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High-Flow Nasal Cannula Therapy for Acute Hypoxemic Respiratory Failure in Adults: A Retrospective Analysis

Woo Hyun Cho[1], Hye Ju Yeo[1], Seong Hoon Yoon[1], SeungEun Lee[1], Doo SooJeon[1], Yun Seong Kim[1], Ki Uk Kim[2], Kwangha Lee[2], Hye Kyung Park[2] and Min Ki Lee[2]

Abstract

Objective High-flow nasal cannula (HFNC) therapy is an oxygen delivery system. However, evidence regarding the clinical applications of HFNC is still emerging. We herein evaluated the clinical predictors of HFNC therapy success for adult patients with acute hypoxemic respiratory failure.

Methods We retrospectively reviewed the medical records of the subjects with acute hypoxemic respiratory failure supported by HFNC therapy in the medical intensive care unit between July 2011 and March 2013. Therapy success was defined as the avoidance of intubation. The patients' baseline characteristics and the serial changes in the respiratory parameters after HFNC therapy at 1 and 24 hours were measured.

Results Of the 75 eligible patients, 62.7% successfully avoided intubation. Overall, HFNC therapy significantly improved the physiologic parameters, such as partial pressure of arterial oxygen (PaO_2), saturation of arterial oxygen (SaO_2), respiratory rate (RR), and heart rate (HR), throughout the first 24 hours. After the adjustment for the other clinical variables, Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA), cardiogenic pulmonary edema, and PaO_2 improvement at 1 and 24 hours were associated with therapy success. The overall intensive care unit (ICU) mortality was 25.3%. However, out of 37.3% of the patients who required intubation, the ICU mortality in this proportion of patients was 67.9%. The ICU mortality in the therapy failure group was associated with the use of a vasopressor and a limited PaO_2 improvement at 1 hour.

Conclusion HFNC therapy showed a good compliance and the improvement of the physiologic parameters in an adult population. The failure to improve oxygenation within 24 hours was a useful predictor of intubation. Among the failure group, the vasopressor use and failed oxygenation improvement were associated with ICU mortality.

Key words: oxygen therapy, high-flow nasal cannula, respiratory failure, hypoxemia, intubation

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Introduction

Oxygen therapy is a mainstay in the first-line therapy for acute hypoxemic respiratory failure (1). Historically, a collection of various conventional oxygen devices, such as nasal prongs and oxygen masks, have been used to deliver oxygen. However, there are some limitations associated with these noninvasive devices. First, the volume of the delivered inspiratory flow and the fraction of the inspired oxygen concentration (FiO_2) do not sufficiently meet the respiratory demand of these severely distressed patients (2). Furthermore, it is difficult to deliver a constant FiO_2 if a patient's inspiratory demand exceeds that of the delivered oxygen flow. To overcome these limitations, high-flow nasal cannula (HFNC), which can deliver up to 100% humidified and heated, blended gas at flow rates of up to 60 L/min into the nares, was developed (3). The efficacy of HFNC for acute hypoxemic respiratory failure has been proven in the neonatal and pediatric fields (4-7). The application of HFNC is

[1]Department of Internal Medicine, Pusan National University Yangsan Hospital, Korea and [2]Department of Internal Medicine, Pusan National University Hospital, Pusan National University School of Medicine, Korea
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Correspondence to Dr. Yun Seong Kim, yskim@pusan.ac.kr

now expanding within the adult population (8-12). Therefore, in this study, we explore the clinical indicators associated with the success of HFNC therapy, as indicated by the avoidance of intubation in the adult patients with acute hypoxemic respiratory failure.

Materials and Methods

This study was approved by the Institutional Review Board and Ethics Committee of the Research Institute for Convergence of Biomedical Science and Technology of Pusan National University Yangsan Hospital.

Study population

We retrospectively collected data from the patients with acute hypoxemic respiratory failure who had consecutively received HFNC therapy in the medical intensive care unit (ICU) of Pusan National University Yangsan Hospital, Korea between July 2011 and March 2013. HFNC therapy was indicated if a patient was hypoxic [partial pressure of arterial oxygen (PaO_2)/FiO_2 (PF ratio) <300] or tachypneic [respiratory rate (RR) >24] despite the use of conventional oxygen therapy, such as an oxygen mask with a reservoir bag (oxygen flow above 8 L/min). The patients younger than 18 years of age, those with hypercapneic respiratory failure (pH <7.2 and partial pressure of carbon dioxide in arterial blood ($PaCO_2$) >45 mmHg), and those with do-not-resuscitate (DNR) orders were excluded from this study.

