



# Role of Oxygenation in Moderate COVID-19 Pneumonia with High Flow Nasal Cannula and Standard Non-Rebreathing Mask: A Comparative Study

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## Key words:

COVID-19, Hypoxemia, High Flow Nasal Cannula, Non rebreathing mask, Oxygen Therapy, Pneumonia

## Abstract:

**Background:** To evaluate the effectiveness of High Flow Nasal Cannula (HFNC) and standard non rebreathing mask (NRBM) as oxygen delivery device, in moderate cases of COVID-19 Pneumonia.

**Methods:** A single-centre, prospective analysis conducted at KBFGH. Eighty enrolled patients were randomly divided into two groups according to the oxygen delivery device used. Group 1 (n = 40) received HFNC and group 2 (n = 40) received NRBM as initial oxygen delivery device, to maintain a target saturation of e" 96% in both groups. The success rate of oxygen therapy, time to progression to severe disease, PaO<sub>2</sub>, PaO<sub>2</sub>/FiO<sub>2</sub> ratio, respiratory rate, heart rate, blood pressure, number of patients requiring NIV or endotracheal intubation, time for de-escalation of oxygen therapy to lower Fio<sub>2</sub> device and patient satisfaction level were compared among the two groups.

**Results:** Demographic, clinical variables and treatment given were comparable in the two groups. In the HFNC group 83.3% patients had successful outcomes with the initial oxygen therapy device used as compared to 66.6% in the NRBM group. However, the use of HFNC resulted in improved oxygenation (P < 0.001), better patient satisfaction (P < 0.001) and shorter time for de-escalation of oxygen therapy to a lower FIO<sub>2</sub> device (3.75 ± 1.032 vs. 6.83 ± 0.928).

**Conclusions:** HFNC is a reliable oxygen therapy modality for moderate category COVID-19 pneumonia that results in better oxygenation and a greater patient satisfaction level as compared to a non-rebreathing mask.

## Introduction

Oxygen therapy delivered via face mask with reservoir bag is usually the first-line treatment in patients with Covid-19 in the form of acute

respiratory failure (ARF). However, this strategy has many limits and fails to provide ventilatory support. The fraction of inspired oxygen (FiO<sub>2</sub>) delivered is limited and comfort is compromised

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by dry gas, which also impairs mucociliary clearance.

The world is still suffering from the novel coronavirus that causes a respiratory illness named coronavirus disease (COVID-19); the clinical manifestations are diverse ranging from asymptomatic infection to acute respiratory distress syndrome that requires intensive care unit (ICU) admission with endotracheal intubation and invasive mechanical ventilation and is associated with high risk of mortality.<sup>1,2</sup>

About 14% of the patients infected with COVID-19 develop severe illness, and 5% of the cases are critical and usually require ICU admission with associated high risk of mortality. According to several reports, the patients admitted to ICU are often in need for oxygen with high flow or mechanical ventilation either invasive or non-invasive.<sup>3</sup>

High flow nasal cannula oxygen (HFNCO) is a relatively new technique used in the management of acute hypoxemic respiratory failure. It delivers heated humidified oxygen through nasal prongs at high flow rates up to 60 liters/minute.<sup>4</sup>

We aimed to compare the benefits of HFNCO with Standard Non-rebreathing mask (NRM) in the management of moderate COVID-19 patients with acute respiratory failure. The COVID-19 pandemic caused by a newly discovered SARS-CoV-2 virus is a primarily respiratory illness that causes acute hypoxemia. Due to its great contagiousness, it spread around the entire globe and led to a public health emergency of international concern.<sup>1</sup> Most COVID 19 positive patients have mild respiratory symptoms. However, 14% of patients have hypoxic respiratory failure requiring hospitalization with supplemental oxygen administration.<sup>2</sup> The incidence of moderate to severe acute respiratory failure despite conventional oxygen therapy is reported to be 5% in COVID 19 pneumonia.<sup>3</sup>

Optimal oxygenation is the cornerstone of the management of moderate & severe COVID pneumonia patients.<sup>4</sup> However, it is unknown which type of support is the most effective, limiting the ability to improve clinical outcomes and appropriately allocate resources

Ministry Of Health And Family Welfare (MOHFW) divided the patients of SARS-CoV-2 into categories

of mild, moderate & severe, based on clinical severity.<sup>5</sup> For the moderate category patients, clinical management includes oxygen therapy to maintain target O<sub>2</sub> saturation  $\leq 92-96\%$ .<sup>5</sup> However, there is no guideline to justify the advantage of one form of oxygen (O<sub>2</sub>) therapy device over the other. Various oxygen devices ranging from simple masks to High Flow Nasal Cannula (HFNC) can be used for these patients.<sup>5</sup>

