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High-flow nasal cannula oxygen therapy versus noninvasive ventilation for elderly chronic obstructive pulmonary disease patients after extubation: a noninferior randomized controlled trial protocol

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Abstract

Introduction Noninvasive ventilation (NIV) is widely used for sequential extubation in patients with chronic obstructive pulmonary disease (COPD). However, NIV may cause many adverse events such as claustrophobia, facial skin compression, air leakage, bloating, and even reflux aspiration, resulting in poor patient compliance/tolerance and high failure rate, especially for older adults who are at high risk of communication difficulties and consciousness disorder. High-flow nasal cannula (HFNC) oxygen therapy is a new alternative support to NIV, but whether it can effectively reduce the rate of re-intubation after extubation in elderly patients with COPD remains controversial. The purpose of this study is to explore the safety and efficacy of HFNC versus NIV for elderly COPD patients after extubation.

Methods and analysis This study is an investigator-initiated, single-center, prospective, non-inferior, randomized controlled trial. Elderly patients (age > 65 years) who have received invasive ventilation and was diagnosed with COPD will be randomly assigned to HFNC group or NIV group immediately after extubation with a planned enrollment of 168 patients. The primary outcomes will be reintubation rates at 72 h and 7 days after extubation. Secondary outcomes will include treatment failure, post-extubation vital signs and arterial blood gases, the scores of compliance and comfort of patients, duration of respiratory support after extubation, respiratory support related adverse events, sleep quality scores, usage of sedative and analgesic drugs after extubation, and the incidence of delirium. Additionally, clinical outcomes such as ventilator-free days at 28 days post-randomization, tracheotomy rate, duration of intensive care unit (ICU) and hospital stay, ICU and hospital mortality will be evaluated.

Ethics and dissemination This study has been approved by the Ethics Committee of West China Hospital of Sichuan University (2023–2284). Informed consent is required. It is expected that a follow-up randomized controlled trial will

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be conducted. The results will be submitted for publication in a peer-reviewed journal and presented at one or more scientific conferences.

Trial registration The study was retrospectively registered at ClinicalTrials.gov (ChiCTR2400087312).

Keywords High-flow nasal cannula oxygen therapy, Noninvasive ventilation, Chronic obstructive pulmonary disease, Elderly, Re-intubation

Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic respiratory symptom of heterogeneity characterized by lung disease, often characterized by persistent, progression of airflow obstruction [1, 2]. COPD is the third leading cause of human death and the most common chronic respiratory disease in China, resulting in a huge economic, social and health care burden [2–7]. Due to the imbalance between the load borne by the respiratory muscles and the neuromuscular capacity, the respiratory work of COPD patients is significantly increased, and ventilator dependence is easy to occur [8, 9]. It has been reported that more than 50% of COPD patients admitted to the intensive care unit (ICU) have difficulty with weaning [10]. Advanced age has been reported to be associated with excess morbidity, longer length of mechanical ventilation and higher rate of weaning failure compared with the general population [11, 12]. How to help patients to wean safely and quickly is the key to the prognosis of elderly COPD patients [13].

It has been convincingly demonstrated that the invasive-noninvasive sequential ventilation strategy in the pulmonary infection control (PIC) window is benefit for COPD patients with early extubation and improved prognosis [13–15]. Noninvasive ventilation (NIV), however, may cause claustrophobia, facial skin compression, air leakage, flatulence and other adverse events, even regurgitation aspiration in severe cases, and is intolerable in more than 15% of patients [16–18]. A previous multicenter study reported a 28.6% treatment failure rate for sequential NIV after extubation in patients with COPD [19]. Among all populations, the elderly appear to be more vulnerable and the tolerance/adherence of NIV will be further reduced due to possible conditions such as communication difficulties and consciousness disorder. An advanced age (age>65 years) was confirmed to be associated with higher NIV failure rate [20]. Sedative/analgesic drugs are often inevitably used to improve the tolerance and compliance of NIV, which may disrupt sleep rhythm and exacerbate consciousness disorder for order patients, thus leading to adverse clinical outcomes as determined previously [21]. According to reports, the incidence of delirium in patients undergoing NIV ranges from 18 to 35%, and advanced age is an independent risk factor [22, 23]. An alternative respiratory method to NIV is urgently needed for elderly COPD patients.

