INTRODUCTION

High flow nasal oxygen (HFNO) delivery devices through a cannula gained major importance during the recent coronavirus disease-2019 (COVID-19) pandemic for effective oxygen therapy in patients presenting with acute hypoxaemic respiratory failure (AHRF). There are conflicting conclusions about the utility of HFNO in terms of reducing mortality or tracheal intubation rate. However, there is no confusion that HFNO delivery is a better modality to deliver humidified oxygen compared to other high flow oxygen devices in terms of better tolerance, improved oxygenation and reduced work of breathing. The Government of India Ministry of Health and Family Welfare published guidelines on clinical management of COVID-19 (version 5 dated 3 July 2020) and mentioned HFNO as the next line of therapy if hypoxia cannot be alleviated by supplemental oxygen therapy. A major limitation to provide oxygen therapy by HFNO is its availability and therefore as an alternative many clinicians use a standard non rebreathing face mask (NRBM) in order to oxygenate their patients where low-flow nasal oxygen or simple facemask oxygen is not providing adequate respiratory support to achieve the target peripheral oxygen saturation ($\text{SpO}_2$). We aimed to determine the clinical effectiveness of HFNO versus NRBM in terms of improving patient outcome among patients admitted to our intensive care unit (ICU) during coronavirus disease-2019 (COVID-19) outbreak. In this prospective open labelled study, 122 COVID-19 patients presenting with acute hypoxaemic respiratory failure (AHRF) were randomised to receive either HFNO or NRBM to achieve the target $\text{SpO}_2$. The primary clinical outcome measured was device failure rate and secondary outcome was all-cause 28-day mortality rate. Results: The device failure rate was significantly higher in HFNO group (39% versus 21%, $P = 0.030$). Oxygen support with NRBM resulted in a reduced all mortality rate over HFNO (26.2% versus 45%) but the mortality rate after treatment failure in either group (HFNO or NRBM) remained high (91% versus 92%). Conclusion: Oxygen support with NRBM results in both reduced device failure rate and higher survival among patients of COVID-19 with AHRF.

Key words: Acute hypoxaemic respiratory failure, COVID-19, high flow nasal oxygen, mortality, non-rebreathing mask, treatment failure
standard non-rebreathing oxygen face mask (NRBM) to oxygenate their patients. NIV can improve oxygenation but it has also been implicated in inducing lung injury because of generation of high tidal volume. As of now there are limited trials evaluating the effectiveness of NRBM compared to HFNO. During the pre-COVID era, there were a few studies that had compared HFNO with NRBM and out of these, one study concluded that HFNO was better during extubation whereas another revealed that HFNO was not efficient as a preoxygenation device when compared to NRBM. The present study aimed at evaluating and comparing the clinical effectiveness of NRBM versus HFNO among patients of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with AHRF in terms of treatment failure rate as primary outcome and all-cause 28-day mortality rate as secondary outcome.

**METHODS**

This prospective randomised open-labelled interventional study was conducted over a period of three months from December 2020 to March 2021 during the first wave of COVID-19 pandemic at a tertiary care state COVID hospital. The study protocol was approved by the institutional ethics committee (IEC no. 1060) and registered in Clinical trial registry, India. (CTRI/2020/12/029803). The study was conducted in accordance with the principles of the Declaration of Helsinki.

All eligible adult conscious patients of more than 18 years age with laboratory confirmed COVID-19 (detection of SARS-CoV-2 by real-time reverse transcription polymerase chain reaction) and presenting with AHRF [ratio of peripheral oxygen saturation to the inspired fraction of oxygen (SpO2/FiO2) <350] were screened for the study inclusion and the ones with SpO2 less than 90% were included after obtaining written informed consent from the study participants or their next responsible attendant. The exclusion criteria set for the study were anatomical factors precluding the use of a nasal cannula; patient’s refusal; patients who present with clear indications for NIV like type 2 respiratory failure or isolated cardiogenic pulmonary oedema; haemodynamic instability requiring vasopressor support, surgery in the preceding weeks. All management decisions other than oxygen therapy were made by the managing physicians in charge according to standard treatment as per the Government of India Ministry of Health and Family Welfare published guidelines on clinical management of COVID-19. Patients were randomised in 1:1 ratio to receive the allocated intervention as per a computer-generated random number table. Allocation concealment was done with sequentially numbered, opaque, sealed envelopes.

