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

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PSK, RK, NG, SC conceptualization, data extraction, investigation, methodology, project administration, analysis, validation, original draft; PI, NKG, MAJ analysis, investigation, methodology, data curation. All the authors read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work

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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 enrolment. This study was a single-centre, 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 NIV group using a computer-generated simple randomization chart. The 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). Of 72 patients, 62 patients were included in the study. Treatment failure occurred in 8 patients (26.67 %) in HFNC group and 8 patients in NIV group (25%) (p=0.881). The mean duration of ICU stay in HFNC group was 5.47±2.26 days and 6.56±3.39 in NIV group (p=0.376). 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.

Keywords: pulmonary disease, chronic obstructive; airway extubation; ventilator weaning; non-invasive ventilation.

Introduction

Approximately 16% of patients with an acute exacerbation of chronic obstructive pulmonary disease (COPD) need hospitalisation; of which 5% require invasive mechanical ventilation for acute life-threatening respiratory failure [1]. In patients of COPD 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 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 in utilizing 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 for preventing 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 FiO_2 between 0.21 to 1.0. Physiological studies have reported that delivering high flow decreases dead space, improves tidal volume, decreases respiratory rate, thereby promoting reduction in $PaCO_2$ 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 HFNC group [6]. Jing *et al*. also reported 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 high-flow nasal cannula versus non-invasive ventilation 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

A prospective, randomized, comparative study of patients admitted to the respiratory intensive care unit of Safdarjung Hospital (New Delhi, India) between June 2021 to September 2022. The 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 enrolment. Patients who were extubated were enrolled for the study. Exclusion criteria were COPD patients on long-term oxygen therapy, domiciliary non-invasive ventilation therapy; contraindication to NIV and HFNC, and lacking informed written consent.

Procedure

Patients were randomized into HFNC group and 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 PEEP was set at 4 cm H2O 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 H2O and was gradually increased to achieve a satisfactory tidal volume, respiratory rate and acceptable tolerance (tidal volume of nearly 6 mL/kg and respiratory rate less than 24 breaths/min were considered acceptable). FiO_2 was adjusted to maintain SpO_2 88-92%. Inspiratory pressures were adjusted to achieve acceptable arterial blood gas values and respiratory rate ≤28/min. Patients received conventional oxygen therapy when off NIV to maintain SpO_2 88-92%.

HFNC was applied immediately after extubation to subjects who were randomized to HFNC group. Size of nasal cannula was chosen based on the patient's nostrils (<50% of nostril diameter). HFNC humidifier temperature was set at 37 degrees. FiO_2 was adjusted to maintain SpO_2 88-92%. Airflow was initially set at 15 L/min and was titrated upwards in 5 L/min and adjusted as per the patient's tolerance. The patient's initial respiratory support was given for initial 24 hours and then continued as needed. NIV or HFNC were discontinued when the total daily treatment duration was less than 4 h. Vitals and ABG were monitored for 72 h 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 / unable to tolerate NIV or HFNC, pH <7.20, altered mental status, increased work of breathing, cardiac arrest, arrhythmia, hemodynamic instability, persistent inability to remove respiratory secretions.

Outcomes

The primary outcome was treatment failure within 72 h after extubation. Secondary outcomes included the length of hospital stay after extubation, vitals and arterial blood

gas trends within 1, 24 and 72 h after extubation and proportion of patients on high flow nasal cannula requiring a switch to non-invasive ventilation.

Sample size and statistical analysis

Based on previous study [6], using incidence post-extubation respiratory failure of 22%, with z-statistics for 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 percentage. The quantitative data were presented as the means ± SD and as median with 25^{th} and 75^{th} percentiles (interquartile range). The data normality was checked by using Kolmogorov-Smirnov test. The cases in which the data was not normal, non-parametric tests were used. The comparison of variables was analysed using 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 the Microsoft EXCEL spreadsheet and the final analysis was done with the use of Statistical Package for Social Sciences [SPSS] software, IBM manufacturer, Chicago, USA, version 25.0. For statistical significance, 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 APACHE II scores were comparable between HFNC and NIV group (Table 1). No significant difference was seen in weaning parameters, vitals and arterial blood gas values prior to extubation. Although a statistically significant difference was seen in respiratory rate and RSBI between HFNC and NIV groups; these results did not hold significant clinical relevance as the observed values were inacceptable range (Table 2). The mean flow rate reached during titration with HFNC was 43.66 +/- 11.36 L/min.