High-flow nasal cannula (HFNC) oxygen therapy is an emerging noninvasive form of respiratory support which can provide continuous high-flow inhaled gas through high-flow nasal congestion, along with regulated and relatively constant oxygen concentration, temperature and humidity. HFNC does not required a mask attached tightly to the patients, leading to higher comfort and tolerance. In addition, HFNC can also produce a certain positive end-expiratory pressure (PEEP), reduce dead cavity ventilation and carbon dioxide partial pressure [1, 24–26]. Previous study found that in patients with hypercapnia respiratory failure, HFNC had the same clinical effect as NIV in improving reintubation rate, mortality rate and arterial blood gases, while patients using HFNC had better comfort, tolerability and a lower incidence of adverse events [27]. A meta-study found that HFNC as an alternative to sequential NIV after extubation in acute exacerbation of chronic obstructive pulmonary disease (AECOPD) did not increase the rate of reintubation [28]. It is worth noting that the study has some noticeable limitations. The sample size of the included studies is generally small, with only one study having a sample size of more than 100; and the studies included in the meta-analysis are biased and heterogeneous. Multicenter randomized controlled studies have found that direct NIV after reintubation may be more beneficial than HFNC in patients with multiple risk factors of reintubation (e.g. advanced age) [29]. Meanwhile, failure of HFNC have been reported to be associated with prolonged duration of NIV [30]. At present, the researches focused on sequential HFNC after extubation in COPD patients are still limited, and none of these studies conducted subgroup analyses based on age.

In this non-inferior randomized controlled trial, we will test the hypothesis that sequential HFNC after extubation is non-inferior to NIV for elderly patients with COPD. This paper outlines the study procedures and planned analyses for this clinical trial, which is registered on ClinicalTrials.gov under number ChiCTR2400087312.

Methods and analysis

Study design

This single-center, non-inferior randomized controlled trial is conducted in a tertiary, grade-A teaching hospital and will recruit 168 elderly COPD patients who have received invasive mechanical ventilation. Patients who

fulfil the eligibility criteria will be randomly divided into HFNC or NIV groups to receive sequential treatment after extubation. The protocol has been written according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 statement [31, 32]. The overall study flow is depicted in Fig. 1.

Study population

The study will enroll elderly COPD patients (age > 65 years) who have been admitted to ICU and have received invasive mechanical ventilation. The Global Initiative for Chronic Obstructive Pulmonary Disease will be utilized to identify patients with COPD. Specific diagnostic criteria are as follows. A diagnosis of COPD should be considered in any patient with dyspnea, chronic cough or sputum production, and/or a history of exposure to disease risk factors, but a forced expiratory volume in one second/forced vital capacity (FEV1/FVC) < 0.7 after bronchodilator by forced spirometry is mandatory for a diagnosis of COPD [2]. Other inclusion criteria include that the respiratory failure needs to be induced by broncho-pulmonary infection, and patients need meet the criteria of the PIC window. The standard of the PIC window was determined by the following items: (1) significantly decreased radiographic infiltrations; (2) significantly reduced quantity of sputum, thinning, and decreased density of sputum; (3) at least one of these accompanying signs: body temperature decreased to < 37.5 °C, leukocyte count $< 10\times10^9$/L or 2×10^9/L less than before; and (4) adjustment of ventilator settings to 10–12 times per minute for synchronized intermittent mechanical ventilation (SIMV) and 10–12 cmH_2O for pressure support ventilation (PSV) [33].

Patients will be excluded if they have undergone tracheotomy; have contraindications for NIV (such as recent esophageal surgery, facial trauma; facial surgery or facial deformities); severe heart, brain, liver, or kidney failure; or are expected to have a poor prognosis or palliative care in a short term. Patients will also be excluded if it is unable to obtain informed consent from family members or themselves.

