ORIGINAL ARTICLE

A Retrospective Study on Experience of High-flow Nasal Cannula Oxygen in Critically Ill COVID-19 Adult Patients Admitted to Intensive Care Unit

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Abstract

Background: The use of high-flow nasal cannula (HFNC) in coronavirus disease-2019 (COVID-19) patients is debated due to its uncertain benefits and risks of aerosol dispersion. This retrospective study was aimed to assess the outcome of treatment with HFNC therapy in adult COVID-19 patients with acute hypoxemic respiratory failure (AHRF) admitted in intensive care units (ICU) and to assess the factors affecting outcome.

Material and methods: We retrieved electronic medical records of all COVID-19 patients who received HFNC for respiratory support after failure to maintain adequate oxygenation with conventional oxygen devices, between June 1 and August 31, 2020. The data retrieved were statistically analyzed.

Results: A total number of 558 COVID-19 patients were admitted to ICUs, out of which 139 patients were identified to be on HFNC and 85 met the inclusion criteria for the study. The success rate of 48.2% with HFNC was observed in these patients. The patients recorded to experience HFNC success were of young age and having higher baseline oxygen saturation compared to those who had its failure. The ROX indices post-initiation were observed to be significantly higher in the success group ($p \leq 0.001$). Awake-prone positioning while receiving HFNC was followed by around more patients in the success group ($p < 0.001$). On multivariate logistic regression analysis, baseline oxygen saturation, awake-prone positioning, and number of days on HFNC were found to be independently affected outcome with HFNC.

Conclusion: Almost half of the cases of moderate-to-severe COVID-19 pneumonia can be managed successfully with HFNC, without the need of mechanical ventilation.

Keywords: Acute hypoxemic respiratory failure (AHRF), COVID-19, High-flow nasal cannula (HFNC) oxygen therapy, Intensive care unit.

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Introduction

The coronavirus disease-2019 (COVID-19) pandemic has strained the healthcare systems globally.[1,2] The high infectivity and predominant involvement of the lungs by the causative virus have resulted in a large number of patients experiencing acute hypoxemic respiratory failure (AHRF). Oxygen therapy and supportive care are the mainstay treatment for COVID-19 pneumonia as none of the antiviral therapies have been proven efficacious so far.[3–5]

High-flow nasal cannula (HFNC) oxygen therapy has been widely applied to critically ill patients with diverse underlying diseases. It delivers humidified, warmed oxygen with predictable fraction of inspired oxygen (FiO_2) via specialized nasal cannula at flow rates up to 60 L/minute. HFNC use has demonstrated to avoid intubation and lower mortality in patients with AHRF compared to conventional oxygen devices.[6,7]

Based on experiences of HFNC in AHRF with etiologies unrelated to COVID-19, many available guidelines have suggested its use in COVID-19 pneumonia, partly because of scarcity of intensive care resources.[8,9] The extent to which the outcomes of non-COVID-19 pneumonia and HFNC treatment are applicable to COVID-19 patients is unknown. The use of HFNC in these patients is further debated due to the risk of aerosol dispersion and spread of infection to healthcare workers.[10] Hence, we decided to conduct a retrospective study with the primary objective to evaluate the outcome of HFNC treatment in adult COVID-19 patients with acute hypoxemic failure and to assess the factors affecting treatment outcome as secondary objective.

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Methodology

This retrospective study included patients with COVID-19-induced AHRF admitted to intensive care units (ICUs) who received HFNC therapy after failure to maintain oxygen saturation (SpO_2) of ≥90% with conventional oxygen delivery devices. Prior to the commencement of study, institutional ethical committee approval was obtained and the study was registered (CTRI/2020/10/028539). We retrieved medical records of all COVID-19 adult patients, who received HFNC for respiratory support between June 1 and August 31, 2020. The patients younger than 18 years of age, those with hypercapnic respiratory failure (PH ≥45 mm Hg), patients who died within 12 hours of ICU admission, and those who needed positive pressure respiratory support within 12 hours of HFNC

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commencement were excluded from this study. The HFNC devices being used were Inspired O2FLO (Smiths Medical) and Monnal T75 ventilator (Air Liquide Medical System). Both devices are capable of delivering FiO_2 from 21 to 100%; the maximum flow rate delivered through Inspired O2FLO is 60 L/minute, whereas it is 80 L/minute through Monnal ventilator. As per our hospital practice, blended gases are delivered through HFNC devices to maintain oxygen saturation (SpO_2) >90% and patients while on HFNC support are encouraged to wear surgical mask on the top of nasal prongs and to follow awake-prone positioning. Once HFNC is started, monitoring of patient's vitals, including pulse rate, respiratory rate, SpO_2, and blood pressure, is done hourly. arterial blood gas analysis (ABGs) are analyzed at 2 and 24 hours after the therapy initiation.

