High flow nasal cannula therapy with sequential noninvasive ventilation versus noninvasive ventilation alone as the initial ventilatory strategy in acute COPD exacerbations: study protocol for a randomized controlled trial

Shuai Liu (liushuai_ed@126.com)
Peking Union Medical College Hospital https://orcid.org/0000-0003-3706-6663
Joseph Harold Walline
The University of Hong Kong
Huadong Zhu
Peking Union Medical College Hospital
Yan Li
Peking Union Medical College Hospital
Chunting Wang
Peking Union Medical College Hospital
Jihai Liu
Peking Union Medical College Hospital

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Abstract

Background: Noninvasive ventilation (NIV) is the recommended mode of ventilation used in acute respiratory failure secondary to an acute exacerbation of chronic obstructive pulmonary disease (AECOPD). Recent data has shown that high-flow nasal cannula (HFNC) treatment can be an alternative for patients with hypercapnic respiratory failure. The purpose of this study is to evaluate HFNC with Sequential NIV versus NIV alone as the initial ventilatory strategy in AECOPD.

Methods: This investigator-initiated, randomized, unblinded, single center, randomized controlled trial will be conducted in the emergency department, emergency intensive care unit, or respiratory intensive care unit of a tertiary-care urban teaching hospital. A total of 66 patients will be enrolled and randomized into the intervention group (HFNT with sequential NIV) or the control group (NIV group). The primary endpoint will be the mean difference in $PaCO_2$ from baseline to 24 hours after randomization. Secondary endpoints include the mean difference in PaCO2 from baseline to 6, 12, and 18 hours, as well as the dyspnea score, overall discomfort score, rate of treatment failure, respiratory rate, rate of endotracheal intubation, length of hospital stay, and mortality.

Discussion: Taking the advantages of both HFNC and NIV on AECOPD patients into account, we designed this clinical trial to investigate the combination of these ventilatory strategies. This trial will help us understand how HFNC with sequential NIV compares to NIV alone in treating AECOPD patients.

Clinical trial registration:

ChiCTR2100054809

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a common disease characterized by persistent respiratory symptoms and airflow limitation due to airway or alveolar abnormalities, and is often caused by exposure to noxious particles or gases[1]. Current guidelines recommend that COPD patients require respiratory support and hospitalization if they develop an acute exacerbation (AECOPD), which is characterized by an acute worsening of respiratory symptoms. Patients with an AECOPD often present in acute respiratory failure (ARF) to the emergency department (ED), with or without carbon dioxide (CO_2) retention and respiratory acidosis[1].

Noninvasive ventilation (NIV) is increasingly one of the most important treatments for patients with AECOPD[2]. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) Criteria recommends NIV as the first and standard mode of ventilation to be used in ARF secondary to AECOPD. For patients with no absolute contraindications, NIV improves gas exchange, decreases respiratory rate, improves acute respiratory acidosis[3], reduces respiratory work load, avoids endotracheal intubation and invasive mechanical ventilation, decreases hospital length of stay, and improves survival[4–7]. However, NIV may face failure under certain real-life clinical circumstances. Patients may not tolerate the ventilatory

machine well because of several factors[8], such as worsening respiratory symptoms, discomfort related to the positive-pressure ventilation, claustrophobia related to the tight-fitting mask, airway secretions, or patient–ventilator interactions[9].

Recent data demonstrated that high-flow nasal cannula (HFNC) therapy has been playing an increasing role in patients with hypercapnic respiratory failure[8,10–12]. HFNC delivers a heated (37◦C) and humidified (44 mg H_2O/L) air-oxygen mixture to patients, with a stable fraction of inspired oxygen (FiO_2). Compared to conventional oxygen therapy, HFNC FiO2 can range from 21 to 100% oxygen with a flow rate up to 60 L/min through a special nasal cannula. The high flow rate creates a positive end-expiratory pressure (PEEP) effect that may help to counterbalance intrinsic PEEP[13], reducing inspiratory resistance, providing adequate airflow, warm gases and enhanced respiratory tract mucus clearance[9]. HFNC also washes out the anatomical dead space of the upper airways, facilitating carbon dioxide removal[13–15]. Based on these potential advantages, there is a reasonable physiological and clinical indication for using HFNC in AECOPD patients[1], but its efficacy and safety in such patients are not clear[16]. In order to unite the advantages of NIV and HFNC, we designed this trial to evaluate the effect of HFNC with sequential NIV versus NIV alone at different times of day on patients with mild-to-moderate AECOPD.