Primary outcome and cause analysis

Treatment failure occurred in 8 patients (26.67%) in HFNC group and 8 patients in NIV group (25%) (p=0.881). Of 8 treatment failure patients in HFNC group, 6 patients required switch to NIV and 2 patients required reintubation. Compared to HFNC group, all 8 patients with treatment failure in NIV group required reintubation. Proportion of patients who needed treatment switch to other modality was significantly higher in HFNC group (p value=0.007). Analysis of cause of treatment failure showed that treatment intolerance was lower in HFNC group, however not statistically significant. The causes for treatment intolerance in NIV group were claustrophobia (n=2), excessive pressure (n=1), headache (n=1), skin breakdown over the nose (n=1). Two patients with treatment intolerance in HFNC group were unable to tolerate the airflow (Table 3).

Secondary outcomes

The mean duration of ICU stay in HFNC group was 5.47±2.26 days and 6.56±3.39 in NIV group (p=0.376). The total mean duration of hospital stay post-extubation in HFNC group and NIV group were 7.87±2.9 days and 8.81±3.52 days, respectively. Heart rate within 72 hours was not significantly different from baseline in HFNC group. In NIV group, statistically significant difference was seen at 72 h as compared to baseline. Mean arterial pressure, Respiratory rate, pH, PaO_2/FiO_2 showed statistically significant difference as compared to baseline values in both groups. There were no significant differences in the duration of post-extubation respiratory support required between HFNC and NIV groups. 30-day mortality in HFNC group was 3.33% (n=1), which was not significantly different from 3.12% (n=1) in NIV group. Cause of mortality in HFNC group was refractory septic shock. In NIV group, 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 AECOPD patients with hypercapnic respiratory failure. However, treatment switch to NIV was significantly higher in patients experiencing post extubation respiratory failure in HFNC group. Treatment failure in HFNC group was attributed to aggravation of hypoxemia, carbon dioxide retention and treatment intolerance. In comparison to patients in HFNC group, 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.

Longer duration of invasive mechanical ventilation is associated with increased incidence of ventilator-associated pneumonia, barotrauma and longer duration of ICU and hospital stay [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 ARF [8]. Based on this physiological rationale, NIV has been utilised in these patients as a means 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 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 in utilizing 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, 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 $PaCO_2$ was 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 AECOPD patients [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 AECOPD patients.

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

Treatment intolerance was higher in NIV group than in HFNC group, suggesting that poor tolerance is an important reason for the failure of NIV treatment. The causes for treatment intolerance in NIV group were claustrophobia, intolerance to pressure, headache, skin breakdown over the nose. Two patients with treatment intolerance in 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 [6,15].

The current study demonstrated that among patients with treatment failure, proportion of patients who needed a switch of treatment modality was significantly higher in HFNC group. Aggravation of hypoxemia and carbon dioxide retention were common causes for treatment failure. Of the 8 patients who required a switch of treatment modality after experiencing post-extubation respiratory failure in 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 had significantly lower reintubation rates of 13 % as compared to 27 % with HFNC alone [16]. The benefit of NIV could probably be explained by improved alveolar ventilation and reduction in dynamic hyperinflation.

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 h [6]. As compared to HFNC group, a slightly higher respiratory rate was reported at all points in 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 [6,17].

An important limitation of our study is being a single centre. 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 high temperature of 37 degrees could have contributed to HFNC intolerance and discomfort [17]. 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 larger sample size are required for further assessing the role of HFNC in post-extubation period in COPD patients with hypercapnic respiratory failure.