Study protocol

This retrospective study included patients with acute hypoxemic respiratory failure who received HFNC therapy according to a predefined clinical therapy protocol. The therapy protocol was as follows. First, we initiated HFNC therapy according to the predefined guidelines and recorded the baseline variables, including the respiratory rate (RR), heart rate (HR), blood pressure (BP), and arterial blood gases (ABGs) before the implementation of HFNC therapy. We delivered blended gases at an initial flow rate of 30-40 L/min and FiO_2 of 40-100% using a HFNC device (Optiflow, Fisher & Paykel, Auckland, New Zealand). The primary therapeutic goal was to maintain a percutaneous oxygen saturation (SpO_2) level of over 92% or a PaO_2 level of over 65 mmHg. The flow rate of the air-oxygen mixture, as well as the FiO_2, was titrated according to the patient's requirement and tolerance levels. ABGs were analyzed at 1and 24 hours after therapy initiation and at the end of therapy. We defined therapeutic success as the avoidance of intubation and subsequent weaning from HFNC. Weaning from HFNC was defined as the maintenance of a SpO_2 level of over 92% or a PaO_2 level of over 65 mmHg without any indication for HFNC. In order to intubate the patients, an attending physician's decision was followed, which was based on a generalized intubation criterion, such as the failure of airway maintenance or failure to maintain an SpO_2 level of over 90% or a PaO_2 level of over 60 mmHg under HFNC at a flow rate of above 50 L/min and 100% FiO_2. Any adverse events or episodes of intolerance were reviewed from the daily medical records. Intolerance was defined when a patient (with a normal mental status and no signs of delirium) insisted on withdrawal from HFNC therapy. An adverse event was defined as a hazardous event requiring the interruption of HFNC therapy, such as aspiration or epistaxis.

Variable measurement

The following baseline data were retrospectively collected: age, gender, the body mass index (BMI), causes of respiratory failure, the Sequential Organ Failure Assessment (SOFA), and the Acute Physiology and Chronic Health Evaluation II (APACHE II) score. Physiological parameters, including the arterial gas profile, vital signs, delivered oxygen concentration, and the rate of gas delivered (L/min), were also recorded at baseline and at 1 and 24 hours after therapy initiation. The following outcome variables were assessed: therapeutic success, adverse or intolerant events, ICU survival, and ICU stay after HFNC implementation.

Statistical analysis

All statistical analyses were performed using the SPSS 21.0 software program (SPSS, Chicago, USA). Continuous variables were expressed as the means ± standard deviation (SD). Categorical variables were presented as the frequency (n) and percentage (%). In all analyses, a p value of <0.05 was considered to be statistically significant. To evaluate the predictors of therapeutic success, a binary logistic regression analysis was performed. The Hosmer-Lemeshow test was performed to assess the goodness of fit for the logistic regression model. A Cox proportional hazards regression analysis was conducted to evaluate the predictors of ICU mortality in the therapeutic failure group. The potential predictors were evaluated using a univariate analysis. For variables with a p value below 0.05, a multivariate analysis was conducted. The backward (likelihood ratio) stepwise method was used for the multivariate analyses, with entry and removal p values set at 0.05.

Results

Baseline characteristics

From July 2011 to March 2013, 212 subjects were treated with HFNC, and 75 patients met the inclusion criteria for this study (Figure). Of the 212 patients, 137 were excluded according to the predefined exclusion criteria.

The baseline demographics of the patients are shown in Table 1. The mean age of the patients was 64.5±12.4 years, 70.7% were men, and the mean duration of HFNC therapy was 4.72±3.83 days. The proportion of patients with underlying disease was not significantly different between the success and failure groups (p=0.469). The most common cause of respiratory failure was pneumonia (36%), followed by post-extubation respiratory failure (30.7%). The baseline

