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ORIGINAL RESEARCH ARTICLE

A Randomised Comparative Study of High-Flow Oxygen Through Nasal Cannula and Non-invasive Ventilation in Patients with Acute Hypoxemic Respiratory Failure

Vishwajeet Rajput[1], Lalit Singh[2*], Yatin Mehta[3]

ABSTRACT

Introduction: Type 1 or acute hypoxemic respiratory failure (AHRF) is a condition of hypoxemia (PaO_2<60 mm of Hg) – insufficient enough to meet the metabolism of the body – thereby requiring ICU admission and use of adequate ventilatory support. Studies have not yet been able to confirm which out of the high-flow oxygen through nasal cannula (HFNC) and non-invasive ventilation (NIV) is better in managing such patients. To compare efficacy and outcome of HFNC and NIV in acute hypoxemic respiratory failure.

Materials and Methods: This randomized comparative study conducted at Critical Care Unit, SRMSIMS, Bareilly from February 2021 to August 2022, included 99 patients with AHRF (≥ 18 years) randomized to either those who received HFNC (n = 41) or those who received NIV (n = 58). The demographic characteristics were noted. The hemodynamic parameters were noted at baseline, 1 to 2, 12 and 24 hours. The outcomes were duration of treatment and mortality rate.

Results: Compared to NIV group, Mean ± SD of FiO_2 (%) at baseline, 1 to 2, at 6, at 12, and 24 hours in HFNC was 97.46 ± 0.5, 93.05 ± 3.01, 82.49 ± 3.25, 74.78 ± 3.32, 58.83 ± 5.62 respectively, which was significantly lower as compared to NIV (100 ± 0, 94.4 ± 2.11, 83.78 ± 2.88, 76.28 ± 2.93, 60.43 ± 3.95, p<0.05). Median (25^{th}–75^{th} percentile) of PaO_2/FiO_2 at baseline, at 1 to 2 hours, at 12 hours, at 24 hours in HFNC was 156 (153–165), 195 (190–202), 237 (233–242), 266 (260–277) respectively which was significantly lower as compared to NIV 164.5 (157–174), 201.5 (191.25–215), 241 (235.25–245), 277.5(262.25–288), respectively (p<0.05). HFNC group had a significantly lower mean duration of respiratory support (2.37 ± 1.09 vs. 3.9 ± 2.03 days, P = 0.0002). Total 9 (21.95%) cases expired in HFNC group as compared to 17 (29.31%) cases in NIV group (p = 0.412).

Conclusion: To conclude, the treatment with non-invasive ventilation was better than high-flow nasal oxygen in patients of AHRF and led to better maintenance of respiratory parameters. Overall, in terms of outcome, both interventions had similar mortality rates. Future studies should be conducted on larger set of the population for verifying the data for providing better outcomes to the patients.

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INTRODUCTION

Type 1 or acute hypoxemic respiratory failure (AHRF) is a condition of hypoxemia (PaO_2<60 mm of Hg) – insufficient enough to meet the metabolism of the body – thereby requiring ICU admission and use of adequate ventilatory support.[1]

The first-line therapy for ARHF remains the delivery of oxygen therapy by using a face mask with bag reservoir. However, it holds limitations in terms of less delivery of fraction of inspired oxygen (FiO_2) and rather more delivery of dry gas, impairing the mucociliary functions of the respiratory tract.[2] Besides, the modes of non-invasive ventilation (NIV) have been rampantly explored especially in respiratory conditions of chronic obstructive pulmonary disease (COPD) and acute cardiogenic pulmonary edema (ACPE);[3,4] however, its use in AHRF has been conflicting with treatment failure rates as high as 50%, with high mortality; thereby requiring further research.[5-7] Moreover, the patients may not tolerate NIV as there are leaks of oxygen around the mask or there may be patients ventilator asynchrony or signs of barotrauma or respiratory distress arising by intake of high tidal volume due to positive pressure.[3,4]

To supersede NIV in patients of AHRF, the use of high-flow nasal cannula (HFNC) has been upcoming and spreading in the clinical practice in adult ICUs after being proven in the pediatric and neonatal ICUs as the first-line treatment for managing respiratory distress syndrome and apnea of prematurity.[8]

HFNC is one of the techniques where hot and humidified air, mainly oxygen, is delivered through the nose with high speed.[9,10] The high flow rates manage the low levels of the positive pressure, allowing for adjustment of the FiO_2 in the driving gas. There are

associated advantages like washing out of the dead space in upper airways, leading to a decrease in the work of breathing. Primarily in the patients of AHRF, HFNC can result in better comfort and oxygenation compared to the standard oxygen therapy delivered through the face mask.[9-18] However, not many studies have compared the effects of HFNC in relation to NIV on intubation rate, mortality and other outcomes of ICU patients who are admitted with AHRF.

