Post-extubation high-flow nasal cannula oxygen therapy *versus* non-invasive ventilation in chronic obstructive pulmonary disease with hypercapnic respiratory failure

Pankti Sheth Ketan, Rohit Kumar, Mahendran AJ, Pranav Ish, Shibdas Chakrabarti, Neeraj Kumar Gupta, Nitesh Gupta

Department of Pulmonary, Critical Care and Sleep Medicine, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India

Correspondence: Nitesh Gupta, Department of Pulmonary, Critical Care and Sleep Medicine, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India.
Tel.: +91.98370 96364.
E-mail: niteshgupta2107@gmail.com

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Abstract

The sequential use of non-invasive ventilation (NIV) for weaning in hypercapnic respiratory failure patients is a recommended practice. However, the effectiveness of weaning on high-flow nasal cannula (HFNC) is unclear. Chronic obstructive pulmonary disease patients with hypercapnic respiratory failure who received invasive ventilation were screened for enrollment. This study was a single-center, prospective, randomized comparative study. The primary outcome was treatment failure within 72 hours after extubation. Patients who were screened positive for extubation were enrolled in the study and randomized into the HFNC group and the NIV group using a computer-generated simple randomization chart. Treatment failure was defined as a return to invasive mechanical ventilation or a switch in respiratory support modality (*i.e.*, changing from HFNC to NIV or from NIV to HFNC). The study included 62 of the 72 patients. Treatment failure occurred in 8 patients (26.67%) in the HFNC group and 8 patients in the NIV group (25%) (p=0.881). The mean duration of intensive care unit stay in the HFNC group was 5.47±2.26 days and 6.56±3.39 in the NIV group (p=0.376). In the current study, HFNC was non-inferior to NIV in preventing post-extubation respiratory failure in chronic obstructive pulmonary disease patients, while HFNC had better treatment tolerance.

Introduction

Approximately 16% of patients with an acute exacerbation of chronic obstructive pulmonary disease (COPD) need hospitalization, of which 5% require invasive mechanical ventilation for acute life-threatening respiratory failure [1]. In COPD patients with hypercapnic respiratory failure, the incidence of reintubation in the initial 72 hours for post-extubation respiratory failure is 23-48% [2]. Reintubation could indicate disease severity as well as an independent risk factor for nosocomial pneumonia, extended hospital stays, and mortality [2]. One of the common causes of post-extubation respiratory failure in COPD patients is the inability of the respiratory muscles to sustain the work of breathing, leading to respiratory muscle fatigue.

Ferrer *et al*. demonstrated that the use of non-invasive ventilation (NIV) post-extubation decreases the reintubation rate as compared to conventional oxygen therapy (15% *versus* 48%) [3]. The European Respiratory Society/American Thoracic Society (ERS/ATS) guidelines recommend the sequential use of NIV after extubation as a COPD weaning strategy [4]. Approximately 23-45% of patients have reported failure to utilize NIV due to discomfort and NIV-associated complications [5]. Alternative methods are urgently warranted for patients who cannot tolerate NIV or have

contraindications to NIV to prevent post-extubation respiratory failure. High-flow nasal cannula (HFNC) is an alternative non-invasive interface that allows for delivering high flow (up to 60-70 L/min) of heated and humidified gas at a fraction of inspired oxygen (FiO_2) between 0.21 and 1.0. Physiological studies have reported that delivering high flow decreases dead space, improves tidal volume, and decreases respiratory rate, thereby promoting a reduction in partial pressure of carbon dioxide ($PaCO_2$) and work of breathing. In COPD patients post-extubation, Tan *et al.* reported treatment intolerance to NIV in 14% of patients, whereas intolerance to HFNC was not reported by any patients in the HFNC group [6]. Jing *et al*. also reported a lower comfort score with NIV as compared to HFNC in COPD patients post-extubation [5].

