The effectiveness of high-flow nasal cannula and standard non-rebreathing mask for oxygen therapy in moderate category COVID-19 pneumonia: Randomised controlled trial

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Background. COVID-19 caused by the highly infectious severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection is a matter of concern and has led to severe health problems all over the world. Oxygen therapy is the mainstay for the management of patients suffering from various stages of the disease.

Objectives. To compare the effectiveness of high-flow nasal cannula (HFNC) and standard non-rebreathing mask (NRBM) as oxygen delivery devices in moderate cases of COVID-19 pneumonia.

Methods. A single-centre, open-label, randomised controlled trial was conducted between February 2021 and April 2021. All the enrolled patients (*N*=120) were randomly allocated into two groups according to the oxygen delivery device used. Group 1 (*n*=60) received HFNC and group 2 (*n*=60) received NRBM as the initial oxygen delivery device, to maintain a target saturation ≥96% in both groups. The progression-free survival without escalation of respiratory support, partial pressure of arterial oxygen (PaO_2), a ratio of partial pressure of arterial oxygen to fractional inspiratory oxygen concentration (PaO_2/FiO_2), respiratory rate, heart rate, blood pressure, number of patients requiring non-invasive ventilation or endotracheal intubation, time for de-escalation of oxygen therapy to lower FiO_2 device, time to progression to severe disease, survival at day 28, and patient satisfaction level were compared between the two groups.

Results. Demographic, clinical variables and treatment received were comparable in the two groups. In the HFNC group, 90% of patients had successful outcomes with the initial oxygen therapy device used as compared with 56.6% in the NRBM group ($p<0.001$; odds ratio (OR) 0.145; 95% confidence interval (CI) 0.054 - 0.389). Using HFNC also resulted in improved oxygenation (PaO_2/FiO_2) ($p<0.001$), better patient satisfaction ($p<0.001$), and a shorter time for de-escalation of oxygen therapy to a lower FiO_2 device ($p<0.001$). The 28-day survival was higher in the HFNC group, but the difference was statistically insignificant ($p=0.468$).

Conclusion. HFNC is a reliable oxygen therapy modality for moderate category COVID-19 pneumonia and results in a higher success rate of oxygen therapy, better oxygenation, and a greater patient satisfaction level as compared with a NRBM.

Keywords. COVID-19; hypoxaemia; ICU; on-invasive ventilation; oxygen therapy; pneumonia; respiratory failure.

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The COVID-19 pandemic caused by the newly discovered severe acute respiratory syndrome–coronavirus 2 (SARS-CoV-2) is primarily a respiratory illness that causes acute hypoxaemia. Due to its great contagiousness, it spread around the entire globe and led to a public health emergency of international concern.[1] Most COVID-19-positive patients have mild respiratory symptoms. However, some patients (14%) have hypoxic respiratory failure requiring hospitalisation with supplemental oxygen administration.[2] The incidence of severe acute respiratory failure despite conventional oxygen therapy (COT) is reported to be 5% in COVID-19 pneumonia.[3]

Optimal oxygenation is the cornerstone of the management of moderate and severe COVID-19 pneumonia patients.[4] However, the effectiveness of the available oxygenation devices is still unknown and needs to be explored. This limits the ability to improve clinical outcomes and appropriately allocate resources.

The updated clinical management guidelines of COVID-19 (dated 03 May 2020, version 5) given by the Government of India, Ministry of Health and Family Welfare (MOHFW), divide COVID-19 patients into categories of mild, moderate and severe, based on the clinical severity.[5] For the moderate category of patients, management includes oxygen therapy to maintain target O_2 saturation ≥92 - 96%.[5] However, there is no guideline to justify the advantage of one form of O_2 therapy device over the other. Various oxygen devices, ranging from simple masks to high-flow nasal cannulae (HFNC) can be used for these patients.[5] To guide clinical practice, it is imperative to understand the comparative effectiveness of the two O_2 therapy devices used most commonly worldwide in moderate cases of COVID-19 pneumonia – standard non-rebreathing mask (NRBM) and HFNC. Hence, this present study was based on the hypothesis that early institution of HFNC in patients with moderate COVID-19 pneumonia results in improved outcomes in terms of the reduced number of patients progressing to severe disease and better oxygenation as compared with NRBM.