Thus, we conducted this study where we randomized patients to either NIV or HFNC and determined the use of mechanical ventilation, rate of intubation, and outcomes in terms of patients' health and discharge and failure of therapy. The study results may help us to know whether HFNC or NIV is better therapy for managing the patients of AHRF.

MATERIAL AND METHODS

A randomized comparative study was done in the critical care department from February 2021 to August 2022 over 18 months. In the case of consecutive patients with AHRF (≥ 18 years) who attended the Critical Care Unit during study period were screened for eligibility based on the following criteria.

Inclusion criteria

- Age ≥ 18 years
- Respiratory rate > 22
- Arterial oxygenation/supplemental oxygenation ratio between 150 to 300
- pCO_2< 45 mmHg
- No underlying chronic respiratory failure

Exclusion criteria

- Chronic lung disease
- Cardiogenic pulmonary edema
- Contraindication to NIV
- Shock
- Hypercapnia> 45 mmHg
- Urgent need of intubation

Sample size

The final sample size chosen for the study was based on the results of a previous study of Frat JP *et al.*[9] who observed that mortality rate in HFNC was 15% and in NIV was 46%.

$$n = ((p_c X(1-p_c) + p_e X(1-p_e)) X (Z_\alpha + Z_\beta)^2)/(p_c - p_e)^2$$

pc= mortality rate in HFNC
pe= mortality rate in NIV

$Z\alpha$ is the value of Z (Normal variate) at two-sided alpha error of 5% and Zβ is the value of Z (Normal variate) at power of 90%.

Calculations

n>=((.15*(1-.15)+.46*(1-.46))*(1.96+1.28)^2)/(.15-.46)^2
>=41.06=41(approx.)

So, a minimum 41 patients were taken in each group. Patients who met the inclusion criteria with no contraindication to NIV or HFNC were included in the study after obtaining their written informed consent. The study protocol was duly approval from the institutional ethics committee and review board.

Randomization

The study population was randomized into two groups as per the computerized randomization technique. For randomly selecting between the two groups, random numbers were generated using the computer function "RANDBETWEEN()" which chose one out of two numbers 1 and 2. On starting this computer function for every patient, if 1 was generated, HFNC group was allocated to the patient and if 2 was generated, NIV group was allocated. So by computerized randomization, 41 were allocated in HFNC and 58 were allocated in NIV. A CONSORT flow of the patients is shown in Figure 1.

Procedure

Detailed history was taken and a physical examination was done. Baseline demographic and clinical characteristics like age, gender, clinical features with duration and comorbidities were noted for all patients. Glasgow coma scale (GCS) and APACHE score was assessed. Hemodynamic and respiratory parameters such as respiratory rate (RR), heart rate (HR), mean arterial pressure (MAP), partial pressure of oxygen (PaO_2), carbon dioxide ($PaCO_2$), FiO2, PaO_2/FiO_2 were assessed at time points of baseline, at 1 to 2 hours, 12 hours and 24 hours after initiation of HFNC/NIV.