**HFNO protocol and management** (inspired O2 FLO, Vincent Medical Manufacturing, Hung Hom, Kowloon, Hong Kong): Oxygen (O2) therapy was initiated at a minimum initial flow of 30 litres per minute (LPM) and temperature set between 34°C and 37°C. To achieve a target SpO2 of 94%, the appropriate FiO2 was used or an increase in flows up to 60 LPM was tried. HFNO was discontinued when the total daily treatment duration came down to less than 4 hours and standard oxygen therapy was given with oxygen mask using flow of 5 LPM.

**Non-rebreathing mask protocol and management:** The NRBM delivered 15 L/min of oxygen. As with the HFNO group, the oxygen-air mixer was started with minimal flow of O2 with 6 LPM to achieve a target SpO2 of 94% and flow was increased accordingly.

Discontinuation of HFNO or NRBM and initiation of NIV or tracheal intubation [invasive mechanical ventilation (IMV)] was considered as treatment failure and was based on the clinical judgement of the primary physician, guided by a standard institutional protocol [presence of persistent/worsening respiratory distress, respiratory rate >40 breaths/min, SpO2 <90%, acidemia with pH <7.35, significant haemodynamic instability (defined as systolic blood pressure <90 mmHg, mean arterial pressure <65 mmHg or vasopressor requirement), deterioration in neurological status (Glasgow coma score <12) or inability to clear secretions]. Patients were discharged from the intensive care unit (ICU) when SpO2 was >94% on standard oxygen therapy (with oxygen mask or nasal prongs <6 LPM).

The primary outcome of the study was treatment failure rate with either device. The secondary outcome was the all-cause 28-day mortality rate. Also, our study tried to evaluate time to achieve target SpO2 defined as institution of a particular oxygen therapy and time to reach target SpO2 of 94%, patient comfort with the assigned device by an 11-point Visual Analogue Scale (VAS), where “0” denotes severe discomfort, and “10” denotes perfect comfort.

The intubation rate with NRBM group has been reported to be 47%. To detect 50% reduction in
intubation rate (treatment failure) with HFNO group, the estimated sample size was 61 subjects per group with a confidence level \( [1 - \alpha] = 95\% \) and power level \( [1 - \beta] = 80\% \).[1]

The continuous variables were described as mean (± standard deviation) or medians (interquartile ranges, 25th to 75th percentiles) and categorical variables as proportions. Between-group comparisons for continuous variables were performed using Student’s two-tailed \( t \)-test or nonparametric Mann-Whitney U-test in the case of non-normal distribution. Chi-square test or Fisher’s exact test, in case of low expected frequencies, was used for comparisons of categorical variables. “Worst case scenario” analysis was done where a patient opting for discharge against medical advice (DAMA) was deemed to have died. All statistical tests were two sided, and \( P < 0.05 \) was considered statistically significant. All data were analysed using the Statistical Package for the Social Sciences (SPSS) statistical software package, version 16.0 for Windows (SPSS, Chicago, IL).

**RESULTS**

One hundred twenty-two COVID-19 patients with AHRF were prescribed to receive either HFNO (HFNO group = 61) or NRBM (NRBM group = 61) as first line oxygen therapy to meet the target \( \text{SpO}_2 \) of 94% as per their random number allocation [Figure 1].

Both the groups had comparable demographic data and baseline clinical variables such as dyspnoea on admission measured on a modified Borg scale,[11] \( \text{SpO}_2/\text{FiO}_2 \) ratio and co-morbidities. Majority of the patients had either diabetes mellitus or hypertension as co-morbidity [Table 1]. Sixty-one patients received HFNO, out of which 37 patients were successfully weaned and 24 patients needed escalation to second line oxygen therapy (treatment failure) but later, six patients had unexpected cardiac arrest in the ICU after successful weaning from HFNO. Among the treatment failure patients, two were prescribed invasive mechanical ventilation with tracheal intubation and 22 were prescribed NIV, of which again two could be weaned off and discharged from the ICU and 22 patients could not be weaned and they expired [Figure 2].