Interventions

Weaning protocol and randomization

COPD patients over 65 years of age and receiving mechanical ventilation in the ICU will be screened every morning. The settings of invasive mechanical ventilation parameters for patients are determined by physician according to the patient's ventilation status and blood gas analysis. The daily assessment of weaning scenario in our center based on the following criteria: (1) reaching the PIC window; (2) having no signs of dyspnea, tachycardia, asphyxia or thoracoabdominal contradictory movement; (3) having stable hemodynamics (without treatment of vasoactive drugs or only using small doses of vasoactive drugs, such as dobutamine < 5-10ug/kg/min); (4) having the ability to protect the airway.

Patients meeting the above criteria will be extubated and randomly assigned to the HFNC group or the NIV group according to the random number generated through Excel's RAND function. Each patient will be ranked from smallest to largest according to the random number obtained and divided into two groups at a ratio of 1:1. Allocation will be concealed through an opaque envelope. Given the nature of the intervention, participants and researchers in this study could not be blinded. The results will be analyzed by statisticians independent of the research team.

HFNC group

All patients assigned to the HFNC group will receive HFNC immediately after extubation. Researchers need to choose the suitable size nasal catheter. The initial airflow is set to 50 L/min and adjusted according to patient tolerance with an absolute humidity setting to 44 mgH_2O/L and the temperature setting to 37 °C. The patient's respiratory rate will be maintained below 30 beats/min or the baseline level before extubation with a SpO2 at 88–92%. HFNC failure is defined as escalation to NIV or invasive mechanical ventilation due to respiratory failure.

NIV group

All patients assigned to the control group will receive NIV immediately after extubation. Researchers will use a standard nose/mask to connect the patient to the ventilator. The patients will be on Spontaneous/Timed (S/T) mode, with the initial end-expiratory pressure setting to 4 cmH_2O. The pressure level will gradually increase to ensure that the patients can trigger the ventilator with each inhalation. The initial inspiratory pressure will be set at 8 cmH_2O and adjusted according to the tidal volume with 6-8 ml/kg and tolerance of patients. The pressure level and the fraction of inspiration oxygen will be adjusted in order to maintain the respiratory rate ≤ 30/min or the baseline level before extubation, a partial pressure of carbon dioxide ($PaCO_2$) at 45–60 mmHg or the last $PaCO_2$ level recorded before extubation, and a pulse oxygen saturation at 88–92%. NIV treatment failure is defined as a return to invasive mechanical ventilation.

All patients will receive HFNC or NIV for at least 2 h after grouping and then patients may receive nasal cannula oxygen or a more advanced form of respiratory support depending on the patient's condition.

Both intervention groups will receive standard treatment. Vibration sputum discharge, bronchoscopy, and bedside physical therapy will be allowed during the trial accordingly. The final decision of reintubation will be taken by the physician, as follows: (1) deterioration of