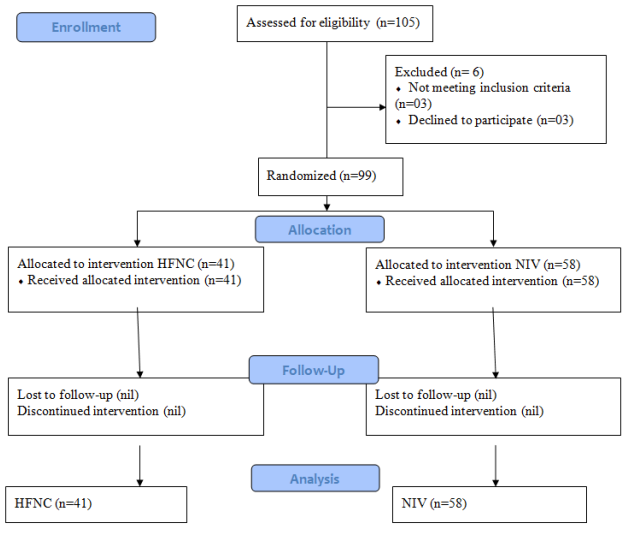

Figure 1: Participant flow algorithm

Outcomes

Outcomes were compared in terms of duration of HFNC/NIV use, success of intervention, need for intubation or switching to another modality as a rescue therapy. For NIV group, the rescue therapy was HFNC if the former became intolerant to the patient and for HFNC, the rescue therapy was NIV if the patient did not require urgent intubation. The patients were followed up till death or discharge.

Statistical analysis

The data are presented as number and percentage (n,%), mean ± SD and as median with 25 and 75th percentiles (interquartile range). The tests used were Mann-Whitney test, Independent t-test and Chi-square test. Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, USA, ver 25.0 was used for statistical analysis. $p < 0.05$ was considered statistically significant.

RESULTS

Demographic and Clinical Characteristics of Study Patients

The mean age of the patients was 43.91 ± 10.68 years. Compared to NIV, HFNC had a significantly lower mean age (36.32 ± 11.39 vs. 49.28 ± 5.87, p<.0001). There were 71 (71.72%) males and 28 (28.28%) females. Compared to NIV, HFNC had a comparable number of males (73.17 vs. 70.69%) and females (26.83 vs. 29.31%) (p = 0.787). The clinical features among the patients comprised of cough (58.59%), breathlessness (73.74%), expectoration if cough is present (23.23%), fever (59.60%), chest pain (27.27%), swelling of legs (17.17%), palpitation (38.38%), abdominal pain (6.06%), and other clinical features (2.02%). The median duration of cough was 28.5 days, breathlessness (28 days), fever (30 days), chest pain (26 days), swelling of legs (29 days), palpitation (31.5 days), abdominal pain (19.5 days), and other clinical features (42 days). The clinical features were more or less similar among the two groups except for expectoration if cough is present (34.15 vs. 15.52%, p = 0.031), which was significantly more in HFNC group. The comorbidities were diabetes mellitus (48.48%), hypertension (37.37%), coronary artery disease (37.37%), thyroid disorder (13.13%), chronic kidney disease (8.08%), and RA, Potts spine, multiple myeloma, SAIO, and obesity. HFNC group had significantly more hypertension (48.78 vs. 29.31%, p = 0.049) and coronary artery disease (48.78 vs. 29.31%, p = 0.049). The comparison of demographic and clinical characteristics of the patients in the two groups in shown in Table 1.

The median GCS and APACHE scores were 11 and 36, respectively. Compared to NIV, HFNC had a significantly higher median GCS score (12 vs. 10, p<.0001) and a significantly lower APACHE score (33 vs 38, p<.0001) (Table 1).

Table 1: Demographic and clinical characteristics of the patients

Parameters	*HFNC (n=41)*	*NIV (n=58)*	*p-value*
Age	36.32 ± 11.39	49.28 ± 5.87	<.0001
Gender			
Males	30 (73.17%)	41 (70.69%)	0.787
Females	11 (26.83%)	17 (29.31%)	
Clinical features			
Cough	24 (58.54%)	34 (58.62%)	0.993
Expectoration	14 (34.15%)	9 (15.52%)	0.031
Breathlessness	32 (78.05%)	41 (70.69%)	0.412
Chest pain	11 (26.83%)	16 (27.59%)	0.934
Fever	24 (58.54%)	35 (60.34%)	0.857
Palpitation	16 (39.02%)	22 (37.93%)	0.604
Swelling of legs	8 (19.51%)	9 (15.52%)	0.396
Abdominal pain	1 (2.44%)	5 (8.62%)	0.169
Other clinical features	2 (4.88%)	0 (0%)	
Co-morbid conditions			
Diabetes mellitus	18 (43.90%)	30 (51.72%)	0.443
Hypertension	20 (48.78%)	17 (29.31%)	0.049
Chronic kidney disease	3 (7.32%)	5 (8.62%)	1
Coronary artery disease	20 (48.78%)	17 (29.31%)	0.049
Any malignancy	0 (0%)	4 (6.90%)	0.14
Obesity	14 (34.15%)	17 (29.31%)	0.609
Cerebrovascular accident	3 (7.32%)	4 (6.90%)	1
Thyroid disorder	4 (9.76%)	9 (15.52%)	0.549
Mean Glasgow coma scale	11.44 ± 1.29	10.14 ± 0.93	<.0001
Mean APACHE score	32.59 ± 2	37.79 ± 1.74	<.0001