Among the 61 patients treated with NRBM, 48 patients were weaned off and the median duration

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**Figure 1:** Consolidated Standards of Reporting Trials (CONSORT) Flow Diagram
The time to achieve target saturation after allocation to a study arm was faster in NRBM group, but patients from HFNO group had a higher comfort score (measured with 11-point VAS) compared to NRBM group. The all-cause 28-day mortality after adding three patients who were discharged against medical advice was significantly lower for NRBM compared to HFNO group (26% versus 45%, \( P = 0.038 \)). Similarly, the device failure rate necessitating institution of second line oxygen therapy (NIV or IMV) was also lower in NRBM group (21% versus 39%, \( P = 0.030 \)). However, the mortality resulting from device failure was high and similar in both the groups. The duration of treatment on the allocated oxygen delivery device (HFNO or NRBM) and duration of ICU stay was significantly longer in patients receiving HFNO compared to NRBM [Table 2].

**DISCUSSION**

In the current pandemic, the drug that can be used beyond doubt for the benefit of a COVID-19 patient is oxygen, and thus oxygen therapy remains the cornerstone therapy in moderate and severely infected patients with SARS-CoV-2. Choosing an appropriate device to deliver oxygen to the needy patient is a basic requirement, while chasing the SpO\(_2\), to reach the...
target of 94%, while aiming for an overall improvement of the patient.

The current study compared two commonly used oxygen delivery devices, namely, HFNO and NRBM, regarding their effectiveness in improving $\text{SpO}_2$. The study results suggest several clinical advantages of NRBM in terms of time to reach target $\text{SpO}_2$, reduced treatment failure rate and improved survivability [Table 1].

One of the major issues in the COVID triage room was accepting patients with much worse health than they realised because of “Happy Hypoxia.” The basic requirement in the COVID triage room was to improve the dropped oxygen saturation to avoid any casualty while triaging the patient to the appropriate care area.

The Brussel study observed a 1–4% increase in $\text{SpO}_2$ when a simple surgical mask was placed on top of a high-flow nasal cannula. The researcher opined that placement of the surgical mask reduced the room air entrainment and dilution of the delivered oxygen through HFNO. However, considering a shortage of oxygen supply in the current pandemic, one finds it difficult to justify the use of such high flow oxygen (60 LPM) through HFNO. In the current study, a tight fitting NRBM was used and a similar increase in $\text{SpO}_2$ within 90 seconds by using a flow rate of 15 LPM could be demonstrated. The time to achieve target saturation is faster with NRBM compared to HFNO [Table 2]. This could be because, though both the devices provide high concentration oxygen, there is a risk that the oxygen delivered through unsealed HFNO might have been affected because of not strictly adopting to size of the nasal cannula in the current study protocol and thereby failing to provide adequate oxygen.

The other strong point in the current study was the application of $\text{SpO}_2$/FiO$_2$ ratio (S/F ratio) to screen our patients for triage unlike majority of the studies. subjecting the patients to an arterial blood gas analysis. The reason for this is twofold; first, the national guidelines which clearly advocate the use of $\text{SpO}_2$ as an alternative to $\text{PaO}_2$, keeping in view the patients convenience, scarce availability of a blood gas analyser and shortage of health care workers, second, the observations from a French study indicating the utility of $\text{SpO}_2$/FiO$_2$ ratio for triage and suggesting a threshold $\text{SpO}_2$/FiO$_2$ ratio of <350 for ICU admission.

Among critically ill patients, it is difficult to assess dyspnoea and comfort as most of the patients are on ventilator, not able to talk and are psychologically depressed. A systematic analysis done in 2019 concluded that HFNO had no impact on comfort and dyspnoea. The intensity of dyspnoea measured with Borg scale was similar in both the groups, whereas patients with HFNO felt relatively comfortable compared to NRBM when measured with VAS [Table 2], similar to a study which revealed that HFNO is more comfortable for patients based on the ease in feeding and communication with health care workers.