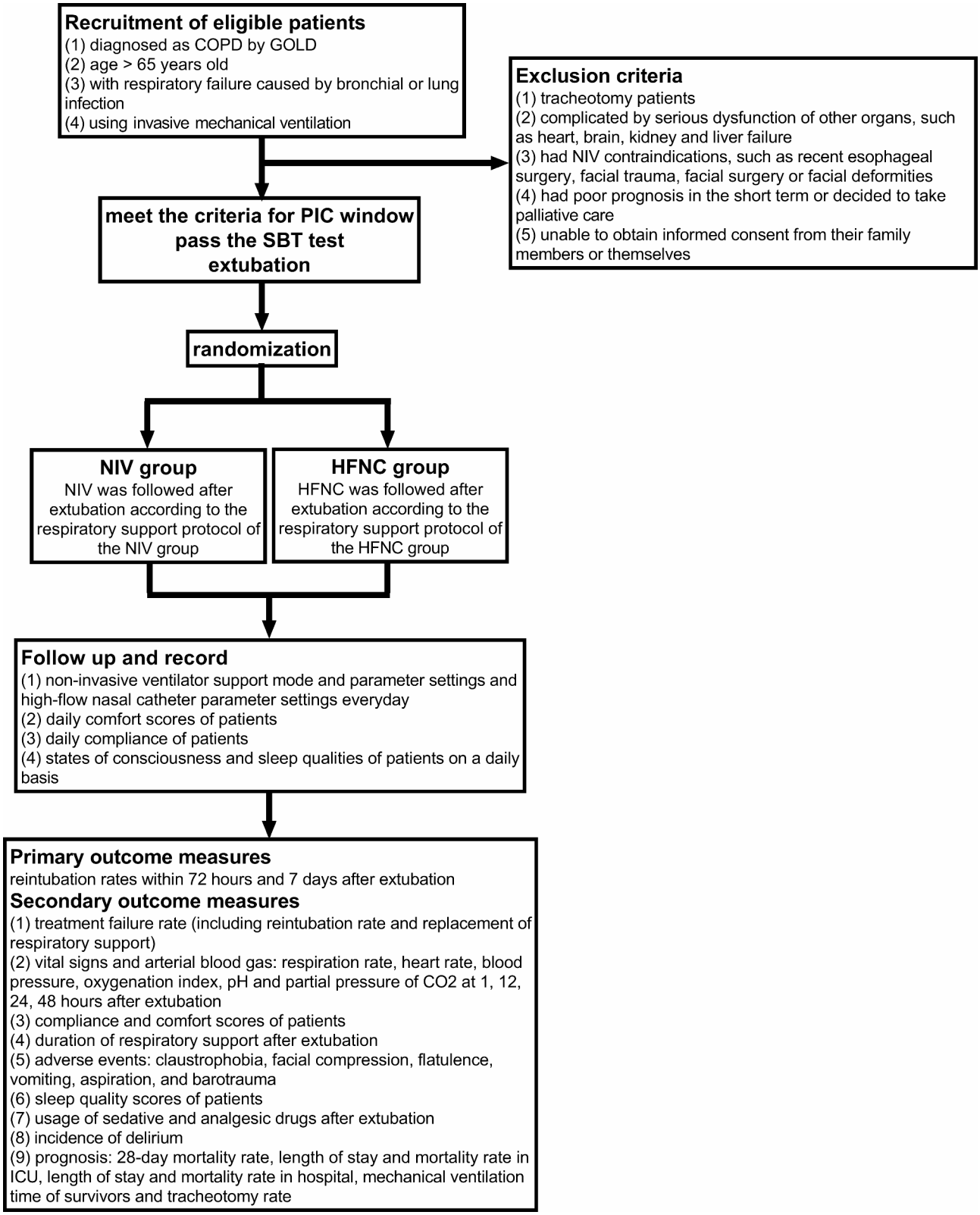

Fig. 1 Flowchart of recruitment, randomization, and follow-up records of patients. COPD, chronic obstructive pulmonary disease; GOLD, the global initiative for chronic obstructive lung disease; PIC, pulmonary infection control window; NIV, noninvasive ventilation; HFNC, high flow nasal cannula; ICU, intensive care unit

the condition, dyspnea (respiratory rate > 35/min) or respiratory depression (respiratory rate < 8/min), (2) significant increase in partial pressure of carbon dioxide and pH ≤ 7.20, (3) refractory hypoxemia ($PaO_2/FiO_2 < 50$ mmHg), (4) aspiration or massive sputum difficult to expel, (5) inability to tolerate NIV, (6) cardiac arrest or significant hemodynamic instability, and (7) severe disturbance of consciousness, such as coma or lethargy.

In this study, the patient will be withdrawn from the study for any of the following reasons: (1) withdrawal of consent, (2) severe adverse events due to NIV or HFNC.

