead status</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Baseline variables
Baseline criteria are age, sex, body mass index, current smoker, American Society of Anesthesiologist’s classification, chronic comorbid disease, Planned surgical procedure, ARISCAT score, MV during surgery; Primary outcomes: incidence of PPCs within 7 days after surgery; Secondary outcomes Incidence of PPCs during hospitalization; length of hospital stay; 28-day mortality; 90-day mortality; NIV or reintubation rates; incidence of surgical complications (surgical site bleeding, infection, wound infection, anastomotic leakage, surgical reintervention), all-cause mortality within 1 year.

Statistical Analyses
The Shapiro–Wilk test will be used to test whether continuous variables are normally distributed, the normal distribution will be expressed as mean ± standard deviation, and the independent samples t-test will be used to compare groups. Non-normally distributed
continuous variables will be expressed as the median (interquartile range) using the Mann–Whitney U test comparison. Enumeration data will be expressed as the number of cases and percentages, and comparisons between groups will be performed using the chi-squared test. Survival time will be analysed using Kaplan–Meier survival analysis, and comparisons between groups will be performed using the log-rank test.

The treatment effect will be analysed according to the following pre-specified subgroups: (1) open surgery and laparoscopic surgery and (2) patients at high risk for PPCs (ARISCAT score ≥ 45).

**Monitoring And Quality Assurance**

Trial monitoring and quality assessment will be performed independently. The research organization must assign the inspectors trained in the research, who need to have the relevant medical professional background to check the research project according to the developed inspection SOP. The monitor checks the site files according to the Medical Research Involving Human Subjects Act (WMO)/Good Clinical Practice (GCP) standards. All relevant observations and findings will be verified and quality control will be performed at every stage of data processing to ensure accuracy and reliability.

**Safety**

The investigators will record all adverse events experienced by the trial subjects and immediately report them to the research team, management department, and ethics committee (See in Additional file 3). The serious adverse events (SAEs) form will be used to collect the SAEs.

**Discussion**

Postoperative pulmonary complications are common after anaesthesia and surgery, especially in patients undergoing thoracic or upper abdominal surgery and ASA level III surgery, with an incidence of approximately 40% or higher\textsuperscript{11}. Postoperative pulmonary complications significantly affect the clinical outcomes of patients. The presence of even one mild postoperative complication significantly increases early postoperative morbidity and mortality and prolongs the hospital stay\textsuperscript{12}. This trial is the first randomised controlled trial designed to verify whether HFNC combined with respiratory training can reduce the incidence of postoperative pulmonary complications and improve patient clinical outcomes.

Effective prevention of PPCs is strongly associated with a shorter hospital stay and reduced early mortality. Current perioperative-related measures that are effective in preventing postoperative pulmonary complications include preoperative education, smoking cessation, preoperative respiratory physiotherapy, intraoperative protective mechanical ventilation, postoperative analgesia, early bed mobility, and the choice of postoperative support modalities. Over time, the current preoperative and intraoperative anaesthetic risk factors associated with PPCs have been significantly reduced, and an increasing number of PPCs are affected by postoperative factors, including respiratory support modality, breathing training, and physical therapy. Current respiratory support modalities include NIV, HFNC, and COT. According to current guidelines, the choice of respiratory support modality after extubation is associated with the risk of developing postoperative respiratory failure. HFNC is preferred over COT in patients at low risk of postoperative respiratory failure, and HFNC can be an alternative to NIV in patients at high risk of respiratory failure because it is not inferior to NIV in preventing acute respiratory failure after extubation and is associated with better comfort and ease of use\textsuperscript{13}. NIV is effective in preventing and treating respiratory failure and in reducing the rate of postoperative tracheal reintubation in different populations\textsuperscript{14,15}. However, the routine prophylactic use of NIV after major abdominal surgery does not reduce PPCs\textsuperscript{16}, and some patients cannot effectively cooperate and tolerate NIV postoperatively due to poor comfort. In addition, the use of NIV after gastrointestinal surgery may increase the risk of gastrointestinal fistulas. Therefore, clinicians do not use NIV as their first choice for postoperative prevention of respiratory failure or postoperative pulmonary complications, although several studies have shown no significant increase in gastrointestinal complications with NIV use after abdominal surgery. These factors limit the use of NIV after extubation.