Methods

This present study was a single-centre, open-label, randomised

controlled trial conducted in a COVID-19 hospital from February 2021 - April 2021. The clinical study was performed following ethical principles for medical research involving human subjects, outlined in the Helsinki Declaration of 1975 (revised 2013). The protocol was approved by the Government Institute of Medical Sciences Ethics Committee and was registered on ctri.nic.in (ref no. CTRI/2021/01/030829). All participants, their next of kin or another surrogate decision-maker supplied written informed consent through electronic communication.

Operational definition of moderate category COVID-19 pneumonia is pneumonia with no signs of severe disease with clinical features comprising dyspnoea (respiratory rate (RR) 24 - 30 breaths/min), hypoxia oxygen saturation (SpO_2) ≤94%; range 90 - 94% on room air), fever and cough. Operational definition of severe category COVID-19 pneumonia is pneumonia with signs of severe disease with clinical features comprising respiratory distress (RR >30 breaths/min), hypoxia (SpO_2 <90% on room air), fever and cough.[5]

Keeping the progression-free survival without escalation of oxygen delivery devices as the primary outcome, we conducted a pilot study with five moderate category COVID-19 patients in each group. The result was a successful outcome in 62% of the patients in group 1 and 36% of patients in group 2. Using the results of the pilot study, we calculated the sample size using open Epi software, version 3 (CDC, USA), with a significance level of $p<0.05$, power of 80%, and allocation ratio of 1:1. The sample size was calculated to be 118 patients, with 59 patients allocated to each group. We enrolled 60 patients in each group to compensate for dropouts.

All COVID-19-positive patients of moderate category, age ≥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. Patients in the severe category of COVID-19 pneumonia, Glasgow Coma Scale ≤12, and those with primary pulmonary disease, tracheostomy, or any nasal/facial defect that could impede HFNC or NRBM use were excluded from the present study.

We randomly divided the patients into two groups using a computer-generated randomisation list. In group 1, patients received oxygen therapy with HFNC set at a flow rate of 40 - 60 L/min, fractional inspiratory oxygen concentration (FiO_2) 0.8 - 1 adjusted to maintain oxygen saturation (SpO_2) ≥96 - 99%. We achieved the control of FiO_2 by using an air oxygen blender (Oxymixture MP04200, Draeger, Germany). In group 2, patients received oxygen therapy with NRBM used at a flow rate of 12 - 15 L/min, FiO_2 0.8 - 1, adjusted to maintain SpO_2 ≥96 - 99%. With NRBM, we measured the FiO_2 using a portable oxygen analyser (MX 300, Teledyne Analytical Instruments, India).

The primary outcome was progression-free survival without escalation of an oxygen delivery device. Secondary outcomes were a partial pressure of arterial oxygen (PaO_2), the ratio PaO_2/FiO_2, RR, heart rate (HR), mean arterial pressure (MAP), number of patients requiring non-invasive ventilation (NIV), number of patients requiring endotracheal intubation, time for de-escalation of oxygen therapy to lower FiO_2 device, the time to progression to severe disease, survival at day 28, and patient satisfaction level. We tracked regularly all participants from day one to day 28. A structured telephone call was made to patients who were discharged from the hospital before day 28 to verify vitals and clinical status.

We measured the patient satisfaction level using a visual analog scale (VAS).[6] A satisfaction VAS is a 100 mm-long horizontal line. There are two adjectives at the beginning and finish that symbolise extremes of satisfaction (i.e. no satisfaction and extreme satisfaction). The patient marked a vertical mark on the 100 mm line to show their level of satisfaction. We translated the millimeter measurement to the same number of decimal points ranging from 0 - 10. 'Are you comfortable with the oxygen therapy device you are using?' was the actual inquiry. Under the VAS horizontal line, there was a standard instruction on how to fill the VAS form.