In order to guide clinical practice, it is imperative to understand the comparative effectiveness of the two oxygen therapy devices used most commonly worldwide in moderate cases of COVID 19 Pneumonia: standard non rebreathing mask (NRBM) or High Flow Nasal Cannula (HFNC). Hence, this study was planned based on the hypothesis that early institution of HFNC in moderate category COVID 19 pneumonia patients results in improved outcome in terms of reduced number of patients progressing to severe disease and better oxygenation as compared to NRBM.

We hereby report the results of a randomized trial conducted to determine whether early treatment with HFNC, as compared to NRBM, can prevent the development of increased hypoxemia in COVID 19 positive patients.

## Methods

In this study, all COVID19 positive patients of moderate category, who were admitted to Kuwait Bangladesh Friendship Govt. hospital in Dhaka, Bangladesh with confirmed COVID-19 associated with hypoxemic respiratory failure in a certain period.

Consent was obtained from the patients or their relatives to use and publish their data. The study was approved by the ethics committee of the hospital.

A single-center, retrospective observational study was conducted. Eighty enrolled patients were randomly divided into two groups according to the oxygen delivery device used. Group 1 (n = 40) received HFNC and group 2 (n = 40) received NRBM as initial oxygen delivery device, to maintain a target saturation of eH 96% in both groups. The success rate of oxygen therapy, time to progression to severe disease, PaO<sub>2</sub>, PaO<sub>2</sub>/FiO<sub>2</sub> ratio, respiratory rate, heart rate, blood pressure, number of patients requiring NIV or endotracheal intubation, time for de-escalation of oxygen therapy to lower

Fio<sub>2</sub> device and patient satisfaction level were compared among the two groups.

### Inclusion criteria

Confirmed COVID-19 patients by real-time reverse transcription polymerase chain reaction (RT-PCR). All included patients had acute hypoxemic respiratory failure and received either HFNCO or NBRM as initial therapy.

### Exclusion criteria

Patients who required invasive mechanical ventilation with endotracheal intubation on admission, or who did not use neither HFNCO nor NBRM as initial therapy. Patients were also excluded in case of missing data necessary for analysis. Patients with no available consent to use their data for publication were also excluded.

All COVID positive patients of moderate category, of age  $\leq 16$  years who were eligible and gave informed consent for study inclusion were randomly allocated into two study groups according to the oxygenation device used. In group 1, patients received oxygen therapy with HFNC set at a flow rate of 40–60 L/min, fractional inspiratory oxygen concentration (FiO<sub>2</sub>) 0.8–1 adjusted to maintain oxygen saturation (SpO<sub>2</sub>)  $\leq 96$ –99%. The control of FiO<sub>2</sub> was achieved by using an air oxygen blender. In group 2, patients received oxygen therapy with NRBM used at a flow rate of 12–15 L/min, FiO<sub>2</sub> 0.8–1, adjusted to maintain SpO<sub>2</sub>  $\leq 96$ –99%. With NRBM, the FiO<sub>2</sub> was measured using a portable oxygen analyzer. (MX 300, Teledyne<sup>®</sup> Analytical Instruments) Patients of severe category of COVID pneumonia, Glasgow Coma scale  $\geq 12$  and those with primary pulmonary disease, tracheostomy or any nasal/facial defect that could impede HFNC or NRBM use were excluded from the study.

Primary outcomes noted were success of oxygen therapy which was defined as not requiring replacement to a higher oxygen delivery device and the time to progression to severe disease. Secondary outcomes noted were, success of oxygen therapy which was defined as not requiring replacement to a higher oxygen delivery device partial pressure of arterial oxygen (PaO<sub>2</sub>), ratio of partial pressure of oxygen to fraction of inspiratory oxygen concentration (PaO<sub>2</sub>/FiO<sub>2</sub>), respiratory rate (RR), heart rate (HR), mean arterial pressure (MAP),

number of patients requiring NIV, number of patients requiring endotracheal intubation, time for de-escalation of oxygen therapy to lower FiO<sub>2</sub> device and patient satisfaction level. The patient satisfaction level was measured using a visual analogue scale (VAS).<sup>6</sup> A satisfaction VAS is a 100-mm long horizontal line. There are two adjectives at the beginning and finish that symbolize extremes of satisfaction (i.e., no satisfaction and extreme satisfaction). The patient marked a vertical mark on the 100-mm line to indicate his level of pleasure. The millimeter measurement was translated to the same number of decimal points, ranging from 0 to 10. “Are you comfortable with the oxygen therapy device you’re using?” was the actual inquiry. Under the VAS horizontal line, there was a standard instruction on how to fill out the VAS form.