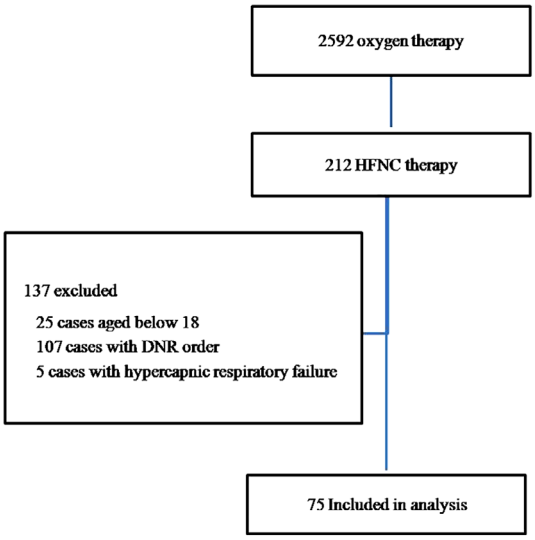

Figure. Flow diagram for the patient recruitment in this study.

parameters, including Glasgow come scale (GCS), the SOFA, and APACHE II scores were significantly lower (p= 0.022, 0.002, and 0.003, respectively) in the failure group than in the success group. Vasopressors were used more frequently in the therapeutic failure group (p=0.022). The overall success and ICU mortality rates were 62.7% and 25.3%, respectively. However, the ICU mortality rate was 67.9% in the patients who required intubation.

Changes in the respiratory parameters after HFNC therapy

There was no difference in the baseline respiratory parameters, including ABGs and RR, between the success and failure groups (Table 1). Serial changes in the respiratory and physiological data after HFNC are shown in Table 2. HFNC therapy significantly improved parameters such as PaO_2, SaO_2, RR, and HR throughout the first 24 hours (Table 2). However, these improvements were not observed in the failure group. An early improvement in the respiratory parameters, such as PaO_2, RR, and HR, at 1 and 24 hours was more frequently observed in the success group. The PaO_2 improvement at 1and 24 hours was observed in 70.2% (33/47) and 63.8% (30/47) of the patients, respectively, in the success group and in 39.3% (11/28) and 28.6% (8/28) of the patients, respectively, in the failure group (p=0.009 and 0.003, respectively). The RR improvement at 1 and 24 hours was observed in 66.0% (31/47) and 85.1% (40/47) of the patients in the success group and in 64.3% (18/28) and 64.3% (18/28) of the patients in the failure group (p=0.883 and 0.037, respectively).

Clinical outcomes of HFNC and the predictors of therapeutic success

A univariate analysis revealed that therapeutic success was associated with low baseline APACHE II scores, the SOFA, and PaO_2 improvement at both 1 and 24 hours, and RR improvement at 24 hours. All these variables were included in a binary logistic regression analysis model. According to a multivariate analysis, low APACHE II and SOFA scores, cardiogenic pulmonary edema as a cause of respiratory failure, and PaO_2 improvement at 1 and 24 hours were independently associated with therapeutic success (Table 3).

In regards to the baseline characteristics, the cause of respiratory failure, the APACHE II scores, and the SOFA were significant predictors of therapeutic success (Table 3). The success rates were 60.0%, 59.3%, and 56.5% for the patients with extrapulmonary acute respiratory distress syndrome (ARDS), pneumonia, and postextubation respiratory failure, respectively. In the patients with cardiogenic pulmonary edema, the success rate was 81.3%, which was significantly higher than that in the patients with other conditions [odds ratio (OR), 13.33; 95% confidence interval (CI), 1.746-101.822, p=0.013]. The APACHE II and SOFA scores were significantly lower in the success group than in the failure group (Table 1).

On the basis of the response to therapy, the success rates were 75% and 78.9% in the patients with PaO_2 improvement at 1 and 24 hours, respectively. However, the success rates for nonresponders at 1 and 24 hours were 45.2% and 45.9%, respectively. The PaO_2 improvement at 1 and 24 hours was independently associated with a higher success rate (Table 3). The RR improvement at 24 hours was significantly associated with therapeutic success in the univariate analysis, but not in the multivariate model. The success rate was 69.0% in the patients with RR improvement at 24 hours; however, it was only 41.2% in nonresponders (OR, 3.175; 95% CI, 1.041-9.677, p=0.042 in the univariate analysis).

The overall ICU mortality rate was 25.3%, while that in the failure group was 67.9%. We evaluated the factors associated with the ICU mortality in the failure group. The univariate analysis revealed a lower APACHE II score, pneumonia as the primary cause of failure, vasopressor use, and limited PaO_2 improvement at 1 hour as significant predictors. All these variables were entered in a Cox proportional hazard model, which revealed that the ICU mortality was independently associated with the vasopressor use and limited PaO_2 improvement at 1 hour (Table 4).