Table 2: Descriptive statistics of HFNC characteristics of study subjects

HFNC characteristics	*Mean ± SD*	*Median(25-75th percentile)*	*Range*
Temperature (°C)			
At baseline	32.68 ± 2	34 (32–35)	31–37
At 1-2 hours	35.56 ± 1.21	36 (34–37)	34–37
At 6 hours	34.93 ± 0.85	35 (34–36)	34–36
At 12 hours	34.41 ± 0.5	34 (34–35)	34–35
At 24 hours	32.51 ± 1	33 (32–33)	31–34
Flow (L/min)			
At baseline	60 ± 0	60 (60–60)	60–60
At 1-2 hours	57.68 ± 1.62	58 (56–59)	55–60
At 6 hours	52.51 ± 1.6	54 (51–54)	50–55
At 12 hours	42.95 ± 2.29	45 (42–47)	40–50
At 24 hours	33.44 ± 3.11	35 (31–37)	30–40

Table 3: Descriptive statistics of NIV characteristics of study subjects

NIV characteristics	*Mean ± SD*	*Median(25-75th percentile)*	*Range*
Inspiratory pressure(cm H_2O)			
At baseline	10.97 ± 0.8	11 (10–12)	10–12
At 1-2 hours	8.87 ± 0.81	9 (8–10)	8–10
At 6 hours	6.98 ± 0.83	8 (6–8)	6–9
At 12 hours	5.65 ± 0.5	5 (5–6)	5–6
At 24 hours	5.12 ± 0	5.34 (5–5)	5–5
PEEP/CPAP(cm H_2O)			
At baseline	14.36 ± 0.83	15 (14–16)	14–16
At 1-2 hours	12.43 ± 0.81	13 (12–14)	12–14
At 6 hours	10.21 ± 0.81	11 (10–12)	10–12
At 12 hours	9.48 ± 0.5	9 (9–10)	9–10
At 24 hours	8.4 ± 0.49	9 (8–9)	8–9

HFNC and NIV

HFNC characteristics were temperature in the range of 31 to 37°C and flow in the range of 30 to 60 L/min as shown in Table 2. NIV characteristics were inspiratory pressure in the 5 to 12 cm H2O range and PEEP/CPAP in the 8 to 16 cm H_2O range as shown in Table 3.

Hemodynamic parameters

Median(25–75th percentile) of respiratory rate(per minute) at baseline, at 1-2 hours, at 12 hours, at 24 hours in HFNC was 31(28–35), 27(25–33), 22(21–24) and 19(18–19) respectively which was significantly lower as compared to NIV (34(30.25–38), 35(33–36), 26(25–27) and 21(20–22) respectively) with statistically significant values at baseline (*p-value*=0.006), at 1 to 2 hours (*p-value*<.0001), at 12 hours (*p-value*<.0001), and at 24 hours (*p-value*<.0001). (Figure 2)

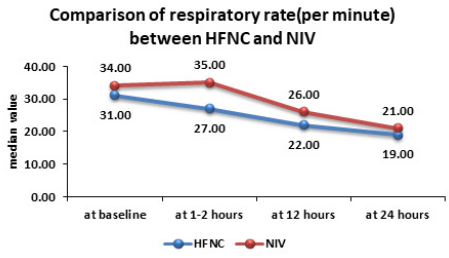

Figure 2: Comparison of trend of respiratory rate(per minute) at different time intervals between HFNC and NIV

Mean ± SD of heart rate(per minute) at baseline, at 1-2 hours, at 12 hours, at 24 hours in HFNC was 122.29 ± 5.88, 103.1 ± 4.59, 88.17 ± 2.9, 70.34 ± 3.47 respectively which was significantly higher as compared to NIV (119.19 ± 6.19, 99.76 ± 5.21, 84.14 ± 2.81, 67.33 ± 1.81 respectively) with statistically significant values at baseline (*p-value*=0.014), at 1-2 hours (*p-value*=0.001), at 12 hours (*p-value*<.0001), at 24 hours (*p-value*<.0001) between HFNC and NIV (Figure 3).