There is a paucity of literature to assess the effectiveness of HFNC *versus* NIV in preventing post-extubation respiratory failure in COPD patients with hypercapnic respiratory failure. The current study was conducted to assess the efficacy of HFNC when compared to NIV for preventing post-extubation respiratory failure and reintubation in COPD patients with hypercapnic respiratory failure.

Materials and Methods

Design, sample and setting

This is a prospective, randomized, comparative study of patients admitted to the respiratory intensive care unit of Safdarjung Hospital (New Delhi, India) between June 2021 and September 2022. This study was approved by the Institutional Ethics Committee. Informed consent was obtained from the closest kin of all enrolled patients.

Participants

COPD patients with hypercapnic respiratory failure who received invasive ventilation were screened for enrollment. Patients who were extubated were enrolled in the study. Exclusion criteria were COPD patients on long-term oxygen therapy, domiciliary NIV therapy, contraindication to NIV and HFNC, and lacking informed written consent.

Procedure

Patients were randomized into the HFNC group and the NIV group using a computer-generated simple randomization chart.

All subjects receiving NIV were set in S/T mode with an oronasal mask. NIV settings were adjusted with an adaptive method: the initial positive end-expiratory pressure (PEEP) was set at 4 cm H_2O and was gradually increased to ensure that the patient triggered the NIV device with each inhalation. The initial inspiratory airway pressure was initially set at 8 cm H_2O and was gradually increased to achieve a satisfactory tidal volume, respiratory rate, and acceptable tolerance (a tidal volume of nearly 6 mL/kg and a respiratory rate of less than 24 breaths/min were considered acceptable). FiO_2 was adjusted to maintain SpO_2 of 88-92%. Inspiratory pressures were adjusted to achieve acceptable arterial blood gas (ABG) values and respiratory rate ≤28/min. Patients received conventional oxygen therapy when off NIV to maintain SpO_2 of 88-92%.

HFNC was applied immediately after extubation to subjects who were randomized to the HFNC group. The size of the nasal cannula was chosen based on the patient's nostrils (<50% of nostril diameter). The HFNC humidifier temperature was set at 37 degrees. FiO_2 was adjusted to maintain SpO_2 of 88-92%. Airflow was initially set at 15 L/min, titrated upwards at 5 L/min, and adjusted as per the patient's tolerance. The patient's initial respiratory support was given for an initial 24 hours and then continued as needed. NIV or HFNC was discontinued when the total daily treatment duration was less than 4 hours. Vitals and ABG were monitored for 72 hours or till complete withdrawal of NIV was achieved (*Supplementary Tables 1 and 2*).

Treatment failure was defined as a return to invasive mechanical ventilation or a switch in respiratory support modality (*i.e.*, changing from HFNC to NIV or from NIV to HFNC). Criteria for reintubation requiring invasive mechanical ventilation were NIV or HFNC failure/inability to tolerate NIV or HFNC, pH<7.20, altered mental status, increased work of breathing, cardiac arrest, arrhythmia, hemodynamic instability, and persistent inability to remove respiratory secretions.

Outcomes

The primary outcome was treatment failure within 72 hours after extubation. Secondary outcomes included the length of hospital stay after extubation, vitals and ABG trends within 1, 24, and 72 hours after extubation, and proportion of patients on HFNC requiring a switch to NIV.

Sample size and statistical analysis

Based on a previous study [6], using an incidence of post-extubation respiratory failure of 22% with z-statistics for the desired level of confidence (*i.e.*, 0.05) of 1.96 and precision of 0.10, the sample size calculated was 30 in each group.

The presentation of the categorical variables was done in the form of numbers and percentages. The quantitative data were presented as the means ± standard deviation and as median with 25^{th} and 75^{th} percentiles (interquartile range). The data normality was checked by using the Kolmogorov-Smirnov test. In cases where the data was not normal, non-parametric tests were used. The comparison of variables was analyzed using the Mann-Whitney test, independent *t*-test, chi-square test, and Fisher's exact test wherever applicable. The comparison of vital signs and blood gas analyses at multiple time points was performed by Friedman's repeated measures analysis of variance on ranks. The data entry was done in EXCEL spreadsheet (Microsoft, Redmond, WA, USA) and the final analysis was done with the use of Statistical Package for Social Sciences software version 25.0 (IBM, Chicago, IL, USA). For statistical significance, a p-value of less than 0.05 was considered statistically significant.