Adverse events, compliance rate, and cause of intubation

No adverse events or episodes of intolerance with HFNC therapy were recorded. Overall, an exacerbation of symptoms caused by hypoxia (14/28) was the most common cause of intubation, followed by an altered mental state (10/28) and the inadequate clearance of secretions (4/28). In postextubation respiratory failure, the causes of intubation were an altered mentality (5/10), inadequate clearance of secretions (3/10), and hypoxia (2/10).

Table 1. Patient Characteristics.

	Total (n=75)	Success(n=47)	Fail (n=28)	p value
Age (years)	64.5±12.4	65.2±11.1	63.3±14.3	0.522
Sex, No of male(%)	53(70.7)	35(74.5%)	18(64.3%)	0.349
BMI	22.6±5.2	22.2±5.1	23.4±5.4	0.383
Cause of respiratory failure, No(%)				0.469
Pneumonia	27(36.0)	16(34.0)	11(39.3)	
Post-extubation respiratory failure	23(30.7)	13(27.7)	10(35.7)	
Cardiogenic pulmonary edema	16(21.3)	13(27.7)	3(10.7)	
Extrapulmonary ARDS	5(6.7)	3(6.4)	2(7.1)	
Acute exacerbation of COPD	3(4.0)	2(4.3)	1(3.6)	
Acute exacerbation of DILD	1(1.3)	0(0.0)	1(3.6)	
Baseline respiratory parameters				
FiO_2	0.68±0.19	0.66±0.19	0.70±0.19	0.806
PaO_2 (mmHg)	78.9±29.0	78.5±33.1	79.5±21.1	0.890
HCO_3 (mEq/L)	20.4±5.1	20.4±4.8	20.4±5.7	0.995
PCO_2 (mmHg)	30.5±9.6	30.9±9.2	30.0±10.4	0.709
Ph	7.43±0.08	7.43±0.06	7.43±0.10	0.799
Respiratory rate (bpm)	28.5±5.9	29.0±5.1	27.6±7.2	0.357
GCS	14.1±1.4	14.4±0.9	13.6±1.9	0.022
SOFA score	5.6±3.5	4.6±2.4	7.4±4.3	0.002
APACHE II score	10.3±4.9	8.9±3.8	12.6±5.7	0.003
HFNC duration (days)	4.7±3.8	5.0±3.0	4.25±5.0	0.472
ICU stay after HFNC (days)	10.8±11.1	6.7±5.0	17.7±14.6	0.001
Hemodynamic parameters				
Mean arterial pressure (mmHg)	87.9±15.7	87.7±14.8	88.4±17.6	0.859
Pulse rate (bpm)	108.2±20.2	108.6±19.7	107.5±21.3	0.823
Use of vasopressor, No(%)	10(13.7)	3(30.0)	7(70.0)	0.022
ICU mortality, No(%)	19(25.3)	0(0.0)	19(67.9)	<0.001

Values given as mean ± standard deviation

ARDS: Acute Respiratory Distress Syndrome, DILD: Diffuse Interstitial Lung Disease, GCS: Glasgow Coma Scale, SOFA: Sequential Organ Failure Assessment, APACHE: Acute Physiology and Chronic Health Evaluation, MV: Mechanical Ventilation, HFNC: high-flow nasal cannulae, ICU: Intensive Care Unit

Initial respiratory parameters are defined as following: FiO_2 (Fraction of Inspired O_2), arterial blood gas profile and respiration rate per minute.

Table 2. Serial Changes in Respiratory Parameters after HFNC Therapy.