Mean ± SD of mean arterial pressure (mmHg) at baseline, at 1 to 2 hours, at 12 hours in HFNC was 62.37 ± 3.06, 70.56 ± 3.91, 78.39 ± 5.76, respectively which was significantly higher as compared to NIV (59.83 ± 3.44, 65.17 ± 5.3, 70.29 ± 3.53, respectively, with statistically significant values at baseline (*p-value* = 0.0003), at 1 to 2 hours (*p-value* <.0001), at 12 hours (*p-value* <.0001), at 24 hours (*p-value* = 0.003). However, mean ± SD of mean arterial pressure (mmHg) at 24 hours in HFNC was 88.05 ± 4.16, significantly lower than NIV (90.31 ± 3.22) (Figure 4).

Median (25–75th percentile) of $PaCO_2$ (mmHg) at baseline, at 1 to 2 hours, at 12 hours, at 24 hours in HFNC was 38 (36–39), 38 (35–41), 36 (35–39), 36 (33–38) respectively which

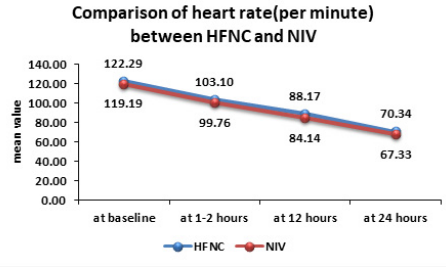

Figure 3: Comparison of trend of heart rate(per minute) at different time intervals between HFNC and NIV

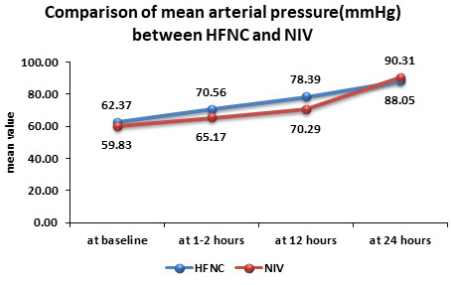

Figure 4: Comparison of trend of mean arterial pressure (mmHg) at different time intervals between HFNC and NIV

was significantly lower as compared to NIV 46 (45–48), 40 (37–42), 40 (37–42), 40 (37–42), respectively with statistically significant values at baseline (*p-value* <.0001), at 1 to 2 hours (*p-value* = 0.013), at 12 hours (*p-value* <.0001), at 24 hours (*p-value* <.0001) (Figure 5).

Median (25–75th percentile) of PaO_2/FiO_2 at baseline, at 1 to 2 hours, at 12 hours, at 24 hours in HFNC was 156 (153–165), 195 (190–202), 237 (233–242), 266 (260–277) respectively which was significantly lower as compared to NIV 164.5 (157–174), 201.5 (191.25–215), 241 (235.25–245), 277.5 (262.25–288), respectively with statistically significant values at baseline (*p-value* = 0.002), at 1 to 2 hours (*p-value* = 0.049), at 12 hours (*p-value* = 0.015), at 24 hours (*p-value* = 0.012) (Figure 6).

Compared to NIV group, Mean ± SD of FiO_2(%) at baseline, 1-2 hours, at 6 hours, at 12 hours, at 24 hours in HFNC was 97.46 ± 0.5, 93.05 ± 3.01, 82.49 ± 3.25, 74.78 ± 3.32, 58.83 ± 5.62, respectively was significantly lower as compared to NIV (100 ± 0, 94.4 ± 2.11, 83.78 ± 2.88, 76.28 ± 2.93, 60.43 ± 3.95 respectively) with statistically significant values at baseline (*p-value* <.0001), at 1 to 2 hours (*p-value* =0.01), at 6 hours(*p-value* = 0.04), at 12 hours (*p-value* = 0.02), at 24 hours (*p-value* = 0.043) (Figure 7).