Variable Measurement

The following baseline data were retrospectively collected: age, gender, comorbidities, and the sequential organ failure assessment (SOFA). Physiological parameters, including the vital signs (heart rate, oxygen saturation, respiratory rate, blood pressure), delivered oxygen concentration, and the rate of gas delivered (L/minute), were also recorded at baseline and at 1, 6, and 12 hours after the therapy initiation. The arterial blood gas analysis done within 24 hours after HFNC initiation was noted. ROX index is defined as the ratio of oxygen saturation as measured by pulse oximetry/FiO_2 to respiratory rate (SpO_2/FiO_2/RR), will be noted at 2, 6, and 12 hours after the initiation of therapy from the vital chart of patients. The following outcome variables were assessed: therapeutic success, adverse or intolerant events, ICU survival, and number of days of ICU stay after HFNC implementation.

HFNC failure is defined as failure to maintain SpO_2 >90% with maximum FiO_2 and flow rate set at the discretion of attending intensivist and need for escalation of respiratory support in the form of noninvasive ventilation (NIV) or mechanical ventilation (MV). Therapeutic success with HFNC was considered when a patient on HFNC was able to maintain SPO_2 >90% without features of increased work of breathing. When a patient with normal mentation insisted on discontinuation of HFNC, it is considered as intolerance to HFNC therapy. An adverse event is defined as a hazardous event requiring the interruption of HFNC therapy, such as nasal bleed, nasal ulcer, or aspiration.

Statistical Analysis

Statistical analyses were performed using the SPSS 21.0 software program (SPSS, Chicago, USA). Continuous variables are expressed as the means ± standard deviation (SD). Nonparametric data are compared using Wilcoxon rank-sum test. Categorical variables were presented as the frequency (*n*) and percentage (%) and were compared using Pearson's Chi-square or Fisher's exact test. In all analyses, a $p \leq 0.05$ was considered to be statistically significant. Forward stepwise multivariate logistic regression analysis was carried out with the outcome of HFNC treatment as dependent variable and variables with $p \leq 0.1$ in univariate analysis as predictor variables.

Results

A total of 558 COVID-19-positive patients were admitted to ICUs from June 1 to August 31, 2020. The number of patients identified on HFNC during this period was 139, out of which 85 met our inclusion criteria. The success of treatment with HFNC was observed in 41 (success group), whereas 44 patients experienced its failure and needed escalation of respiratory support (failure group).

On comparison of baseline characteristics, age and baseline oxygen saturation on room air were found to be significantly different between the success and failure group of HFNC treatment. The mean age of patients in the success group was 53.95 ± 14.53 years compared to 60.50 ± 13.90 years in those who experienced HFNC failure ($p = 0.037$). The baseline oxygen saturation (SpO_2 at the time of institution of HFNC) was 79.02 ± 8.04% and 72.68 ± 13.77%, respectively, in the success and failure group, respectively ($p = 0.012$). Rest of the parameters, including gender, presence of comorbid conditions, D-dimer value, and SOFA score on admission, were found to be comparable between the groups (Table 1). In patients experiencing failure of HFNC, there was significantly higher proportion of those with