Device failure was considered if the patient progressed to severe category COVID 19 pneumonia while on the study device and required escalation of oxygen therapy.<sup>5</sup> In case of device failure, the decision for shifting to higher oxygen delivery device (including HFNC for the patients in NRBM group or NIV or endotracheal intubation) was done according to the attending anesthesiologist decision taking respiratory rate, work of breathing and oxygen saturation into account.

The patients were followed up daily for monitoring disease progression by various vital parameters up to 14 days. Vital parameters including HR, MAP, RR, PaO<sub>2</sub>, PaO<sub>2</sub>/FiO<sub>2</sub>, SpO<sub>2</sub> and arterial blood gas (ABG) analysis were done as per Intensive Care Unit (ICU) protocol. In both groups, SpO<sub>2</sub> was monitored continuously and FiO<sub>2</sub> was titrated on an hourly basis to maintain SpO<sub>2</sub> between  $\geq 96$ %.

The assigned treatment was administered continuously and patients were assessed for treatment success. Patients were weaned to a lower FiO<sub>2</sub> oxygen therapy device when the following criteria were met: respiratory rate  $\leq 24$  breaths/min; no recruitment of accessory muscles during calm breathing; haemodynamic stability (HR  $< 120$ /min; MAP between 70 and 110 mmHg with no hemodynamically significant arrhythmias), PaO<sub>2</sub>  $> 80$  and SpO<sub>2</sub>  $\geq 96$ %. Patients from both groups underwent a standard treatment for COVID 19 with physiotherapy and awake proning protocol.

Operational definition of moderate category COVID 19 pneumonia: Pneumonia with no signs of severe disease with clinical features consisting of dyspnoea (respiratory rate 24–30/min), hypoxia ( $SpO_2$ :  $\leq 94\%$  [range 90–94%] on room air), fever and cough. Operational definition of severe category COVID 19 pneumonia<sup>5</sup>: Pneumonia with signs of severe disease with clinical features consisting of respiratory distress (respiratory rate  $>30$ /min), hypoxia ( $SpO_2$ :  $< 90\%$  on room air), fever and cough.

### HFNCO

Whenever HFNCO was used, the settings were adjusted according to published consensus and experts' opinion [5]. The flow was set from 30–60 l/min according to the patient's condition, and the temperature was set in the range between 31 and 37°C. The fraction of inspired oxygen ( $FiO_2$ ) was adjusted to keep the peripheral blood oxygen saturation ( $SpO_2$ ) above 93%. Close monitoring of the vital signs and arterial blood gases, and if the management with HFNCO was not successful (persistent severe symptoms, mainly dyspnea, in addition to failure in maintaining the oxygenation at the desired levels), then NIV was started if no necessary urgent endo-tracheal intubation, and in case of no or poor response to NIV, respiratory support was escalated with urgent endotracheal intubation and invasive mechanical ventilation according to the guidelines.<sup>6</sup>

### Statistical analysis

SPSS version 20.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Test results are reported as mean and standard deviations (SD) for normally distributed continuous variables. A chi-square test was performed for categorical variables. An independent sample t test

was conducted for parametric data. P values of  $<0.05$  were considered statistically significant.

### Results

After the analysis of the files 80 patients who consented to participate in this study were randomly divided into two groups (Fig. 1). 40 patients were included in group 1 (HFNC group) and 40 patients in group 2 (NRBM group). Demographics, most relevant clinical characteristics, main comorbidities, ABG on admission and treatment received were comparable in the two study groups (Table I).

Among the 80 patients, 50 were successfully treated with the initial oxygen therapy device they received. In group 1, 27 out of 40 patients (83.3%) had successful outcomes on HFNC and in group 2, 23 out of 40 (66.6%) were successfully managed on NRBM. Although the success rate of oxygen therapy by HFNC was higher than that by the non-rebreathing mask, the difference was not statistically significant (Table II) ( $P=0.136$ ). The median time to progression to severe disease was 6 and 5.5 days in group 1 and 2 respectively, with no statistically significant difference among the two groups (Table II) ( $P=0.859$ ).