	All patients			Success group			Failure group		
	baseline	at 1h	at 24h	baseline	at 1h	at 24h	baseline	at 1h	at 24h
PaO_2	78.9±29.0	**105.7±45.6	**105.3±34.6	78.5±33.1	**111.4±45.4	**107.9±33.4	79.5±21.1	93.5±44.7	96.7±38.4
$PaCO_2$	30.5±9.6	30.8±10.0	31.6±12.0	30.9±9.2	31.0±10.1	31.6±13.1	30.0±10.4	30.3±10.1	31.7±8.1
pH	7.43±0.08	7.44±0.09	7.46±0.05	7.43±0.06	7.44±0.06	7.46±0.05	7.43±0.10	7.43±0.13	7.46±0.06
HCO_3^-	20.4±5.1	20.9±5.2	21.6±4.6	20.4±4.8	21.1±5.0	21.6±4.6	20.4±5.7	20.5±5.8	22.5±4.6
SaO_2	93.4±5.0	**96.4±4.3	**97.2±2.9	92.4±5.5	**97.0±3.6	**97.6±2.0	95.2±3.5	95.1±5.5	95.9±4.6
RR	28.5±5.9	**25.5±5.9	**23.1±5.9	29.0±5.1	**25.7±5.3	**22.8±6.3	27.6±7.2	25.1±6.7	24.1±4.9
HR	108.2±20.2	*102.9±21.9	**95.2±18.5	108.6±19.7	*102.5±19.5	**92.8±16.8	107.5±21.3	103.5±26.0	101.8±21.5

Values given as mean ± standard deviation

RR: Respiration Rate, HR: Heart rate

$^{*}p<0.05$, $^{**}p<0.01$: significant change from baseline values

Discussion

The present study demonstrated that HFNC therapy was well tolerated and useful for early oxygenation during acute hypoxemic respiratory failure. Successful therapy was independently associated with a low APACHE II and SOFA score, cardiogenic pulmonary edema as a cause of respiratory failure, and PaO_2 improvement at 1 and 24 hours. However, in the failure group, the patients requiring vasopressors or those without PaO_2 improvement at 1 hour were associated with a higher ICU mortality rate.

Previously, HFNC was developed for and evaluated in a neonatal population (4-7). In some reports, HFNC improved the respiratory physiological parameters and was well tolerated in adults (8, 9, 13). Two prospective observational studies described an early physiological benefit, relief from respiratory distress, and good tolerance in the patients with acute hypoxemic respiratory failure treated by HFNC (10, 11).

In the present study, we administered HFNC therapy in an adult population with acute hypoxemic respiratory failure.

Table 3. Clinical Predictors Associated with Treatment Success.

	Univariate analysis		Multivariate analysis	
	OR (95% C.I.)	p	OR (95% C.I.)	p
APACHE II score	0.84 (0.74-0.94)	0.003	0.82 (0.69-0.97)	0.019
SOFA score	0.77 (0.65-0.97)	0.002	0.70 (0.54-0.91)	0.007
Cardiogenic pulmonary edema	3.19 (0.82-12.38)	0.094	13.3 (1.75-101.82)	0.013
PaO_2 improvement at 1h	3.64 (1.36-9.73)	0.010	5.59 (1.07-29.25)	0.042
PaO_2 improvement at 24h	4.41 (1.60-12.15)	0.004	5.36 (1.12-25.61)	0.035

Hosmer-Lemeshow test (Chi-square = 6.372, df = 8, p=0.606)
OR: odds ratio, CI: confidence interval

Table 4. Factors Associated with Intensive Care Unit Mortality in the Treatment Failure Group.

	No.	Unadjusted HR		Adjusted HR	
	Death/Total (%)	HR (95% CI)	p	HR (95% CI)	p
APACHE II score		1.12 (1.01–1.25)	0.030	1.07 (0.96–1.17)	0.235
Cause of respiratory failure					
Other causes	9/17 (52.9)	1			
Pneumonia	10/11 (90.9)	3.85 (1.43–10.38)	0.008	1.78 (0.61–5.21)	0.296
Vasopressor					
Not used	13/21 (61.9)	1			
Used	6/7 (85.7)	5.55 (1.81–17.02)	0.003	4.22 (1.24–14.37)	0.021
PaO_2 improvement at 1 h					
No	14/17 (82.4)	3.90 (1.27–11.98)	0.017	3.379 (1.04–11.02)	0.043
Yes	5/11 (45.5)	1			

HR: hazard ratio, CI: confidence interval, APACHE II: Acute Physiology and Chronic Health Evaluation II

HFNC was well tolerated and improved the early physiologic parameters, including PaO_2, RR, and HR, for acute hypoxemic respiratory failure (Table 2). Overall, the success rate of HFNC (62.7%) in the present study was comparable with the outcomes of two previous prospective studies (10, 11).