HFNC uses heated humidification, high flow (up to 60 L/min), and a high oxygen concentration (up to 100%). At high flow rates, HFNC is believed to increase positive end-expiratory pressure by 4–6 cmH\textsubscript{2}O\textsuperscript{17}, and HFNC is more comfortable than NIV or COT. Studies have shown that there is no increased treatment failure between prophylactic use of HFNC after extubation and intermittent NIV in thoracic surgery patients at a higher risk for postoperative pulmonary complications\textsuperscript{5}. This study supports the application of HFNC in
populations at high risk for PPCs, especially in those with hypoxic respiratory failure. It has been shown not to be inferior to NIV and traditional mask oxygen delivery. Frat compared the effects of HFNC, COT, and NIV in hypoxic respiratory failure in 2015 and found that the 90-day mortality rate was lowest in the HFNC group, although no significant difference was observed in the reintubation rate. Many studies have investigated the application of HFNC after surgical removal of endotracheal intubation. Compared with traditional Venturi mask oxygen administration, HFNC has a better oxygenation effect at the same oxygen inhalation concentration setting, better comfort, less desaturation and interface displacement, and lower reintubation rate. HFNC is not inferior to NIV in preventing reintubation and post-extubation respiratory failure in populations at high risk of reintubation and can also reduce the reintubation rate for people at low risk of reintubation compared with COT. The OPERA trial, one of the largest trials investigating the potential role of HFNC in the prevention of postoperative hypoxaemia, randomised 220 patients after abdominal surgery to receive HFNC or standard oxygen therapy at risk of hypoxaemia. No significant difference was found between the two groups in terms of absolute reduction in hypoxaemia risk. However, the duration of HFNC treatment in this study was 15h (12–18h), while postoperative respiratory failure mostly occurred within 72h after surgery, and the lowest functional residual capacity (FRC) value was usually observed 1–2 days after upper abdominal surgery, and slowly returned to normal after 5–7 days. As mentioned above, decreased FRC and atelectasis were the core segments of PPCs, and the HFNC duration in this trial was short, which may not be sufficient to show the efficacy of preventive PPCs.

Postoperative diaphragmatic dysfunction is the pathophysiological basis of PPCs. Preoperative inspiratory training is believed to reduce the occurrence of pulmonary complications after major chest and abdominal operations. The Acapella vibrating positive pressure ventilation therapy system produces a positive pressure of 5–15 cmH₂O at the end of the expiratory period to maintain lung expansion. It can promote sputum excretion, strengthen respiratory muscle, and reduce the incidence of alveolar collapse, pneumonia, and hypoxaemia, thereby shortening hospitalisation stays and promoting rapid patient recovery. Studies have shown that this therapeutic system is as effective as other airway clearance techniques in improving respiratory symptoms, expectoration, lung capacity, and health-related quality of life. However, previous studies have shown that the routine use of incentive spirometry for breathing training after major upper abdominal surgery did not reduce the incidence of PPCs, and the difference was not significant. Well-designed clinical trials are urgently required for further validation.

These two interventions have theoretical benefits for the prevention of PPCs; however, previous clinical studies have shown that neither HFNC nor breathing training after surgery show a significant difference in the occurrence of PPCs, hypoxaemia, reintubation, or respiratory failure. We believe that this randomised controlled study will provide new evidence for the prevention of PPCs and improve the long-term prognosis.

In conclusion, the trial is a single-centre randomised controlled trial that verifies whether HFNC combined with respiratory training reduces the incidence of postoperative pulmonary complications and improves clinical outcomes in patients undergoing major abdominal surgery, as compared to COT.

**Trial Status**

The trial was registered on 8 June 2021 as ChiCTR2100047146. (http://www.chictr.org.cn/index.aspx) The first patient was randomized on 1 November 2021 and enrollment is expected to be finished in August 2025.

**Abbreviations**


**Declarations**

Consent for publication:

Not applicable, the study results will not contain any data from any individual person.

Availability of data and materials:
Patients are coded by a randomization code, and the principal investigator is the only person with access to this code. The source data are kept by the project leader in the data center. All data from this study will be included in the published results.

Competing interests:

The authors declare that they have no competing interests.

Funding:

The trial is supported by "The Seventh Affiliated Hospital, Sun Yat-sen University Clinical Research 735 Program". The Sponsors have no influence on the design of the study, data collection, results or publication.

Authors' contributions:

B Jin drafted the manuscript, B Jin and MJ Yao co-authored the writing of the manuscript. B Jin, WJ Shen, L Fu, P Liu, X Zheng, Tx Zhan, L Luo participated in the design of the study and performed the statistical analysis. All authors read and approved the final manuscript.

Acknowledgements:

Not Applicable.

References


Figures
Figure 1
Flowchart of this research.

Supplementary Files
This is a list of supplementary files associated with this preprint. Click to download.

- Additionalfile1.docx
- Additionalfile2.docx
- Additionalfile3.docx
- SPIRITchecklist.docx