Materials And Methods: Participants, Interventions, And Outcomes

Study setting

This is an investigator-initiated, unblinded, single center, randomized controlled trial. This trial will be conducted in the emergency department, emergency intensive care unit, and respiratory intensive care unit of a large, urban, tertiary-care, teaching hospital. Written informed consent will be gained from all patients or their legal representatives.

Participants and eligibility criteria

We will enroll adult patients of any gender who are 18 years old or older with a diagnosis of mild-to-moderate AECOPD according to the most recent GOLD criteria. Mild-to-moderate AECOPD is currently defined as an acute hypercapnic respiratory failure with an arterial pH between 7.25 and 7.35 and a PaCO2 ≥55 mmHg[4,17,18].

Exclusion criteria are: (1) those who have home care with NIV; (2) those who have received HFNC or NIV prior to this study enrollment; (3) those who have unstable clinical conditions, such as the need for vasopressors to maintain blood pressure, acute coronary syndrome, life-threatening arrhythmias, cardiac or respiratory arrest requiring cardiopulmonary resuscitation or tracheal intubation; (4) those who refuse informed consent; (5) those who are agitated or have altered mental status characterized by a Richmond Agitation Sedation Scale (RASS) ≥2[17]; (6) those who are diagnosed with a failure in two or more than two organs; (7) those who have recent facial or neck trauma, congenital or pre-existing facial or neck

deformities which may influence the proper application of HFNC or NIV; (8) pregnancy; (9) those who have been enrolled in other trials recently[19].

Interventions

Intervention description

In the intervention group, patients will receive HFNC when they are awake in daytime and early evening hours. When they are asleep or at night between 10pm and 6am, these patients will change to NIV. The HFNC group will be given a flow rate of 60 L/min and a temperature of 37° C[17]. If a patient is not tolerating these settings, flow rate and temperature will be titrated to the maximum tolerated level.

In the control group as well as during the NIV period of the intervention group, patients will receive NIV through full or nasal mask with any available ventilator in the hospital. The ventilator will be set to Pressure Support Ventilation (PSV) mode according to usual practice, including a maximal tolerated inspiratory pressure to obtain an expired tidal volume of 6-8 $mL \cdot kg^{-1}$ of ideal body weight and a PEEP between 3 and 5 cm H_2O[17].

The FiO2 will be set for both groups to maintain a peripheral oxygen saturation (SpO2) of 88-92%[4]. Besides the ventilatory support listed above, other standard therapies will be given based on current GOLD guidelines.

Criteria for discontinuing the trial

Each patient's attending physician will make the decision to cease HFNC or NIV if the patient shows signs of worsening respiratory failure or if they show one or more of the following conditions: respiratory pauses with a loss of consciousness, bradycardia (heart rate <50 beats per minute (bpm)), hypotension with a blood pressure <90/60 mmHg, acute respiratory acidosis with an abnormal arterial blood gas (pH <7.35; $PaCO_2$ >45 mm Hg)[11], psychomotor agitation making nursing care impossible or requiring sedation[2], respiratory or cardiopulmonary arrest. If such conditions happen to the patient, they may need to be intubated either to protect the airway or to manage tracheal secretions, and given mechanical ventilation as per usual practice. Finally, the trial will end if the patient or legal representative rescinds their informed consent.

Outcomes

The primary endpoint is the mean difference in $PaCO_2$ from baseline to 24 hours after randomization. Secondary endpoints include: (1) the mean difference in $PaCO_2$ from baseline to 6, 12, and 18 hours after randomization; (2) dyspnea score at 6, 12, 18 and 24 hours; (3) overall discomfort score related to the ventilatory strategy and proportion of patients showing poor tolerance to treatment at 24 hours (e.g. complaining about noise, pressure, temperature, gastric distension, vomiting, or claustrophobia); (4) the proportion of patients who change treatment strategies (switch to the other ventilatory strategy or to no

support); (5) rate of treatment failure, defined as the proportion of patients who had PaCO2 worsening or reduction <10 mmHg from baseline, or worsening with no improvement of the dyspnea or respiratory rate >30 breaths per minute; (6) respiratory rate; (7) rate of endotracheal intubation within 24 hours (8) length of hospital stay; and (9) all-cause mortality.

Sample size calculation

Based on previous studies[20], we set the non-inferiority cutoff at 10mmHg. So after the High flow nasal cannula therapy with sequential noninvasive ventilation, in intervention group, PaCO2 may not elevated more than 10mmHg after 24h.To assess non-inferiority using an $\alpha = 0.50$, power = 0.80, and 1-sided testing, 66 subjects were needed totally.