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Figure 1. Patient enrolment flowchart of the study

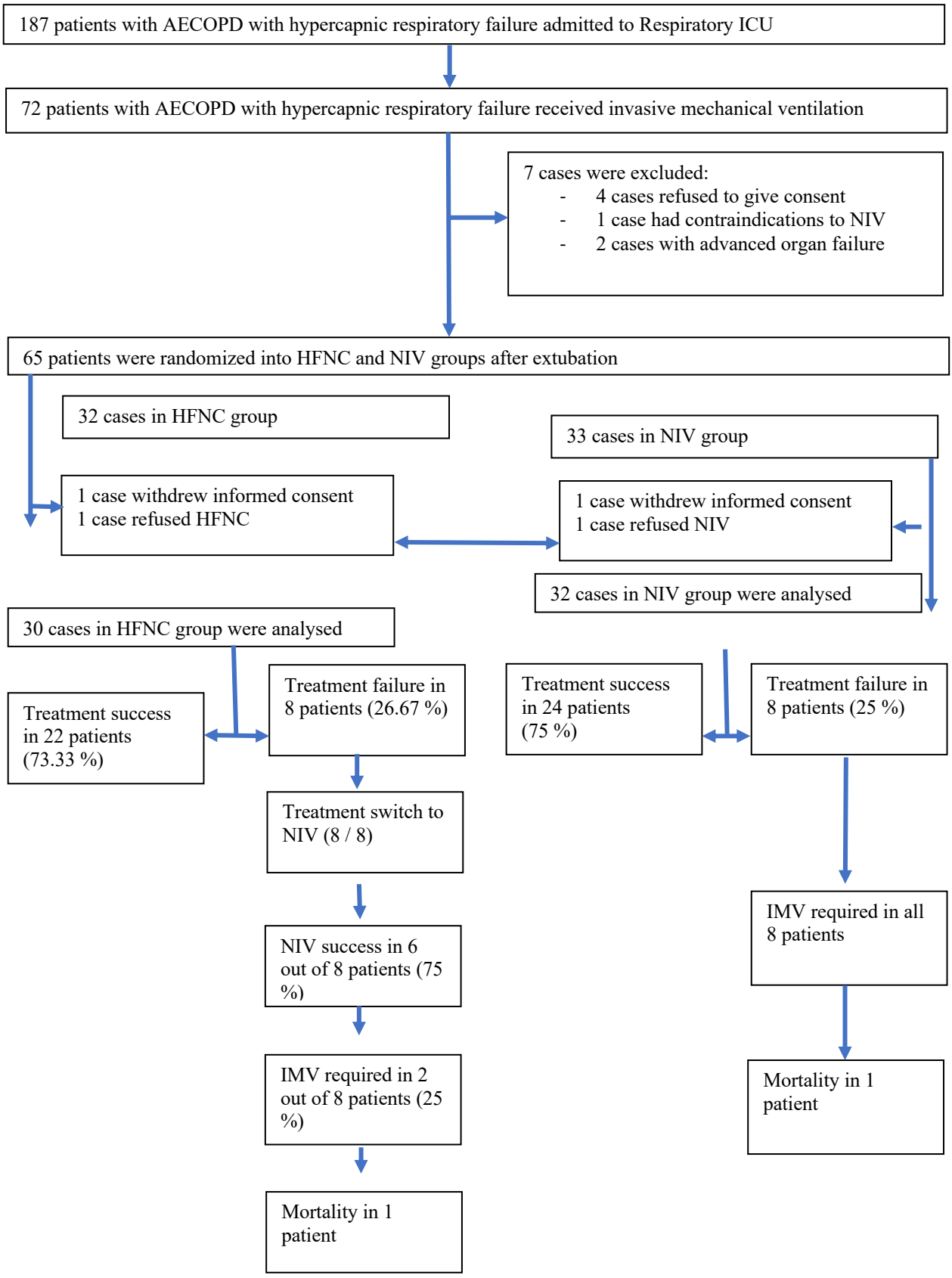

Table 1. Characteristics of enrolled patients

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, n (%)		
- Current smoker	14 (46.67%)	16 (50%)
- Reformed smoker	12 (40%)	10 (31.25%)
- Non smoker	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	6 (20%)	6 (18.75%)
- Group C	12 (40%)	12 (37.50%)
- Group D	12 (40%)	14 (43.75%)
APACHE II score at admission	17.87 ± 4.73	18.62 ± 3.92

‡ 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-value
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§
PaCO2 (mmHG)	48 ± 7.91	47 ± 4.81	0.296§
PaO2 (mmHG)	70.4 ± 11.77	65.69 ± 11.29	0.194§
PaO2 / FiO2	244.67 ± 71.95	267.81 ± 47.98	0.139‡

‡ 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-value
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%)	

† Chi square test, * Fisher's exact test