We considered device failure if the patient progressed to severe category COVID-19 pneumonia while on the study device and required an escalation of oxygen therapy.[5] In case of device failure, the decision for shifting to a higher oxygen delivery device (NIV or endotracheal intubation) was done according to the pre-specified criteria. (Table 1).

Vital parameters including HR, MAP, RR, PaO_2, PaO_2/FiO_2, SpO_2, and arterial blood gas (ABG) analysis were done as per intensive care unit (ICU) protocol. In both groups, SpO_2 was monitored continuously and FiO_2 was titrated hourly to maintain SpO_2 ≥96%. The assigned treatment was administered continuously, and patients were assessed for treatment success. Patients were weaned to a lower FiO_2 oxygen therapy device when the following criteria were met: respiratory rate ≤ 24 breaths/min; no recruitment of accessory muscles during calm breathing; haemodynamic stability (HR < 120 beats/min); MAP between 70 and 110 mmHg with no haemodynamically significant arrhythmias), PaO_2 >80 and SpO_2 ≥96%. Patients from both groups underwent a standard protocol for physiotherapy and awake proning protocol. The use of steroids, antibiotics, antivirals, anticoagulants, antimicrobial agents and other COVID-19-related treatments was according to a standardised protocol prepared by treating physicians, which was comparable in the two study groups (Table 2).

We performed statistical analysis using SPSS for Windows, version 24.0 (IBM Corp., USA). Categorical variables were reported as count and frequency/percent while continuous variables were reported as either mean and standard deviation or median and interquartile range depending on their respective distribution. We tested the associations using the Student *t*-test for parametrically distributed continuous variables and used the Mann-Whitney *U*-test for non-parametrically distributed variables. For categorical variables, associations were tested using either the chi-squared test or Fisher's exact test. The alpha level was set at 0.05 for statistical significance.

Results

We randomly divided 120 patients who consented to take part in this present study into two groups between February 2021 and April 2021 (Fig. 1). We allocated 60 patients in group 1 (HFNC group) and 60 patients in group 2 (NRBM group). Demographics, most relevant clinical characteristics, main comorbidities, and ABG on admission were comparable in the two study groups (Table 3).

Among the 120 patients, 88 were successfully treated with the initial oxygen therapy device they received. In group 1, almost all patients (90%; n=54/60) had progression-free survival on HFNC and only 56.6% (n=34/60) were successfully managed on NRBM and the difference was statistically significant ($p<0.001$) (Table 4).

In group 1, six patients failed to respond to the initial treatment with HFNC and progressed to the severe category, and received NIV. Two patients among these six were later intubated and mechanically

Table 1. Criteria for escalation of oxygen delivery device (non-invasive ventilation/intubation)

1. Persistent respiratory distress - RR >40 breaths/ min, signs of laboured breathing, use of accessory muscles of respiration.
2. Copious airway secretions.
3. ABG: metabolic/respiratory acidosis, pH <7.25, PaO2 <55 mmHg, $PaCO_2$ >55 mmHg.
4. SpO_2 <90% on current oxygen delivery device.
5. Signs of haemodynamic instability - MAP < 60 mmHg, requirement of ionotropic support (norepinephrine >0.10 µgr.kg.min-1) with normal CVP, CRT >10 seconds, lactate ≥4.0 mmol/L
6. Neurological impairment (GCS ≤8)

RR = respiratory rate; ABG = arterial blood gas; MAP = mean arterial pressure; CVP = central venous pressure; CRT = capillary refill time; GCS = Glasgow coma scale.

Table 2. Comparison of proning protocol and treatment therapies given in both the groups.