Table 1: Demographic parameters and treatment characteristics of patients

	Success	*Failure*	*p value*
Age (in years)	53.95 ± 14.53	60.50 ± 13.90	**0.037**
Gender (% of patients)			
Male	68.2	65.9	0.81
Female	31.7	34	
Presence of comorbidities (% of patients)	68.2	81.8	0.149
SpO_2 on room air (in %)	79.02 ± 8.04	72.68 ± 13.77	**0.012**
D-dimer (ng/mL)	1972.40 ± 1531.87	2582.20 ± 1860.62	0.126
SOFA score	2.63 ± 1.37	3.18 ± 1.56	0.09
ROX index (2 hours)	5.43 ± 1.42	4.44 ± 1.13	**0.001**
ROX index (6 hours)	5.74 ± 1.53	4.59 ± 1.06	<**0.001**
ROX index (12 hours)	6.12 ± 1.54	4.72 ± 1.32	<**0.001**
PaO_2/FiO_2	115 ± 54	87 ± 41.3	**0.009**
HFNC FiO_2 (%)	78.05 ± 15.3	91 ± 21.3	**0.002**
HFNC flow(L/minute)	60 ± 11.8	64.8 ± 13.01	0.062
Number of days on HFNC	8.13 ± 4.9	4.98 ± 2.7	<0.001
Awake-prone position (% of patients)	80.4	34%	<**0.001**
Treatment with steroids (% of patients)	92.6	95.4	0.58
Treatment with remdesivir (% of patients)	41.4	34	0.42

Bold values indicate significant *p* value

cardiac diseases, including hypertension, coronary artery diseases (59% vs 29.2%; $p = 0.006$), as shown in Figure 1.

The analysis of treatment characteristics, as shown in Table 2, showed that the ROX indices at 2, 6, and 12 hours post-initiation were significantly observed to be higher in the success group ($p \leq 0.001$). The PaO_2/FiO_2 measured within 24 hours after starting HFNC was higher in the success group (115 ± 54 vs 87 ± 41.3; $p = 0.009$). Higher FiO_2 through HFNC was delivered to patients experiencing its failure as opposed to those who were recorded to have success (91 ± 21.3 vs 78.05 ± 15.3; $p = 0.002$). Around 80.4% of patients in the success group were found to follow awake-prone positioning while receiving HFNC as compared to only 34% patients in failure group ($p < 0.001$). Treatment with steroids and remdesivir was not found to affect the outcome of HFNC (Table 1). The incidence of intolerance and adverse events with HFNC was comparable between groups. On forward stepwise multivariate logistic regression analysis, three variables, namely, baseline oxygen saturation, awake-prone positioning, and number of days on HFNC, were found to be independently affected outcome with HFNC (Table 2).

Higher baseline oxygen saturation at the time of initiation of HFNC, observing awake-prone position during treatment, and higher number of days spent on HFNC were observed to have positive effects on HFNC treatment.

One-unit increase in baseline oxygen saturation of patient was found to decrease the chances of failure of HFNC by 0.83 times, whereas 1-day increase in patient being on HFNC decreases the chances of failure by 0.55 times. Not assuming prone position while on HFNC is observed to increase odds of failure of HFNC by 4.55 times.

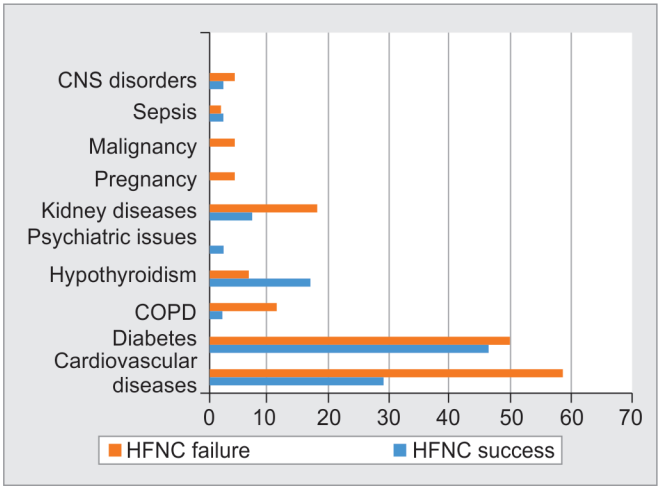

Fig. 1: Comorbidities in patients (%) receiving HFNC treatment

Table 2: Multivariate logistic regression result of significant independent variables affecting the outcome of HFNC treatment

Variables	*OR*	*95% CL*	*p value*
SpO_2 on room air	0.83	0.70–0.92	0.021
Awake-prone position	4.55	4.47–5.93	0.006
Number of days on HFNC	0.55	0.331–0.932	0.026

Discussion

This retrospective observational study showed that HFNC as respiratory support is a successful strategy for moderate-to-severe COVID-19 ARDS in about half of patients. Previously, FLORALI trial in non-COVID-19-related acute hypoxemic failure has reported a reduction in 90-day mortality of patients treated with HFNC compared to standard oxygen delivery methods.[7] Based on the literature from non-COVID-19-related ARDS etiologies, HFNC has been recommended by many guidelines and expert opinions for oxygen support in COVID-19.[8,9] There is, however, limited evidence on the utility of HFNC in COVID-19 patients.