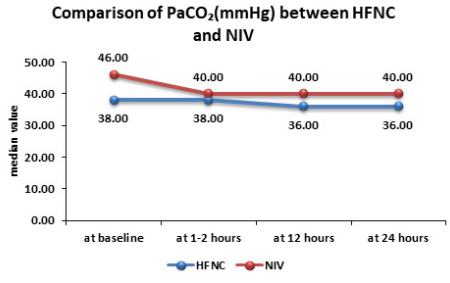

Figure 5: Comparison of $PaCO_2$ (mmHg) trend at different time intervals between HFNC and NIV

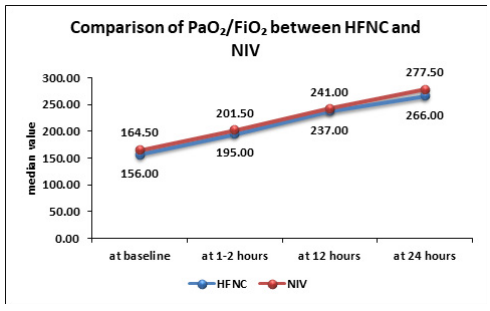

Figure 6: Comparison of trend of PaO_2/FiO_2 at different time intervals between HFNC and NIV

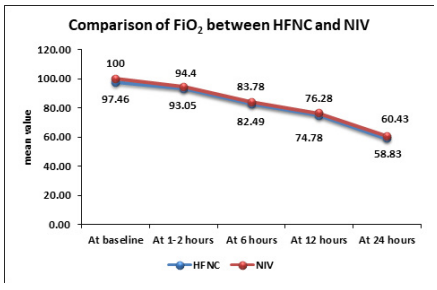

Figure 7: Comparison of FiO_2 between HFNC and NIV

Table 4: Comparison of outcomes between HFNC and NIV

Outcomes	*HFNC (n=41)*	*NIV (n=58)*	*p-value*
Duration (days)	2.37 ± 1.09	3.9 ± 2.03	0.0002
Mortality	9 (21.95%)	17 (29.31%)	0.412

Outcomes

The intervention showed success in both groups with no failures. HFNC group had a significantly lower mean duration of HFNC/NIV (2.37 ± 1.09 vs. 3.9 ± 2.03 days, p = 0.0002). A total 9 (21.95%) cases expired in HFNC group as compared to 17 (29.31%) cases in NIV group with no significant difference in the mortality rate in two groups (p = 0.412) (Table 4).

DISCUSSION

AHRF patients generally present with higher respiratory rate and lower levels of PaO2/FiO2, which is a devastating condition whose diagnosis and management remains critical while managing the ICU. In the present study, PaO_2/FiO_2 was monitored at baseline and then at 1 to 2 hours, 12 hours and 24 hours. The median values of PaO_2/FiO_2 in HFNC group were 156 to 266 and in NIV group were 164.5 to 277.5 at different time periods. Overall, there was better maintenance of PaO_2/FiO_2 in NIV group. This was in slight contrast with the findings by Duan *et al.* who observed that compared to NIV, HFNC had similar mean PaO2/FiO2 (mm Hg) at baseline (196 vs. 165), 1 to 2 hours (210 vs. 211), 12 hours (212 vs. 203), and 24 hours (224 vs. 202) (p>0.05).[19] Among other earlier studies, Nair *et al.* found that there was no significant difference in PaO_2/FiO_2 ratio in the HFNC and NIV groups (112.1 vs. 115.3, p>0.05), but they measured hemodynamic parameters up to 48 hours only.[20] Peng Y *et al.* conducted a meta-analysis including 23 studies that evaluated HFNC and NIV in COVID-19 patients with AHRF. Compared to HFNC group, the NIV group had similar PaO2/FiO2 (p>0.05).[21] The different findings can be because of different patient characteristics.