Proning and treatment received	HFNC (*n*=60), *n* (%)*	NRBM (*n*=60), *n* (%)*	*p*-value
Awake prone position	48 (80)	45 (75)	0.256
Average time (h) in awake prone position per day, median (IQR)	9 (6 - 11)	9 (8 - 11)	0.134
Prone position during mechanical ventilation	6 (10)	12 (20)	0.068
Time (h) in prone position during mechanical ventilation (NIV/IMV), median (IQR)	14(12 - 15)	16 (14 - 17)	0.598
Steroids	56 (93.3)	58 (96.6)	0.206
Anticoagulant	58 (96.6)	55 (91.6)	0.130
Remdesivir	36 (60)	41 (68.3)	0.170
Convalescent plasma	32 (53.3)	28 (46.6)	0.233
Tocilizuma	0	0	
Baricitinib	0	0	
Hydroxychloroquine	0	0	

HFNC = high-flow nasal cannula; NRBM = non-rebreathing mask; IQR = interquartile range; NIV = non-invasive ventilation; IMV = intermittent mandatory ventilation.
* Unless otherwise specified.

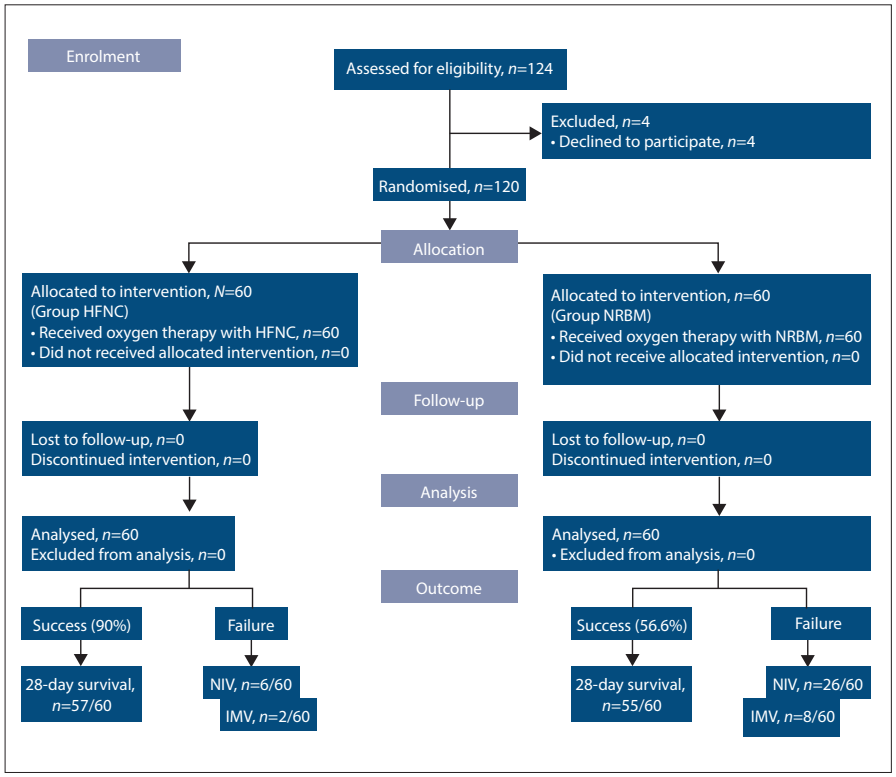

Fig. 1. Consort flow diagram. (HFNC = high-flow nasal cannula; SNBM = standard non-rebreathing mask; NIV = non-invasive ventilation; IMV = intermittent mandatory ventilation.)

ventilated. In group 2, 26 patients required an escalation of the oxygen therapy device. These 26 patients were shifted to NIV, out of which 18 were successfully managed on NIV. The remaining eight patients were later intubated and mechanically ventilated. The survival following failure on HFNC was 50% (*n*=3/6) compared with survival following failure on NRBM of 81% (*n*=5/26). There was no statistically significant difference (*p*=0.468) between the two groups on 28-day survival rate (Table 4).