In particular, the success rate was more apparent in the patients with cardiogenic pulmonary edema (81.4%) than in those with other causes of respiratory failure. We hypothesized the following reasons for this finding. First, HFNC provides a dynamic level of positive end-expiratory pressure (PEEP) (14, 15), resulting in a positive effect on the heart function (16). Second, cardiogenic pulmonary edema is effectively treated with continuous positive airway pressure (CPAP) using noninvasive ventilation (NIV) (17-21). NIV is a good treatment modality for cardiogenic pulmonary edema. However, there are conflicting evidences regarding the impact of NIV on the mortality in the patients with acute cardiogenic pulmonary edema (20, 21) Specifically, the mortality benefits from bilevel positive airway pressure (BiPAP) were not significant even though the need for intubation was reduced. HFNC suggests a modest level of PEEP (3-4 cmH_2O) similar to the CPAP mode. Thus, the patients who were refractory to HFNC therapy were considered as potentially unresponsive to NIV. Consequently, we did not apply NIV for rescue therapy in the failure group.

In the patients with postextubation respiratory failure, the success rate was 56.5%. The reintubation rate in the present study was inferior to the generally acceptable standard, which ranges from 13% to 19% (22-25). However, the present study included the subjects with postextubation respiratory failure after an unplanned extubation. Reintubation is generally required in approximately 50% of the patients with unplanned extubation (26, 27).

In the present study, HFNC success was independently associated with the baseline disease severity and early PaO_2 improvement (Table 3). The PaO_2 improvement at 1and 24 hours was a significant (p= 0.042 and 0.035, respectively) predictor of therapeutic success. However, the baseline PaO_2 did not differ between the groups (78.5±33.1 vs. 79.5±21.1, p=0.877), suggesting that therapeutic success may be dependent on the early response to therapy, not on the baseline degree of hypoxemia. Therefore, HFNC may prove to be the best bridge therapy for acute hypoxemic respiratory failure if the patient's oxygenation immediately improves. However, if PaO_2 improvement at 1 and 24 hours is not evident, timely intubation may be considered because therapeutic failure was associated with a high mortality rate. The findings from the present study suggest that the ICU mortality in the failure group was much lower in early responders than in nonresponders (Table 4). This result was also consistent with the findings in previous studies on the use of NIV (28-31), suggesting that the prognosis may be worse for the patients who are ultimately intubated and ventilated secondary to a failed NIV attempt. In a recent observational study, intubation was performed for a median of 4 hours, and 35 of 38 patients in the failure group survived (11). However, in the present study, the mean duration of HFNC therapy in the failure group was 4.91 days. Therefore, our results suggest an important lesson regarding HFNC therapy.

Timely intubation should be considered if the patients do not show early improvements in oxygenation.

Our data also suggests that the use of vasopressors was inversely correlated with ICU survival in the failure group. Rello J et al. showed that the vasopressor use was a significant predictor of HFNC failure (8). Therefore, the patients requiring vasopressors were cautiously monitored.

There were several limitations associated with the present study, with the retrospective design being the primary limitation. In addition, we excluded postoperative patients, those with a DNR order, and those younger than 18 years of age. In reality, HFNC may be applied to both postoperative patients and patients with a DNR order due to its noninvasiveness and ease of use. However, because one of the aims of the present study was to evaluate the clinical benefits and outcome predictors of HFNC in terms of ICU survival, we excluded the patients with a DNR order. Our retrospective cohort included patients admitted to the medical ICU. Therefore, we could not evaluate those with postoperative respiratory failure. In addition, minor complications or temporary intolerance were possibly overlooked. However, no complication warranting the interruption of HFNC therapy was recorded. There were no standard criteria for intubation; therefore, the decision to intubate was dependent on the attending physician. Although we followed the general intubation guidelines focusing on oxygenation or the mental status, these guidelines do not guarantee success because the degree of patients' respiratory distress may be underestimated, leading to delayed intubation and poor outcomes. Therefore, our results should be interpreted with caution.

Conclusion

This study demonstrated that HFNC may be a bridge therapy for the patients with acute hypoxemic respiratory failure, particularly those with cardiogenic pulmonary edema. An early improvement in oxygenation was a useful predictor of success. However, early intubation should be considered for initially unresponsive patients. A well-designed, randomized trial is required to confirm the results derived from this retrospective study.

The authors state that they have no Conflict of Interest (COI).

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