Many initial studies have confirmed the beneficial effect of HFNO in improving the oxygen saturation and delaying institution of second-line therapy like NIV or tracheal intubation. On the other hand, later studies questioned the utility of HFNO in the current COVID-19 pandemic citing its potential for viral spread. A South African bi-centre study observed an overall mortality of 44% in 293 consecutive patients with COVID-19-related AHRF treated with HFNO which is similar to our study (45%) where 28 patients expired among HFNO group and device failure rate was 39% (n = 24/61) among HFNO group which is very similar to a retrospective study where 39% patients failed with HFNO (40/105). However, it is interesting to note that, simple application of NRBM in place of HFNO not only reduced the mortality by 19% [Figure 2], but it also significantly reduced the

### Table 2: Comparison of outcome measures between HFNO and NRBM

| Parameter                           | HFNO $(n=61)$ | NRBM $(n=61)$ | $P$   |
|-------------------------------------|---------------|---------------|-------|
| Time to reach $\text{SpO}_2$ of 94% in seconds mean (SD) | 63 (12)       | 53.4 (10)     | <0.001 |
| Patient comfort on a VAS, median (IQR 25-75%) | 6 (4-8)       | 4 (3-6)       | =0.008 |
| Duration of treatment in days, median (IQR 25-75%) | 8 (6-19.5)    | 7 (5.5-9)     | <0.001 |
| Treatment failure rate n (%)        | 24 (39.3%)    | 13 (21%)      | =0.030 |
| Days in ICU, median (IQR 25-75%)    | 12 (8-24)     | 10 (8-13)     | =0.001 |
| Mortality*, n (%)                   | 28 (45)       | 16 (26)       | =0.038 |

HFNO - high flow nasal oxygen cannula; NRBM - non-rebreathing oxygen face mask; $\text{SpO}_2$ - peripheral arterial oxygen saturation measured by pulse oximeter; SD - standard deviation; VAS - visual analogue scale for measuring patient comfort; *Patients who got discharged against medical advice and ICU mortality combined.
device failure rate by 18% [Figure 2]. This is in contrast to a French study where the control group (simple oxygen face mask) had a mortality of 30%.\[10\]

To our knowledge, to date, this is the first randomised interventional study to evaluate the effectiveness and outcomes of HFNO versus NRBM in a prospective cohort of 122 confirmed COVID-19 patients with AHRF. The only other study which compared HFNO versus NRBM plus nasal cannula is a non-peer-reviewed small retrospective study of 54 patients published in preprint format. In the study, no difference was observed between the two interventions in terms of mortality and the need for invasive mechanical ventilation.\[22\]

One area of concern in our study results was the high mortality rate in the treatment failure group with either device (HFNO or NRBM). This implies that, both HFNO and NRBM could bring the target oxygen saturation to an acceptable level but do not actually reduce the mortality related to device failure. On the other hand, we could clearly demonstrate that NRBM reduced the mortality significantly [Figure 1].

Nevertheless, most of the available literature\[2,19\] suggests similar trends in the treatment failure group, thus raising the doubt whether our study intervention [median interquartile range (IQR)\[25-79\%\], 8 (6–19.5) days with HFNO versus 7 (5.5–9)]with NRBM [Table 2] delayed the institution of second-line therapy and thus contributed to the high mortality. A retrospective observational study from a tertiary care centre in India suggested that early tracheal intubation reduces the mortality associated with severe COVID-19-associated acute respiratory distress syndrome (ARDS). However, the accompanying editorial suggests a cautious approach while deciding for tracheal intubation and permits the use of alternative modes of oxygenation if clinical judgment permits.\[23,24\] Considering the fact that COVID-19 is a complex disease with features suggestive of both ARDS and acute vascular distress syndrome, one has to do further randomised controlled trials to find out the best time to intervene and the best possible therapy in case of first-line treatment failure.\[25,26\]

There are a few limitations to our study. First, we have not done any statistical analysis to decide age or comorbidity adjusted mortality to draw a firm conclusion. Second, the likelihood of differential treatment to the study participants might have been affected by the lack of blinding. Third, serial blood gas analysis was not done to find out any carbon dioxide build up which could have resulted in device failure.

**CONCLUSION**

Based on the observations, we conclude that, NRBM is an effective first line oxygen delivery device in COVID-19 patients presenting with AHRF. HFNO is more comfortable compared to NRBM. Oxygen support with NRBM not only results in a lower mortality rate but also provides shorter duration of ICU stay and reduced device failure rate. However, treatment failure with either device is associated with higher all-cause 28-day mortality.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

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