Results

Among 72 COPD patients who received invasive mechanical ventilation during the study period, 62 patients were included in the study (Figure 1). Demographic characteristics, smoking history, history of COPD in terms of duration of illness and medications used prior to the current exacerbation, comorbidities, modality used prior to starting invasive mechanical ventilation, and on-admission Acute Physiology and Chronic Health Evaluation II scores were comparable between the HFNC and NIV groups (Table 1). No significant difference was seen in weaning parameters, vitals, or ABG values before extubation. Although a statistically significant difference was seen in respiratory rate and Rapid Shallow Breathing Index between the HFNC and NIV groups, these results did not hold significant clinical relevance as the observed values were in an unacceptable range (Table 2). The mean flow rate reached during titration with HFNC was 43.66+/-11.36 L/min.

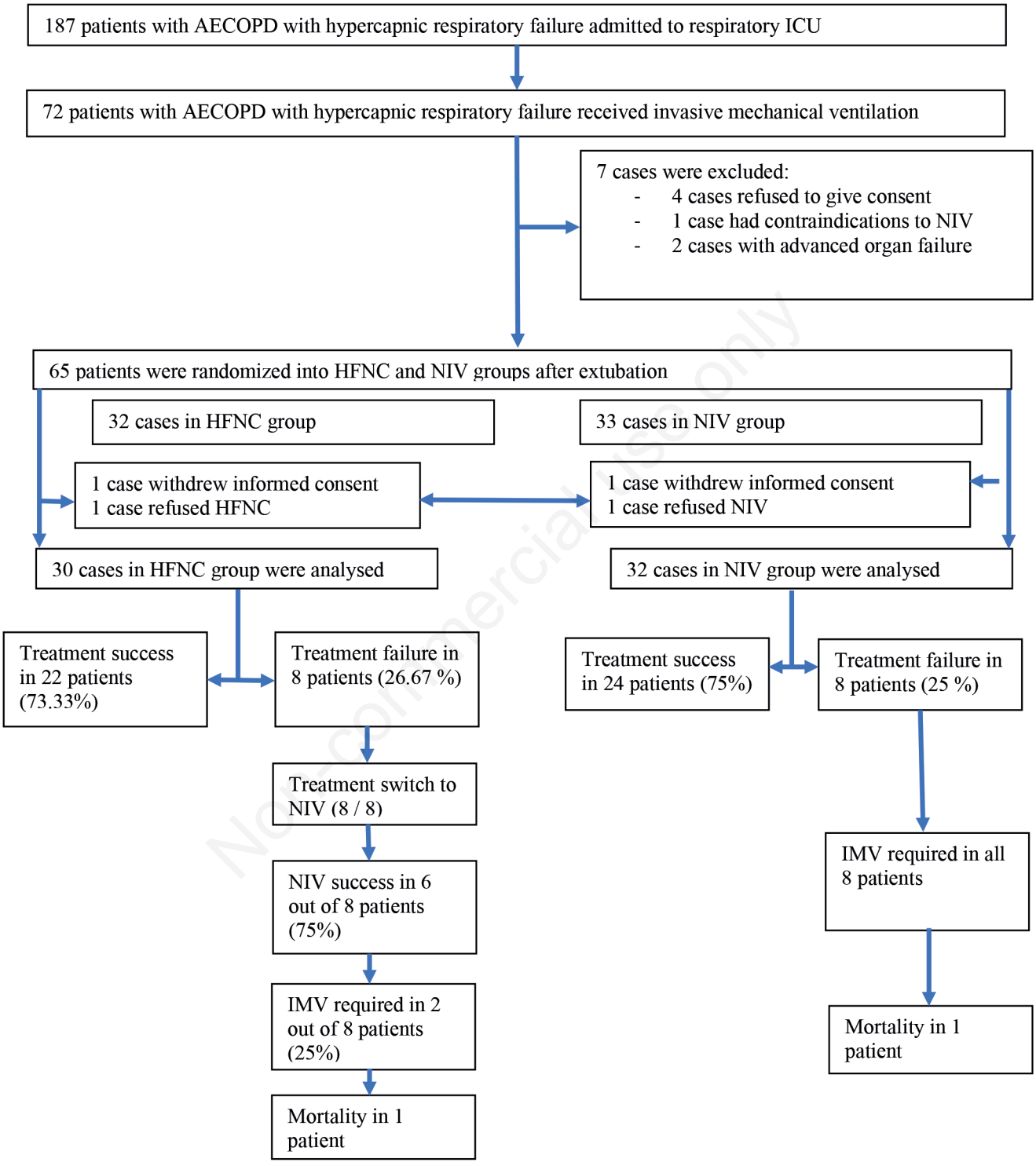

Figure 1. Patient enrolment flowchart of the study. ICU, intensive care unit; AECOPD, acute exacerbations of chronic obstructive pulmonary disease; HFNC, high-flow nasal cannula; NIV, non-invasive ventilation; IMV, invasive mechanical ventilation.

Primary outcome and cause analysis

Treatment failure occurred in 8 patients (26.67%) in the HFNC group and 8 patients in the NIV group (25%) (p=0.881). Of the 8 treatment failure patients in the HFNC group, 6 patients required a switch to NIV, and 2 patients required reintubation. Compared to the HFNC group, all 8 patients with treatment failure in the NIV group required reintubation. The proportion of patients who needed treatment switched to another modality was significantly higher in the HFNC group (p=0.007). Analysis of the cause of treatment failure showed that treatment intolerance was lower in the HFNC