To improve adherence to our intervention protocol, all medical personnel will be trained to use NIV and HFNC professionally before the trial. The selection of appropriate patient-ventilator interfaces will be carefully considered after starting the trial and during the use of it, and the medical personnel will adjust the mask in time according to the patient's feedback. In addition, the data will be reviewed by a professional during the process.

Outcomes

Primary outcome measures

The primary outcomes of this study will be the rate of reintubation at 72 h and 7 days after extubation.

Secondary outcome measures

The secondary outcomes will include: (1) treatment failure rate (including reintubation rate and replacement of respiratory support: for patients in the HFNC group, treatment failure means to upgrade to NIV or invasive mechanical ventilation; for patients in the NIV group, treatment failure means to change to invasive mechanical ventilation); (2) vital signs and arterial blood gas: respiratory rate, heart rate, blood pressure, oxygenation index, pH, and partial pressure of CO_2 at 1, 12, 24, and 48 h after extubation; (3) the scores of compliance and comfort of patients (the Richmond Agitation-Sedation Scale (RASS), Critical Care Pain Observation Tool (CPOT), Numeric Rating Scale (NRS)); (4) duration of respiratory support after extubation; (5) respiratory support related adverse events; (6) sleep quality scores; (7) usage of sedative and analgesic drugs after extubation; (8) the incidence of delirium; (9) clinical outcomes: ventilator-free days at 28 days post-randomization, tracheotomy rate, duration of ICU and hospital stay, ICU mortality, hospital mortality.

Subgroup analysis will be performed based on the presence or absence of other risk factors and level of oxygenation and carbon dioxide (such as patients with or without hypercapnia) at extubation. The participant timeline for this study is shown in Table 1.

Adverse events

Adverse events may occur during this trial, such as facial compression, oropharyngeal discomfort, gastrointestinal discomfort or claustrophobia. Serious adverse events such as aspiration, barotrauma, cardiac arrest even death are also possible. If serious adverse events related to the trial occur, the investigator should promptly report them to hospital superiors. The researchers will then take action under the guidance of the relevant hospital departments.

Table 1 Schedule of enrolment, intervention and follow-up for the trial

	STUDY PERIOD			
	Enrolment	Post-allocation		Follow-up
TIME POINT	Day-0	Day1 ~ Day_x after randomization	End of hospitalization	Day28
ENROLMENT:				
Eligibility screen	X			
Informed consent	X			
Patients information	X			
Randomization	X			
INTERVENTIONS:				
HFNC		X		
NIV		X		
ASSESSMENTS:				
Baseline values	X			
Information at extubation	X			
HFNC/NIV parameter settings		X		
Primary outcomes		X		
Secondary outcomes		X	X	
Adverse events		X	X	
Live status: dead or alive		X	X	X

Sample size and recruitment

Reintubation rate will be used as the main study index. According to a study published in 2016 on respiratory support after extubation in high-risk patients with reintubation, the reintubation rate in patients with sequential NIV after extubation was approximately 22.8% and the reintubation rate in patients with sequential HFNC after extubation was 19.1% [34]. The sample size of the two groups will be designed to be 1:1. Assuming that the probability of Class I error in this study is $\alpha=0.05$, the degree of assurance $(1-\beta)=80\%$ and the non-inferiority margin value is 15%, the sample size of the two groups is calculated to be equal, and $n1=n2=1/2\ N\approx75$. The total sample size was 150 cases. Accounting for approximately 10% loss in follow-up, enrollment of 168 patients (84 in each group) is necessary.

Intubated COPD patients will be recruited by the principal investigator. The study physician is responsible for obtaining informed consent before each patient is enrolled.

Data collection and management

The basic information of the patient will be collected through the electronic medical record system, including age, gender, height, weight, diagnosis, acute physiological and chronic health score II (APACHE II), sequential organ failure score, and COPD severity. Vital signs, arterial blood gas, and APACHEII score at extubation will be recorded by research assistant, who will also be in charge of data quality management. After grouping, information to be collected on a daily basis will include NIV support mode and parameter settings, HFNC parameter settings, daily compliance and comfort scores, daily sedative and analgesic drug use, state of consciousness, and sleep quality of patients by using the Richards-Campbell Sleep Questionnaire (RCSQ) [35]. We will conduct personnel training before data collection.