Assignment of interventions, allocation and concealment mechanisms

Patients will be randomized into either an intervention group and a control group through a 1:1 ratio using a computer-generated randomization sequence via an independent investigator, who will not be involved in the trial. Allocation concealment will be maintained using sequentially numbered sealed opaque envelopes. Each envelope contains the patient's allocation to either control or intervention group, with a unique study patient code. The baseline is defined as the time of randomization.

Assignment of interventions: blinding

Because of the design of this trial using HCNC or NIV, neither the investigators nor the patients can be blinded to the treatment allocation.

Recruitment

We will recruit participants from the emergency department, emergency intensive care unit and respiratory intensive care unit of a large, urban, tertiary-care, teaching hospital. Investigators will explain the purpose, methods, possible risks, benefits and rights to patients who are eligible to participant in this trial. If the participant agrees to be enrolled and meets the eligibility criteria, the investigator will ask the patient or their guardian to sign the study's informed consent form.

Participant retention and withdrawal

Once the participants are enrolled, the research team has the responsibility to achieve a low rate of loss to intervention. Before the start of the intervention, investigators will take the time to educate, detail the duration of the intervention and possible adverse effects. All patients will be informed that they have the right to withdraw from the study at any time during the intervention and the Data Monitoring Committee (DMC) will discuss and analyze the reasons for dropouts with data collectors, which will be documented in a standardized form.

Data collection and measurement

We will collect patient personal and baseline clinical characteristics as delineated above (e.g., age, gender, RASS, etc.). Furthermore, we will collect vital signs, systolic and diastolic pressure, heart rate, peripheral oxygen saturation, the presence of dyspnea based on the Borg dyspnea scale(score from 0 to 10 after 6 minutes' walk, 0 means no dyspnea, 10 means the maximum), the arterial blood gas at inclusion, starting time and settings for HFNC/NIV at 6, 12, 18, and 24 hours. During the study intervention, patients will have continuous SpO_2, electrocardiogram, respiratory rate, and noninvasive blood pressure monitoring. All relevant variables and endpoints will be evaluated at 6, 12, 18, and 24 hours after randomization. In particular, we will record the NIV and HFNC settings as well as the proportion of patients who change treatment modality during the study period (i.e., switch to the other ventilatory strategy or to no ventilatory support). The discomfort score related to different ventilatory strategies will also be assessed at the established time points, and the proportion of patients showing poor tolerance to the treatment but who do not interrupt or withdrawal due to noise, temperature of flow, gastric distension, vomiting, or claustrophobia will be recorded. We will also record the rate of treatment failure due to a worsening PaCO2, a less than 10 mmHg reduction in PaCO2 from baseline, a worsening or lack of improvement in dyspnea, or a respiratory rate >30 breaths per minute. Hospital length of stay and any-cause in-hospital mortality will all be collected.

Statistical analysis

We will use descriptive statistical methods to measure patient characteristics and baseline clinical features. For primary and secondary outcomes, continuous variables will be presented as means ± standard deviations or median interquartile ranges (IQR). Categorical variables will be expressed as counts with percentages. We will use Student's T-tests or Mann–Whitney U-tests to evaluate the differences between treatments in continuous variables according to normal distribution. Categorical variables will be compared using Chi-squared or Fisher's exact tests. All data collected will be analyzed by an independent statistical expert using SPSS (SPSS 22.0). A p-value <0.05 will be considered statistically significant.

Discussion

In the past few years, there have been multiple studies investigating the application of NIV and HFNC in AECOPD patients, but a consensus has remained elusive. Previous studies have shown that HFNC has several properties superior to NIV in AECOPD patients, such as better patient tolerance and improved patient–ventilator interaction. Nevertheless, NIV has a longer clinical track-record with high quality evidence supporting its position as the gold-standard respiratory support method for managing AECOPD patients.