Table 1. Characteristics of enrolled patients.

Characteristics	HFNC group (n=30)	NIV group (n=32)
Age (years)	65.3±7.79	65.38±9.76
Gender, n (%)		
Male	20 (66.67)	22 (68.75)
Female	10 (33.33)	10 (31.25)
Smoking history		
Current smoker, n (%)	14 (46.67)	16 (50)
Reformed smoker, n (%)	12 (40)	10 (31.25)
Non smoker, n (%)	4 (13.33)	6 (18.75)
Pack years	22.85±12.18	18.31±7.59
History of COPD		
Duration (years)	4.93±3.05	5.19±2.92
Group B, n (%)	6 (20)	6 (18.75)
Group C, n (%)	12 (40)	12 (37.50)
Group D, n (%)	12 (40)	14 (43.75)
APACHE II score at admission	17.87±4.73	18.62±3.92

HFNC, high-flow nasal cannula; NIV, non-invasive ventilation; COPD, chronic obstructive pulmonary disease; ‡independent *t*-test; †chi-square test; *Fisher's exact test; §Mann-Whitney test; data are shown as means ± standard deviation, number (%) patients.

Table 2. Comparison of weaning parameters before extubation.

Weaning parameters before extubation	HFNC group (n=30)	NIV group (n=32)	p
Pressure support (cm H_2O)	2.6±2.7	3.38±3.02	0.275§
PEEP (cm H_2O)	6.4±0.72	6.5±0.88	0.883§
Tidal volume (mL)	456.67±39.07	451.88±43.14	0.629§
Minute ventilation (L/min)	7.34±0.89	7.94±0.8	0.007‡
Respiratory rate (per min)	16.27±2.05	17.75±2.23	0.004§
RSBI	36.4±6.47	40.88±7.42	0.012§
Heart rate (per/min)	90.27±16.77	91.75±17.68	0.736‡
Mean arterial pressure (mmHG)	75.33±5.94	75.38±6.57	0.977§
pH	7.42±0.04	7.42±0.03	0.776§
$PaCO_2$ (mmHG)	48±7.91	47±4.81	0.296§
PaO_2 (mmHG)	70.4±11.77	65.69±11.29	0.194§
PaO_2/FiO_2	244.67±71.95	267.81±47.98	0.139‡

HFNC, high-flow nasal cannula; NIV, non-invasive ventilation; PEEP, positive end-expiratory pressure; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen; FiO_2, fraction of inspired oxygen; ‡independent *t*-test; §Mann-Whitney test; data are shown as means ± standard deviation, number (%) patients.