In addition, outcome indicators will be recorded by primary research assistant. All patients will be followed up until discharge or death. All personal information will be kept confidential for research purposes only. Patient data collected will be stored in both paper and electronic formats. To ensure that the data entered is correct, range checks for data values will be performed. The use of the data will comply with the requirements of the Personal Information Protection Law of the People's Republic of China. All study data will be collected anonymously and assigned an individual study number on all case report forms.

Statistical analysis

Statistical methods for analysing primary and secondary outcomes

The normal distribution data will be expressed as mean ± standard deviation and compared by the T-test, while the continuously skewed distribution variables will be expressed as median and quartile spacing and compared by the Mann-Whitney U test. Categorical variables will be expressed as number and percentages, and comparisons between groups are made using Chi-square tests or Fisher exact probability tests. Measurements at multiple time points, such as vital signs and blood gas analysis, will be compared between groups by using repeated measure ANOVA. A two-sided P value <0.05 will be considered statistically significant.

Statistical analysis will be performed in an intention-to-treat population, including all the randomised patients except patients who withdraw their consent and patients with missing data on the primary. We plan to conduct a sensitivity analysis for the primary outcome using multiple imputation techniques where appropriate. The primary outcome will be assessed using Kaplan-Meier curves and the ratio will be calculated with a 95% confidence interval using the Cox proportional hazard model. A logistic regression will be used for the analysis of the primary outcome with OR of failure calculation, before and after adjustment on confounding variables. Interim analyses will be performed after recruiting half of the planned sample size evaluate effects on clinical outcomes. The data monitoring committee would consider stopping the trial if there was evidence of harm with a one-sided P value <0.01.

Data monitoring committee

The Data and Safety Monitoring Board (DSMB) will independently perform an interim analysis after recruiting half of the planned sample size. If a serious adverse event occurs during this trial, the DSMB will decide whether to continue the trial or not.

Ethics and dissemination

The study project has been approved by the clinical research ethics boards of the West China Hospital (2023–2284). Study purposes, procedures, risks, and benefits will be discussed with the patients/next of kin. Written informed consent is required and obtained from legally authorized representatives. The study is conducted in accordance with the Declaration of Helsinki. Trial methods and results will be reported according to the Consolidated Standards of Reporting Trials (CONSORT) 2010 guidelines [36]. Findings will be published in peer-reviewed journals and presented at local, national and international meetings and conferences to publicise

and explain the research to clinicians, commissioners and service users.

Protocol amendments

Any modifications to the protocol which may impact on the conduct of the study, potential benefit of the patient or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be agreed upon by study group and Ethics Committee prior to implementation.

Discussion

Sequential use of NIV after extubation is recommended as a COPD weaning strategy by the recent guideline. However, concerns about NIV due to poor compliance, patients' discomfort, a high rate of adverse events and treatment failure are receiving increasing attention [37–39]. HFNC is becoming increasingly widespread for great comfort/tolerance, and physiological advantages, such as producing a certain PEEP and reducing physiological dead space. Plenty of previous studies have demonstrated that HFNC can replace NIV in the treatment of hypoxic respiratory failure [28, 34, 40, 41]. For COPD patients, data is limited to draw a conclusion for small simple size and significant heterogeneity among studies. As for elderly COPD patients, no research has been published before. To our knowledge, this study is first randomized controlled trial to determine whether HFNC is not inferior to NIV in the sequential extubation for elderly patients with COPD. This study may, to some extent, fill the gap in the sequential study of elderly patients with COPD after extubation. Our hypothesis is that the use of HFNC immediately after extubation is noninferior to NIV in prevent reintubation and is associated with better comfort/tolerance, and decreased risk of adverse events for elderly COPD patients. Considering that the aging population will become more and more serious in the future, the results of this study will help clinicians or respiratory therapists to manage COPD patients better and improve patient's prognosis.