The median (interquartile range (IQR) time for de-escalation of oxygen therapy to a lower FiO_2 device was also significantly shorter in group 1 (3 (2.87 - 4) days) than group 2 (7 (6 - 7) days (*p*<0.001). However, there was no significant difference in the median time to disease progression (*p*=0.859) (Table 4). The use of HFNC in group 1 significantly improved the mean (SD) PaO_2 (84.23 (9.202) v. 74.27 (4.160) and PaO_2/FiO_2 ratio (264.60 (42.019) v. 216.62 (23.868)) during treatment as compared with the NRBM. The mean (SD) RR in group 1 (23.17 (2.086)) was significantly lower than in group 2 (25.52(0.871); *p*< 0.001) (Table 5).

There was no significant difference in HR and MAP between the two groups. Patient satisfaction level as measured by VAS was higher in the HFNC group than in the NRBM group (p<0.001) (Fig. 2).

Discussion

The primary strategy for COVID-19 pneumonia patients is supportive care, including oxygen therapy for hypoxaemic patients in whom HFNC has been reported to be effective in improving oxygenation. [7,8]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 present study was the progression-free survival without escalation of oxygenation device compared between the two groups. The success rate of oxygen therapy by HFNC was higher than that of the NRBM, and the difference was statistically significant (p<0.001).

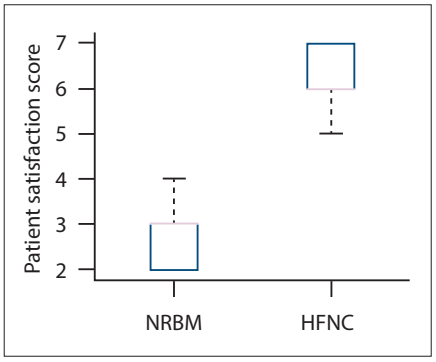

Fig. 2. Patient satisfaction score. (HFNC = high-flow nasal cannula; SNBM = standard non-rebreathing mask.)

On analysis of secondary outcomes, we noted that the use of the HFNC resulted in improved oxygenation and decreased work in 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 hypoxaemic COVID-19 patients and could have resulted in better patient outcomes. In addition, a fixed FiO_2 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.[9,10]

Patients in group 1 also reported better satisfaction with a shorter time of de-escalation to lower oxygen delivery devices as compared with 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.[11-13] The results of our present study stand in agreement with our hypothesis.

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

Table 3. Baseline patient characteristics

Parameters	HFNC, mean (SD)*	NRBM, mean (SD)*	p-value
Gender (male), n	28	32	-
Age, years	54.00 (11.58)	56.50 (3.03)	0.257
HR	85.03 (1.829)	84.23 (2.582)	0.171
MAP	73.50 (2.146)	73.23 (1.870)	0.60
PaO_2	65.07 (1.701)	65.73 (1.999)	0.173
PaO_2/FiO_2	207.03 (4.56)	207.67 (3.790)	0.556
SpO_2	91 (1.541)	90.8 (1.022)	0.555
RR	28.20 (1.157)	28.1 (1.242)	0.748

HFNC = high-flow nasal cannula; NRBM = non-rebreathing mask; SD = standard deviation; HR = heart rate; MAP= mean arterial pressure; PaO_2 = partial pressure of oxygen; PaO_2/FiO_2 = ratio of partial pressure of oxygen and fraction of inspiratory oxygen concentration; SpO_2: oxygen saturation; RR = respiration rate.

* Unless otherwise specified.