Table 3. Primary outcome and cause analysis.

	HFNC (n=30)	NIV (n=32)	p
Primary outcome, n (%)			
Treatment failure	8 (26.67)	8 (25)	0.881
Invasive ventilation	2 (25)	8 (100)	0.007*
Treatment switch	6 (75)	0 (0)	0.007*
Analysis of treatment failure, n (%)			
Aggravation of hypoxemia	2 (25)	0 (0)	
Carbon dioxide retention	4 (50)	3 (37.50)	0.292*
Treatment intolerance	2 (25)	5 (62.50)	

HFNC, high-flow nasal cannula; NIV, non-invasive ventilation; †chi-square test; *Fisher's exact test.

group; however, it was not statistically significant. The causes of treatment intolerance in the NIV group were claustrophobia (n=2), excessive pressure (n=1), headache (n=1), and skin breakdown over the nose (n=1). A total of 2 patients with treatment intolerance in the HFNC group were unable to tolerate the airflow (Table 3).

Secondary outcomes

The mean duration of ICU stay in the HFNC group was 5.47±2.26 days and 6.56±3.39 in the NIV group (p=0.376). The total mean duration of hospital stay post-extubation in the HFNC group and the NIV group was 7.87±2.9 days and 8.81±3.52 days, respectively. Heart rate within 72 hours was not significantly different from baseline in the HFNC group. In the NIV group, a statistically significant difference was seen at 72 hours as compared to baseline. Mean arterial pressure, respiratory rate, pH, and partial pressure of oxygen/FiO_2 showed statistically significant differences as compared to baseline values in both groups. There were no significant differences in the duration of post-extubation respiratory support required between the HFNC and NIV groups. 30-day mortality in the HFNC group was 3.33% (n=1), which was not significantly different from 3.12% (n=1) in the NIV group. The cause of mortality in the HFNC group was refractory septic shock. In the NIV group, the cause of mortality was sudden cardiac death.

Discussion

The current prospective, randomized comparative study demonstrated that HFNC was non-inferior to NIV in preventing post-extubation respiratory failure in patients with acute exacerbations of COPD with hypercapnic respiratory failure. However, the treatment switch to NIV was significantly higher in patients experiencing post-extubation respiratory failure in the HFNC group. Treatment failure in the HFNC group was attributed to aggravation of hypoxemia, carbon dioxide retention, and treatment intolerance. In comparison to patients in the HFNC group, a higher number of patients experienced treatment failure due to intolerance to NIV. HFNC appears to be an effective means of respiratory support for COPD patients extubated after severe hypercapnic respiratory failure.

A longer duration of invasive mechanical ventilation is associated with an increased incidence of ventilator-associated pneumonia and barotrauma and a longer duration of intensive care unit and hospital stays [7]. NIV has been shown to be as effective as invasive mechanical ventilation in reducing inspiratory effort by providing support to diaphragmatic muscle, counteracting auto-PEEP, and maintaining adequate gas exchange during the weaning phase in selected patients intubated and ventilated for hypercapnic acute respiratory failure [8]. Based on this physiological rationale, NIV has been utilized in these patients to speed up the weaning process and reduce the incidence of post-extubation respiratory failure [9-11]. Sequential use of NIV as a COPD weaning strategy has been recommended by the ERS/ATS guideline [4]. The duration of COPD and the age of the patient are important predictors of outcome in critically ill patients. In comparison to the study by Jing *et al*., the current study enrolled patients who had a lower mean age; thus, COPD was shorter in duration. This could be one of the reasons for the shorter duration of COPD in the present study. Failure to utilize NIV to prevent re-intubation was reported in 23-35% of patients due to poor compliance, patient discomfort, and NIV-related complications [6].