The recent systematic review from Pisani, et al. reported that HFNC has been used successfully in AECOPD patients as an alternative to NIV due to its reduction in work of breathing and comfort[1]. Another recent ultrasound study examined diaphragm displacement and diaphragm thickening fraction in a cross-over study including 30 AECOPD patients with hypercapnic acute respiratory failure receiving NIV

for more than 24 hours[21]. That study found that the diaphragm thickening fraction in the HFNC group remained unchanged which implied equivalent clinical efficacy to NIV, while improving patient comfort[12]. A single-center randomized controlled cross-over study concluded that treatment with NIV led to a greater reduction in $PaCO_2$ than treatment with HFNC, but the latter was superior across a range of tolerability aspects[9,22]. In a short-term crossover clinical trial, Rezaei, et al. found no difference in any parameters between AECOPD patients treated with NIV or HFNC (e.g. respiratory rate and PaCO2), however, HFNC appeared better in patients with AECOPD to reduce dyspnea scores and improve respiratory distress[23]. Li et al. conducted a prospective, randomized, controlled trial which enrolled 320 patients with AECOPD who were given either HFNC or conventional oxygen therapy, finding that the PaCO2 of the HFNC group was lower at 24 hours and these patients had improved prognoses[24]. Xu-Yan Li, et al. conducted a prospective randomized controlled study comparing the effectiveness of NHFC to conventional oxygen therapy in AECOPD patients, and found HFNC had improved the treatment failure[24]. However, other prospective study compared the effect of NHFC to NIV in hospitalized severe AECOPD patients, and found no significant differences in 6 and 24 hour ABG analyses, as well as 30-day intubation and mortality rates[25]. NHFC has been associated with fewer complications, better tolerance, and less naso-facial skin breakdown than NIV[15]. Most significantly, Cortegiani et al. performed a multicenter, non-inferiority randomized trial comparing HFNC to NIV in nine centers in Italy. The patients they randomized to the HFNC group had worsening oxygenation during the first six hours. Subsequently, 32% of these patients underwent NIV during their hospitalization, but they also had a longer length of NIV than those originally allocated to the NIV group[17]. These findings suggest that HFNC and NIV may play a complementary role in AECOPD treatment.

Above all, no matter the clinical parameters or prognosis, HFNC may be noninferior to NIV. HFNC shows advantages in better patient comfort and tolerance, fewer complications, improved warming and humidification of their respiratory tracts and better sputum excretion. However, if AECOPD patients are asleep, HFNC may increase the risk of CO2 retention and respiratory acidosis. On the other hand, NIV may face failure because of discomfort related to the ventilation and the mask, decreased secretion clearance, and patient–ventilator interaction mismatch.

This study aims to try to take advantage of both the strengths of HFNC and NIV to improve clinical care for AECOPD patients in the ED and critical care environments. We believe that the work of this trial will help us better understand whether HFNC with sequential NIV has any advantages over NIV alone. If this ventilatory strategy proves beneficial or non-inferior, it could provide crucial clinical evidence for improving care for AECOPD patients.

Trial status

Participant enrollment will be started on 1 November 2022.The completion is expected to be finished on 31 January 2025.

Abbreviations

COPD: Chronic Obstructive Pulmonary Disease; HFNC: high-flow nasal cannula; NIV: Noninvasive ventilation; AECOPD: acute exacerbation of chronic obstructive pulmonary disease; GOLD: Global Initiative for Chronic Obstructive Lung Disease; FiO2: inspired fraction of oxygen; PEEP: positive end-expiratory pressure; PaCO2: partial pressure of arterial carbon dioxide.

Declarations

Acknowledgements

We are particularly grateful to anyone who provided helpful advice on the design of this trial. Meanwhile, we appreciate the help from the patients participating in the trial.

Authors' contributions

Shuai Liu drafted the protocol. Joseph Harold Walline revised the manuscript. Huadong Zhu, Yan Li, Chunting Wang, Jihai Liu contributed to the conception and design of the trial. All the authors read and approved the final manuscript.

Ethics approval and consent to participate

Ethical approval will be obtained from the Peking Union Medical College Hospital, Chinese Academy of Medical Science and Peking Union Medical College Ethics Committee before the clinical trial started and the patients recruitment. The study was registered with the Chinese Clinical Trial Registry (ChiCTR2100054809). Prior to the trial, patients who meet the inclusion criteria will be briefed on the purpose of the study, the intervention, the possible risks, and their rights in the trial. Patients are given 24 h to consider and will sign an informed consent form if they agree to participate.

Consent for publication

Not applicable.

Availability of data and material

After this study is completed, the final trial data and statistical codes will be available from the corresponding authors upon reasonable request, except for participants' personal information. The results will be published in peer reviewed journals. Findings will be shared with the participants, healthcare workers, the general public, and relevant departments through open-access articles, public talks, conferences, and final reports.

Competing interests

The authors declare that they have no competing interests.

