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Comparison of non invasive ventilation and high-flow nasal cannula oxygenation in patients with covid-19: A randomized clinical study

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Abstract: *Introduction:* Non invasive ventilation (NIV) is a pressure-targeted modality and due to pressure efficacy of NIV is determined. High-flow nasal cannula (HFNC) is a non invasive ventilator which provides oxygenation with high flow and is well-tolerated assist device. There are limited studies comparing the effect of two methods of oxygen administration among covid-19 patients. Hence this study was conducted to compare the use of HFNC and NIV as first line of treatment in covid -19 patients with respiratory failure. *Methods:* This study was done on 82 patients diagnosed with covid-19 infection, 41 patients in NIV group and 41 patients in HFNC group. Patients with rtPCR positive in hypoxemic respiratory failure who require NIV or HFNC as first line of treatment, patients aged between 20-60 years and weighing between 40-80kgs were included in the study. *Results:* There was no significant difference statistically in regards to mean heart rate, mean respiratory rate, pH and $PaCO_2$ .There was no significant statistical difference in oxygen saturation (Spo_2) from admission till 48 hours in between the two groups and there was statistically significant difference from 48 hours of admission to day 6. In NIV group, 4.9% required intubation and in HFNC group 19.5% required intubation. *Conclusion:* Patients who are diagnosed with covid-19 and in acutehypoxemic respiratory failure can be treated either with NIV or HFNC as a first line of treatment. NIV is more effective in terms of improvement in saturation, reduced respiratory rate and decrease in ICU stay with good haemodynamic stabilty. NIV group had less intubation rate and more compliance compared to HFNC group.

Keywords: High-Flow Nasal Cannula, Non Invasive Ventilation, Covid-19, Hypoxemic Respizratory Failure, Oxygen Therapy, Intensive Care Unit.

Introduction

A novel corona virus was first isolated in 2019 now named as severe acute respiratory syndrome corona virus 2 (SARS-Cov-2) [1]. It resulted in aggregation of acute respiratory illness, corona virus disease 2019 (Covid-19) [2]. It was later found to be air-borne as a major mode of transmission [3]. World health organization (WHO) declared the outbreak of covid-19 as a global pandemic on March 11, 2020. According to previous study 14% of the patients were severe and 5% as critical in covid -19 positive patients [4]. A review article had analysed 31 articles including 46959 covid -19 positive cases and documented the incidence of intensive care unit (ICU) admission was 29.3% [5]. In previous studies NIV or HFNC was used in the early stage of hypoxemic respiratory failure in 24% of hospitalized patients [2]. The use of NIV and HFNC was 37% and 31% respectively in critically ill patients [6].

High flow nasal cannula (HFNC) delivers high-flow oxygenated gas via nasal cannula, heated and humidified at flow rates ranging from 40 to 80 L/min depending on the severity of hypoxemia [7]. The heating and humidification helps to maintain hydration, clearance of secretions and preserving mucociliary function. The soft loosely fitting nasal interface does not impede in speech or eating during use. In HFNC it has been shown that there is increased end- expiratory lung volume due to expiratory impedance, which creates positive expiratory pressure of

1cmH_2O/10 L/min with high flow oxygen which peaks during early exhalation. Thus HFNC is not only oxygen supplementation with high flows, it is well-tolerated non invasive ventilator assist device with many physiological benefits which is safe and easy to use.

NIV basically is, a pressure-targeted modality and it is the pressure that contributes to its efficacy. Currently there are two indications, these are acute hypoxemic respiratory failure in chronic obstructive pulmonary disease (COPD) exacerbation [8] and in acute cardiogenic pulmonary oedema by applying continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BiPAP). In recent study they demonstrated usefulness of NIV in acute hypoxemic respiratory failure due to community acquired pneumonia and they found that CPAP 10 cm of H_2O improved gas exchange and reduced the need of endotracheal intubation [9] .Hence this study was conducted with the aim to compare the use of NIV and HFNC in Covid-19 patients with hypoxemic respiratory failure as first line of treatment. Objective of our study is to compare NIV and HFNC in terms of improvement in oxygen saturation (SpO2>90%), decrease in respiratory distress and with regards to duration of ICU stay and incidence of failed HFNO and NIV who needs intubation.

Material and Methods

This prospective randomised comparative study was carried out in our institution in the Department of Anaesthesiology for a period of 6 months. Institutional ethical committee approval was obtained (BLDEDU/IEC/494/2020-21). This study was registered under clinical trial registry of India (CTRI/2020/11/029356). Written informed consent for participation in the study was taken. The study was conducted in accordance with the Helsinki Declaration 2000.