HFNC is often better tolerated than NIV, but data on COPD patients so far has been limited. As compared to NIV, the beneficial role of HFNC in terms of better comfort scores, no difference in 30-day mortality and intubation rate, and similar efficacy in the reduction of $PaCO_2$ were demonstrated in the literature [6,12,13]. A recent meta-analysis based on 8 studies concluded that the application of HFNC can be used as an alternative treatment for NIV after extubation in patients with acute exacerbations of COPD [14]. However, a limitation was that the majority of studies were from a single geographic region. To our knowledge, this is the first study in India to assess the non-inferiority of HFNC as compared to NIV to prevent respiratory failure post-extubation in patients with acute exacerbations of COPD.

In the present study, treatment failure occurred in 26.67% of patients in the HFNC group and 25% of patients in the NIV group. The results were similar to those of the study conducted by Tan *et al*. [6]. Our results also accord with those of Thille *et al.,* where the reintubation rate in the HFNC group was 27 % in patients with acute exacerbations of COPD [14].

Treatment intolerance was higher in the NIV group than in the HFNC group, suggesting that poor tolerance is an important reason for the failure of NIV treatment. The causes of treatment intolerance in the NIV group were claustrophobia, intolerance to pressure, headaches, and skin breakdown over the nose. A total of 2 patients with treatment intolerance in the HFNC group were unable to tolerate the airflow. Randomized control trials conducted by Tan *et al.* and Jing *et al.* in COPD patients post-extubation demonstrated statistically significant higher comfort scores with HFNC as compared to NIV [5,6].

The current study demonstrated that among patients with treatment failure, the proportion of patients who needed a switch in treatment modality was significantly higher in the HFNC group. Aggravation of hypoxemia and carbon dioxide retention were common causes of treatment failure. Of the 8 patients who required a switch of treatment modality after experiencing post-extubation respiratory failure in the HFNC group, 6 patients improved with NIV therapy, and 2 patients required reintubation. Thille *et al*. reported similar results in COPD patients who were treated with NIV alternating with HFNC post-extubation and had significantly lower reintubation rates of 13% as compared to 27% with HFNC alone [15]. The benefit of NIV could probably be explained by improved alveolar ventilation and a reduction in dynamic hyperinflation.

The respiratory rate in both groups of our study increased after extubation as compared to baseline. This may be related to the relatively lower intensity of respiratory support after extubation. Similar results were observed in an RCT conducted by Tan *et al.,* where a higher respiratory rate was reported in the NIV group at 24 hours [6]. As compared to the HFNC group, a slightly higher respiratory rate was reported at all points in the NIV group. This can be explained by the relatively poor tolerance of NIV. Both HFNC and NIV groups had similar ABG trends at all points in our study, a finding similar to the literature review [6,16].

An important limitation of our study is that it is a single center. Another limitation was that the primary endpoint of this study was a composite of reintubation rate and switch of treatment modality; the latter criterion added an element of physician subjectivity and bias. Thirdly, the settings for the HFNC gas flow in this study were based on each patient's tolerance level, which is subjective. Also, probably a high temperature of 37 degrees could have contributed to HFNC intolerance and discomfort [16]. The majority of patients did not have pulmonary function tests; therefore, we could not identify the relationship between the patient's pulmonary function status and the success of HFNC and NIV.

Conclusions

In the current study, HFNC was non-inferior to NIV in preventing post-extubation respiratory failure in COPD patients, while HFNC had better treatment tolerance. These findings support the use of HFNC in patients who are unable to tolerate NIV. Studies with a larger sample size are required for further assessing the role of HFNC in the post-extubation period in COPD patients with hypercapnic respiratory failure.

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Online supplementary material:

Supplementary Table 1. Parameters of high-flow nasal cannula and non-invasive ventilation.

Supplementary Table 2. Arterial blood gas analysis parameters.