In the present study, compared to NIV group, HFNC group had significantly lower mean duration of use (2.37 ± 1.09 vs. 3.9 ± 2.03 days, p = 0.0002).This was in accordance with the finding by Costa *et al.*,[17] who reported a longer therapy time in the HFNC group than NIV group (700 vs. 200 min, p<0.05). However, Papachatzakis Y *et al.* found that the median continuous for 24 hours use of either HFNC or NIV was 2 ± 2 days. There was no significant difference in duration of continuous for 24 hours in HFNC and NIV groups (2 ± 1 vs. 2 ± 9, *p* = 0.078).[18]

Regarding mortality, we found that 9 (21.95%) cases expired in HFNC group compared to 17 (29.31%) cases in NIV group; but the values failed to cross the boundaries of statistical significance. (*p-value* = 0.412). This is in line with the studies by Costa *et al.*,[17] who reported that the

median 30-day and overall mortality rates were 6 and 10%, respectively. In comparison with NIV, HFNC had similar rate of 30-day mortality (3 vs. 3%, p >0.05) and overall mortality rate (5 vs. 5%, p >0.05). Similarly, Nair *et al.* found that there was no significant difference in hospital mortality between HFNC and NIV groups (29.1% vs. 46.2%) (relative risk: 0.6, 95% CI: 0.38–1.04, p = .06).[20] Even Papachatzakis Y *et al.* found that the rate of mortality was 15%. There was no significant difference in HFNC and NIV groups in terms of mortality (15 vs. 15%, p = 0.669).[18] Frat JP *et al.* found that there was a significantly higher mortality risk at 90 days in the NIV group with hazard ratio of 2.50 (compared with HFNC group, p = 0.006).[9] Peng Y *et al.* conducted a meta-analysis including 23 studies that evaluated HFNC and NIV in COVID-19 patients with AHRF. Compared to HFNC group, the NIV group had a significantly higher mortality rate (OR = 0.66, 95% CI: 0.51–0.84, p = 0.0008). The difference in the findings might be because of different diagnoses especially in relation to COVID-19.[21]

Overall, the study showed that HFNC/NIV both holds equal weightage in improving the oxygenation of the patients with AHRF without causing significant side-effects with NIV showing superiority over HFNC in maintaining the respiratory parameters. This holds practical importance in providing data of use of these interventions in the present times of pandemic of COVID-19 for which the commonest reason of ICU admission was hypoxemia. Though it was a randomized study, there were differences in the age group of the patients, clinical features and comorbidities of the patients in the two groups, but more or less both groups faired well when followed up for 24 hours after initiation of therapy. But nonetheless, this fact cannot be ignored that higher age and comorbidities like diabetes mellitus, hypertension and coronary heart disease can have detrimental effects on the outcomes of the patients, especially in relation to COVID-19.[16]

In the present study, the mean age of the patients was 43.91 ± 10.68 years and compared to NIV, HFNC had significantly lower mean age (36.32 ± 11.39 vs. 49.28 ± 5.87, p<.0001). In comparison, previous studies report a more elderly population such as Costa WNDS *et al.*[17] who reported results on a population of mean age of 68.8 ± 18.5 years, Papachatzakis *et al.* (77 years)[18] and Frat JP *et al.* (61 years).[9] This could bring about variation in the outcomes of the patients with respect to the intervention. Moreover, the study had higher M:F ratio (3:1) which is in line with other studies [9,17,18] of male predominance accounted by the more outgoing nature of males and habits of alcohol and smoking. Also, the two groups' comorbidities like hypertension and coronary heart disease were differently present, which may account for variation in the outcomes.

Limitations of the study

- The effectiveness of NIV and HFNC may be limited because we were unable to determine how they affected patient discomfort.
- Following a longer experimental protocol was difficult for patients experiencing acute respiratory distress.
- The results of the current study cannot be generalized because it was a single-center study.
- Although the randomization ensured the comparable baseline characteristics of both groups' patients, we could not do blinding of the procedures for the operator.
- Complications associated with HFNC and NIV were not assessed.

CONCLUSION

The treatment with NIV was observed to be better than HFNC and led to better maintenance of respiratory parameters such as respiratory rate, $PaCO_2$, and PaO_2/FiO_2. Overall, in terms of outcome, both interventions had similar mortality rates. However, it must be noted that the success and duration of treatment of non-invasive strategies depend on tolerance and patient compliance. The disease's severity and the patient's condition may affect the individual treatment. It is recommended to conduct future studies on a larger population for verifying and further elaborating the data for better patient outcomes.

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