In group 1, five patients failed to respond to the initial treatment with the HFNC and progressed to the severe category and received NIV. One patient among these five was later intubated and mechanically ventilated. In group 2, a total of ten patients required escalation of oxygen therapy device. Among these ten patients, five were shifted to HFNC, out of which three were successfully managed. Remaining seven patients received NIV and three were later intubated and mechanically ventilated.

**Table I.** Baseline Patient Characteristics

Parameters	HFNC*	NRBM*	P value†
Gender (Male)‡	19 (n = 40)	21 (n = 40)	
AGE	54.00 ± 11.447	59.63 ± 3.034	0.012
HEART RATE	88.03 ± 1.829	86.23 ± 2.582	0.029
MAP§	73.50 ± 2.146	73.23 ± 1.870	0.6
PaO <sub>2</sub>	65.07 ± 1.701	65.73 ± 1.999	0.1736
PaO <sub>2</sub> /FiO <sub>2</sub> ¶	207.03 ± 4.56	207.67 ± 3.790	0.556
SpO <sub>2</sub> **	91 ± 1.541	92 ± 1.022	0.044
Respiratory Rate	28.20 ± 1.157	28.10 ± 1.242	0.748

\*Values are presented as mean ± SD. †P value less than 0.05 is considered significant. ‡Values expressed as numbers, §MAP: mean arterial blood pressure, || PaO<sub>2</sub>: Partial Pressure of Oxygen, ¶ PaO<sub>2</sub>/FiO<sub>2</sub>: ratio of Partial Pressure of Oxygen and Fraction of inspiratory oxygen concentration \*\* SpO<sub>2</sub>: Saturation of oxygen, \*\*, ††, ‡‡

**Table II. Primary and Secondary Outcomes**

Parameters	HFNS (n = 40)	NRBM (n = 40)	P value †
Success of oxygen therapy	25 (83.3)	20 (66.6)	0.136
Patients requiring escalation of oxygen therapy	5(16.6)	10 (33.3)	0.136
Time to progression to severe disease‡	6(4.5–6.5) ‡	5.5 (5–6)	0.859
Patients requiring intubation	1(3.3)	3 (10)	0.612

\*Values are presented as numbers (%). †P value less than 0.05 is considered significant. ‡Median with interquartile range

**Table III. Time and Vital Parameters on the Study Device**

Parameters	HFNC*	NRBM*	P value†	95% of CI of difference‡
Average time for de-escalation of oxygen therapy	3.75 ± 1.032	6.83 ± 0.928	<0.001	-3.078 (-3.619-[-2.537])
PaO <sub>2</sub> on device§	84.23 ± 9.202	74.27 ± 4.160	0.0001	9.967 (6.276–13.657)
PaO <sub>2</sub> /FiO <sub>2</sub> on device	264.60 ± 42.019	216.62 ± 23.868	0.0001	47.979 (30.080-65.878)
SpO <sub>2</sub> on device¶	95.17 ± 4.662	93.53 ± 4.911	0.7719	1.633 (-0.841-4.108)
Respiratory Rate	23.17 ± 2.086	25.52 ± 0.871	0.0018	-1.351 (-2.189-[-0.512])
Heart Rate	86.83 ± 3.815	87.03 ± 1.732	0.794	-0.20 (-1.0731-1.331)
MAP**	74.00 ± 1.661	73.20 ± 1.648	0.661	0.80 (-0.055-1.655)
Patient Satisfaction Level	6.07 ± 0.691	2.80 ± 0.761	0.001	

\*Values are presented as mean and standard deviation, †P value less than 0.05 is considered significant. ‡CI: Confidence Interval, §PaO<sub>2</sub>: Partial Pressure of Oxygen, ||PaO<sub>2</sub>/FiO<sub>2</sub>: ratio of Partial Pressure of Oxygen and Fraction of inspiratory oxygen, ¶SpO<sub>2</sub>: Saturation of oxygen, \*\*MAP: mean arterial blood pressure.

No significant difference in HR and MAP was observed among the groups. Patient satisfaction level as measured by VAS Scale was higher in the HFNC group than in the NRBM group (P < 0.001) (Fig. 2).

Use of HFNC in group 1, significantly improved the PaO<sub>2</sub> and PaO<sub>2</sub>/FiO<sub>2</sub> ratio during the course of treatment as compared to the non-rebreathing mask (84.23 ± 9.202 vs. 74.27 ± 4.160 and 264.60 ± 42.019 vs. 216.62 ± 23.868, respectively). Respiratory rate in group 1 (23.17 ± 2.086) was significantly lower than in group 2 (25.52 ± 0.871) (P=0.0018). Time for de-escalation of oxygen therapy to a lower FiO<sub>2</sub> device was also significantly shorter in the group 1 (3.75 ± 1.032 vs. 6.83 ± 0.928) (P < 0.001) (Table III).