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Table

Table 1. Schedule of enrolment, intervention, and assessment

Table 1: Schedule of enrollment, intervention, and assessment

Time point	Study period						
	Enrollment	Allocation	Post-allocation				
			Start	6h	12h	18h	24h
Enrollment							
Eligibility	×						
Informed consent	×						
Allocation		×					
Intervention							
Intervention group			×	×	×	×	×
Control group			×	×	×	×	×
Assessment							
Patient characteristics	×						
Vital signs	×		×	×	×	×	×
Medical history	×						
Laboratory results							
ABG			×	×	×	×	×
RASS score			×			×	×
Brog Dyspnea score			×			×	×
Discomfort score			×			×	×
Secretions							
Treatment change							×
Treatment failure							×
Endotracheal intubation							×

Figures

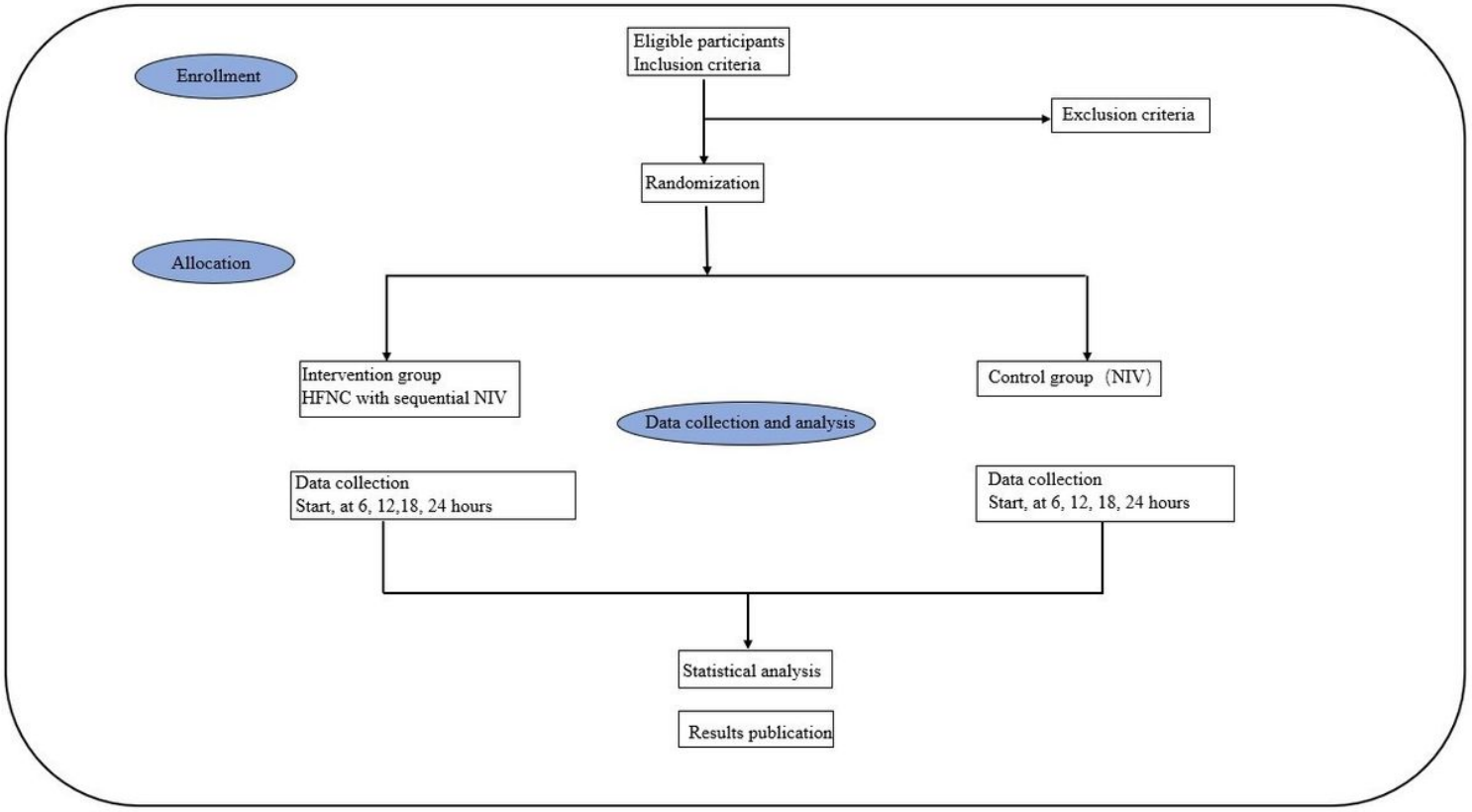

Figure 1

Clinical trial flow chart