Gattionoi et al. proposed two time-related phenotypes of COVID-19 pneumonia L and H. In L phenotype, hypoxemia is due to dysregulation of perfusion and loss of hypoxic pulmonary vasoconstriction.[11] The type L lungs have nearly normal compliance and low ventilation-to-perfusion ratio (V/Q); lung weight is only moderately increased; and as amount of non-aerated tissue is very low, recruitability is low. As lung volumes are fairly normal, patients with L-phenotype may not be dyspneic and they respond well to non-invasive respiratory supports such as HFNC and continuous positive airway pressure (CPAP). The type H patterns, present in 20–30% of patients, have features similar to severe ARDS. The lung compliance is low; there are remarkably high lung weight, high right to left shunt due to wasted perfusion in diseased lungs, and higher lung recruitability. In this subset, there is significantly reduced lung volume due to alveolar and interstitial edema and positive end expiratory pressure (PEEP) is often required for recruiting alveoli and reducing shunting. HFNC may be less likely to be successful in these patients as it provides only minimal PEEP.[12]

The patients may present with either ends of spectrum or in phases of transition between two. The transition from L to H phenotype is determined by the progression of disease and has been partly attributed to patient's self-inflicted lung injury (P-SILI) caused by increased work of breathing.[12] Accounting for this concern, it has been argued that HFNC may delay the recognition of clinical deterioration during disease progression, thereby prolonging time to intubation and worsening due to P-SILI. Hernandez-Romieu et al., however, studied the impact of time to intubation and use of HFNC on clinical outcomes in patients with COVID-19. They concluded that HFNC use prior to intubation is not associated with an increased mortality. The static compliance of lung was also not significantly influenced by timing of intubation.[13]

Nevertheless, as the recognition of transition from L to H phenotype is possible only with computed tomography (CT) imaging, which is not feasible for every patient in current scenario, it is vital to monitor patient receiving HFNC. ROX index is a simple bedside clinical tool, which has been validated for timely identification of success or failure of HFNC in AHRF patients. As studies on HFNC have previously reported that most of the intubations occur between 12 and 24 hours after its initiation, it has been suggested that from 12 hours onward, if the ROX index is more than or equal to 4.88, there are higher chances of success.[14] The chances of failure are high if ROX index is less than 3.85; however, between 3.85 and 4.88, the prediction of outcome of HFNC is difficult to conclude. In these patients falling in gray zone of ROX index, timely clinical reassessment has been recommended.

Calligro et al. found that ROX index at 6 hours of commencement of HFNC in COVID-19 patient was closely related ($r = 0.870$) to outcome. A ROX-6 score of more than 3.7 was 80% predictive of HFNC success, while the value less than 2.2 was 74% predictive

of its failure.[15] In our study, ROX indices at 2, 6, and 12 hours were found to be significantly higher in patients having success of HFNC treatment; however, on multivariate analysis, they were not found to be the independent predictors of outcome. This may be attributed to the exclusion of patients who experienced HFNC failure within 12 hours of treatment initiation in our study.

In our multivariate logistic regression model, awake-prone positioning in combination with HFNC is found to be a strong independent predictor of its outcome. Prone positioning is an established evidence-based strategy in patients with ARDS receiving invasive MV. The evidence for prone positioning in awake spontaneous breathing patients is, however, available as case series and small observational studies.[16,17] As the majority of COVID-19 patients have been speculated to have L-phenotype lungs with lower recruitability, benefits of awake-prone position in them remain questionable. Achieving prone position in non-intubated patients of comparable duration (12–16 hours/day) as in those receiving invasive MV is another concern to be considered.[18] As awake-prone position is logistically easy to execute, we have been utilizing it in all cooperative patients at our center.