Existing studies have some controversies on the clinical effect of HFNC vs. NIV sequential which generally have small sample size and limited outcome indicators, resulting in weak persuasive results [19, 40, 42–44]. The study of Tan et al. [19] is the largest existing study on the sequential comparison of HFNC and NIV in COPD patients after extubation with 44 subjects in the HFNC group and 42 in the NIV group, which may not be enough to explain the test results. In our study design, we will increase the sample size to 168 to make the test results more comprehensive. In addition, we will innovatively include the sleep quality score of patients, the usage of analgesic and sedative drugs after extubation and the incidence of delirium of patients as outcome indicators. The sleep quality and consciousness state of patients after extubation should be given sufficient attention.

No previous studies specifically focused on HFNC versus NIV after extubation in COPD patients older than 65 years. Compared with general population, elderly COPD patients have a higher extubation failure rate and a higher risk of death, which should be paid more attention [45, 46]. In addition, given the specific physiological characteristics of the elderly population, including more fragile skin conditions, less effective communication and sleep rhythms easily disrupted by sedative or analgesic, NIV used in the elderly population may cause more adverse events, which needs to be clarified in further studies.

Our study has several significant limitations. First, a blinded design is not possible for the obvious differences between the different respiratory support equipment, which may be prone to bias. But we excluded patients from clinical decisions, controlling for confounders as much as possible by randomizing groups. Second, the study was a single-center study, which means that the experimental design of this study may not be applicable to all other centers. But we will collect a large enough sample size to complete the trial at an existing center. In the future, we will consider a multicenter clinical trial if conditions permit.

Conclusion

In conclusion, this study is the first randomized controlled trial focused on the safety and efficacy of HFNC versus NIV in the sequential treatment of elderly patients with COPD after extubation. Hope the results of the study can provide new evidence for sequential treatment of elderly COPD patients after extubation.

Abbreviations

AECOPD	Acute exacerbation of chronic obstructive pulmonary disease
APACHE II	Acute physiological and chronic health score II
CONSORT	The Consolidated Standards of Reporting Trials
COPD	Chronic obstructive pulmonary disease
CPOT	Critical Care Pain Observation Tool
DSMB	Data and Safety Monitoring Board
FEV1/FVC	Forced expiratory volume in one second/forced vital capacity
HFNC	High-flow nasal cannula
ICU	Intensive care unit
NIV	Noninvasive ventilation
NRS	Numeric Rating Scale
PaCO2	Partial pressure of carbon dioxide
PEEP	Positive end-expiratory pressure
PIC window	Pulmonary infection control window
PSV	Pressure support ventilation
RASS	The Richmond Agitation-Sedation Scale
RCSQ	The Richards-Campbell Sleep Questionnaire
SIMV	Synchronized intermittent mechanical ventilation
SPIRIT	The Standard Protocol Items: Recommendations for Interventional Trials
S/T mode	Spontaneous/Timed mode

Supplementary Information

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Supplementary Material 1

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Author contributions
GPL and JIC are the principal investigator, and designed the study protocol; YXY and JIC wrote and revised the manuscript; all authors contributed to revise the manuscript, and read and approved the final manuscript.

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Data availability
Any data collected during this study can be acquired from the corresponding author upon a reasonable request.

Declarations

Ethics approval and consent to participate
The study project has been approved by the clinical research ethics boards of the West China Hospital (2023–2284). Approvals for the protocol and informed consent documents are obtained from the Institutional Review Board of each participating institution prior to enrolling study participants. Written informed consent is required and obtained from legally authorized representatives at each participating site.

Consent for publication
Not applicable.

Trial update
The initial patient was recruited on July 19, 2024, and recruitment is currently ongoing. The study is expected to be completed by December 2025.

Competing interests
The authors declare no competing interests.

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