In our study, the survival following failure on HFNC is 50% (n=3/6) compared with survival following failure on NRBM which is 81% (n=5/26). This reflects that HFNC is a feasible intervention to reduce the need for mechanical ventilation, but for those who fail, their outcomes on mechanical ventilation are poor. This effect is more apparent in patients with severe hypoxaemia as stated by Calligaro *et al.*[16]

This present study emphasises the importance of timely management of moderate category hypoxaemic COVID-19 patients. Early institution of HFNC may improve the oxygenation status of the patient; hence, reducing morbidity associated with this condition. Similarly to our findings, Calligaro *et al.*[16] also emphasised that the use of HFNC outside the ICU could be a rational practice in such patients, resulting in a 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.[16]

During this COVID-19 outbreak, symptomatic care to restore oxygenation in severe acute respiratory failure has been a key challenge. A study by Demoule *et al.*[17] concluded that although HFNC lowers intubation and subsequent invasive mechanical ventilation, it does not affect the mortality rate. In a recent randomised clinical trial comparing the effect of high-flow oxygen therapy v. COT on invasive mechanical ventilation and clinical recovery in patients with severe COVID-19, high-flow oxygen therapy was found to significantly reduce the need for mechanical ventilation support and the time to clinical recovery when compared with COT. In agreement with our findings, their findings suggest that high-flow oxygen therapy reduced inspiratory effort early, potentially reducing self-inflicted lung injury and enhancing clinical outcomes.[18]

A comparison of helmet non-invasive ventilation and high-flow nasal oxygen in COVID-19 pneumonia patients in the moderate to severe categories revealed no significant differences in the number of days free of respiratory support over the study period. In comparison with high-flow oxygen therapy, the non-invasive ventilation group

Table 4. Primary and secondary outcomes

Parameters	HFNC (*N*=60), *n* (%)*	NRBM (*N*=60), *n* (%)*	*p*-value	OR (95% CI)
Success of oxygen therapy (progression-free survival)	54 (90)	34 (56.6)	<0.001	0.145 (0.054 - 0.389)
Patients requiring intubation	2 (3.3)	8 (13.3)	0.070	0.224 (0.455 - 1.103)
Time to progression to severe disease (days), median (IQR)	6 (4.5 - 6.5)	5.5 (5 - 6)	0.859	-
Time for de-escalation of oxygen therapy (days), median (IQR)	3 (2.87 - 4)	7 (6 - 8)	<0.001	-
Survival at day 28	57/60	55/60	0.468	0.578 (0.132 - 2.539)

HFNC = high-flow nasal cannula; NRBM = non-rebreathing mask; OR = odds ratio; CI = confidence interval; IQR = interquartile range.
* Unless otherwise specified.

Table 5. Vital parameters on the device

Parameters	HFNC, mean (SD)	NRBM, mean (SD)	*p*-value	OR (95% CI)
PaO_2 on device	84.23 (9.202)	74.27 (4.160)	<0.001	9.967 (6.276 - 13.657)
PaO_2/FiO_2 on device	264.60 (42.019)	216.62 (23.868)	<0.001	47.979 (30.080 - 65.878)
SpO_2 on device	95.17 (4.662)	93.53 (4.911)	0.7719	1.633 (–0.841 - 4.108)
RR	23.17 (2.086)	25.52 (0.871)	0.001	–1.351(–2.189 - [–0.512])
HR	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	-

HFNC = high-flow nasal cannula; NRBM = non-rebreathing mask; OR = odds ratio; CI = confidence interval; PaO_2 = partial pressure of oxygen; PaO_2/FiO_2 = ratio of partial pressure of oxygen and fraction of inspiratory oxygen; SpO_2 = oxygen saturation; RR = respiration rate; HR = heart rate; MAP = mean arterial pressure.

had a much lower rate of intubation and a significantly higher number of days free of invasive ventilation.[19]

The concern for aerosol dispersion has been a major limiting factor in the use of HFNC in COVID-19 patients.[20,21] Adequate personal protective equipment, adequate room ventilation, and the use of high-filtration fit-tested respirators for all healthcare workers attending to patients were available. In addition, the 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 on the use of a face mask.[22,23] On-going field experiments and clinical studies may provide additional information.

Study limitations

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

Conclusions

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

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