## Discussion

The primary strategy for COVID-19 pneumonia patients is supportive care, including oxygen therapy for hypoxemic patients,<sup>7</sup> in which High-Flow Nasal Cannula (HFNC) has been reported to be effective

in improving oxygenation.<sup>8</sup> The choice of oxygen support devices for oxygen therapy is essential in these patients in terms of effectiveness, patient comfort and generation of aerosol.

The primary outcome noted in our study were success of oxygen therapy compared between the two groups and the time of progression to severe disease. Although the success rate of oxygen therapy by HFNC was higher than that by the non-rebreathing mask (NRBM), the difference was not statistically significant (P = 0.136). Also, the difference in median time of progression to severe disease among the two groups was statistically insignificant (P = 0.859).

On analysis of secondary outcomes, we noted that the use of the HFNC resulted in improved oxygenation and a decreased work of breathing. The high flow rates (up to 60 L/min) delivered by HFNC that match patients' peak inspiratory flow, meet the higher oxygen requirements of dyspnoeic

hypoxemic COVID patients and could have resulted in better patient outcomes.

In addition, a fixed FiO<sub>2</sub> with a small degree of positive pressure in the airways that increases end-expiratory volume and decreases the nasopharyngeal dead space enhances carbon dioxide removal by preventing rebreathing.<sup>9,10</sup>

Patients in group 1 also reported better satisfaction with a shorter time of de-escalation to lower oxygen requirement as compared to group 2. Delivery of heated and humidified oxygen from 21–100% by HFNC makes it more comfortable for the airways resulting in increased tolerance and better patient satisfaction.<sup>11,12,13</sup> The results of our study stand in agreement with our prior hypothesis.

A similar study by Song et al.<sup>14</sup> (before the COVID pandemic) concluded that at a fixed inspired oxygen fraction, the application of a HFNC after extubation achieves a higher success rate of oxygen therapy and less discomfort at 24h than an air entrainment mask in patients with acute respiratory failure. A Systematic review on the effectiveness of HFNC and conventional oxygen therapy (COT) concluded that the use HFNC may reduce the need for invasive ventilation and escalation of therapy compared with COT in COVID-19 patients with acute hypoxemic respiratory failure (although the review did not include any eligible study in COVID19 patients).<sup>15</sup>

The concern for aerosol dispersion has been a major limiting factor in the use of HFNC in COVID 19 patients.<sup>16,17</sup> Adequate personal protective equipment, adequate room ventilation and use of high filtration tested respirators for all healthcare workers attending to patients were available. In addition, use of a surgical face mask on patients receiving HFNC was mandatory as per our hospital protocol. Now the evidence also suggests that the risk of airborne transmission is no greater than the use of a face mask.<sup>18,19</sup> On-going field experiments and clinical studies during the current COVID pandemic may provide additional information.

This study emphasizes the importance of timely management of moderate category hypoxemic COVID-19 patients. Early institution of HFNC may help reduce the mortality and morbidity associated with this condition. In addition, the use of HFNC outside the ICU could be a rational practice in such patients resulting in substantial reduction in demand

for ventilators. This could increase the capacity to manage COVID-19 pneumonia patients in a resource limited setting where the infrastructure and or expertise of ICU care is limited.<sup>20</sup>

To our knowledge and a thorough literature search, we did not come across a similar study done on COVID-19 pneumonia patients. There are some studies comparing effectiveness of HFNC Vs. conventional oxygen therapies before the emergence of COVID 19.<sup>20</sup> However, no randomized controlled trial that has included COVID-19 patients for such comparison could be found.

The limitations of our study were that firstly, it is an open label study so the possibility of information bias can't be excluded although most of our variables were objective in nature. Another limitation was that the study only reflected the experience from a single center with a small sample size which may have overestimated the effect of treatment. This could limit generalization of the results.

## Conclusion

HFNC as an oxygen therapy modality for moderate category COVID-19 pneumonia is a feasible option which can result in better oxygenation and a greater patient satisfaction level than a non-rebreathing mask. Early institution of HFNC during the moderate phase of disease may shorten the time to de-escalation of oxygen device, and thus avoiding non-invasive ventilation and intubation. This can reduce the burden of critical care in the testing time of pandemic.

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**Conflict of Interest:** None

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