Previous studies have showed the success rate for HFNC in COVID-19 patients to be ranging from 45 to 64.2%.[15,19–21] Markers of severe COVID-19 diseases, including lower PaO_2/FiO_2 and higher D-dimer and CRP, have been associated with failure of HFNC. Similar to their findings, we found that lower SpO_2 on room air, lower PaO_2/FiO_2 ratio, and higher requirement of FiO_2 through HFNC were associated with failure of HFNC and requirement of escalation of respiratory support. Although D-dimer value at admission is an independent predictor of disease severity, in our study it was not seen to be associated with the failure of HFNC. The value of D-dimer changes dynamically depending on disease trajectory and treatment given to patients; therefore, it requires serial measurements for estimating disease progression.[22] Furthermore, D-dimer level in COVID-19 patients is related to inflammation and has a limited role as a predictor of thrombosis. A low correlation between Padua venous thromboembolism (VTE) score and D-dimer levels has been found.[23] As thrombotic complications contribute significantly to COVID-19 morbidity and mortality, the value of D-dimer at admission used for predicting the outcome of patient is uncertain.

We found that patients having higher age and those with hypertension, CAD, or other cardiovascular diseases are at a significant risk of experiencing failure of HFNC. These demographic characteristics have been identified as risk factors for severe and fatal disease course. Hypertension has been reported as the most prevalent comorbidity and pooled odds ratio compared to non-severe patient for hypertension and cardiovascular diseases were 2.36–3.42, respectively.[24] Case fatality rate has been observed to be elevated in CVDs compared to other comorbid conditions. Wu and McGoogan in 44,672 COVID-19-positive patients reported the overall case fatality rate of 2.3% and it was increased in patients with CVDs (10.5%), diabetes (7.3%), chronic respiratory diseases (6.3%), and hypertension (6%).[25] Therefore, failure of HFNC treatment in patients with higher age and CVDs may be at least partly due to the presence of more severe disease course in them.

During the initial stage of current pandemic, there was trend to avoid HFNC in COVID-19 patients due to the concern of increase in aerosol dispersion with high gas flow rates utilized in HFNC. Using smoke simulation via a manikin model, the risk of aerosol dispersion is, however, observed to be similar to standard oxygen masks.[10] At 60 L/minute flow in HFNC, exhaled air dispersion is noted to be 17 cm in healthy lungs and 4.4 cm in severely diseased lungs.[26] Leung et al. compared HFNC at 60 L/minute with an oxygen mask at 8.6 ± 2.2 L/minute in 19 ICU patients with bacterial pneumonia on the environmental contamination. No significant difference in bacterial counts was reported in the air sample and settling plates between the two oxygen devices at 1, 2, and 5 days of incubation.[27] Aerosol generation has been observed to be influenced more by the breathing pattern of patient and by coughing than by the mode of oxygen therapy applied.[28] To mitigate the risk of aerosol to healthcare workers, it has been recommended to use the modality in single room, if negative pressure room is not available and adequate personal protective equipment to be used. To further reduce the risk, the patient should wear a surgical mask on top of HFNC interface, the nasal prongs should not be loosely placed over the nose of patient and the flow rate should be set to minimal acceptable.[29]

There are, however, certain limitations to the present study. It was a retrospective study from a single center. Future studies from multiple centers with large sample size are warranted to establish the utility of HFNC and the variables affecting its outcome. Second, we did not obtain data on proportion of patients with dyspnea at the time of initiation of HFNC. Many patients with COVID-19 pneumonia exhibit lack of dyspnea despite low levels of oxygen saturation as measured on pulse oximetry. Instead, most of them have tachypnea and tachycardia.[30] Xie et al. reported that dyspnea is a significant predictor of mortality in COVID-19 patients.[31] Patients not experiencing dyspnea, tachypnea, and hypoxemia respond well to an increase in FiO_2 when ventilation to perfusion drives hypoxemia (L phenotype). In contrast, hypoxia and tachypnea due to shunt are less likely to improve with an increment of FiO_2 (H type).[32]

Conclusion

HFNC can be used for successful respiratory support in moderate-to-severe cases of COVID-19 in almost half of the cases without need for mechanical ventilation. Monitoring ROX index in patients receiving HFNC is vital as it helps in predicting success or failure of therapy. The patients having severe course of disease appears to be at risk of HFNC failure and hence they need vigilant monitoring and those with lower PaO_2/FiO_2 found in the failure group, and hence, they need vigilant monitoring while receiving HFNC.

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