Inclusion criteria: Patients with rtPCR positive who are confirmed case of Covid-19 infection who require HFNC and NIV as first line therapy, aged between 20-60years and BMI <30kg/m^2 were included in the study.

Exclusion criteria: Patients with pH < 7.20, children, pregnant females and BMI>30 were excluded from the study.

Hypoxemic respiratory failure is defined as with PaO_2< 55mmHg, FiO_2 >0.6, $PaCO_2$>45mmHg with signs of respiratory distress. Indications of NIV and HFNC are respiratory rate >35/min, Spo_2 <92%, PaO_2 / FiO_2 < 200.

Eighty two (41 per group) patients are required to have a 90% chance of detecting a decrease in the primary outcome measure from 85.9% in the NIV group and 79.3% in the HFNC group with 5% level of significance, (based on our hospital records observed among covid-19 patients with rtPCR positive in ICU from Jun-Aug 2020). The patients were divided into two groups of 41 each by computer generated block randomization.

Statistical analysis: Data was entered into Microsoft excel data sheet (Microsoft office 10) and was analyzed using SPSS for windows version 22 (IBM SPSS Statistics, Somers NY, USA) software. Categorical data was analysed as the number and percentage. Continuous data was represented as mean and standard deviation. Independent t test was used as test of significance to identify the mean difference between two variables. Normality of data was verified by skewness, kurtosis, stem leaf diagram, box plot, normal Q-Q plots and histogram.

Paired 't' test was used to test the statistical significance between the groups, on admission and follow-up HRCT (high resolution computerised tomography) score. A p value of <0.05 was considered as statistically significant.

HFNC AND NIV Application: NIV was administered according to recent guidelines [10-11], Non invasive ventilation was initiated by BiPAP in spontaneous/timed mode (Maquet, Monnal T75, Prisma VENT40) supplied with an identical set of NIV masks. Face mask was selected depending on the face type of the patient with humidified air to avoid oral and nasal dryness. Inspiratory pressure was set at 8 cm of H_2O and end expiratory pressure at 4cm of H_2O, later ventilator settings, expiratory and inspiratory pressures were gradually increased to the

maximum tolerated level over 1 hour according to response of the patient to relieve respiratory distress. The fraction of inspired oxygen was titrated in order to maintain SpO2 >93%. Depending on patients response BiPAP/CPAP was administered**.** If patient failed to maintain oxygen saturation with NIV then invasive ventilation was started.

Compliance is the efficacy of method of ventilation which will be tolerated by the patients during the course of the disease. After applying NIV or HFNC if patients saturation improves more than 95, reduced respiratory rate, reduced work of breathing and stable haemodynamics can be grouped in excellent compliance, if saturation is less than 93, No significant change in respiratory rate, marginal reduction in work of breathing grouped into good compliance, if patient with unstable vitals, not responding to NIV or HFNC application grouped into poor compliance. Each of the five lobes of both the lungs were observed for the presence of inflammation, presence of ground-glass opacities and consolidation. Each lobe could be awarded 0 to 4 points, depending on the percentage of the involved lobe: 0 (0%), 1 (1-25%), 2 (26-50%), 3 (51-75%), or 4 (76-100%) (The total severity score (TSS) was then reached by summing the points from each of the five lobes. The TSS cut-off for identifying severe-critical type of 7.5 with 82.6% sensitivity and 100% specificity [12].

In HFNC group, high flow oxygen was delivered using an optiflow nasal interface connected to the PT101AZ (Airvo2) humidifier (Fisher & Paykel Healthcare) based on current consensus and expert's opinion [13] Therapy typically was initiated at a flow of 35L/min titrating flow upward if tolerated to 45–50 L/min. The fraction of inspired oxygen was adjusted in order to maintain SpO2> 93%. Vital parameters and arterial blood gases were monitored. In HFNC group patients who were not maintaining saturation and not in need of immediate intubation in such patients NIV was applied as rescue therapy. Patients who did not maintain SpO2> 90 on NIV or HFNC were intubated with all precautions in view of aerosol generation. Patients who improved with symptoms, vital signs, Spo_2 and relieved from respiratory distress such patients were put on intermittent NIV or HFNC and patients were gradually weaned by administering conventional oxygen face mask. All patients were observed for one week from admission after application of NIV or HFNC.

Results

In both the groups age, gender, height, weight and BMI were compared and was not statistically significant. Percentage of patients with co- morbidities like diabetes mellitus, hypertension, chronic respiratory disease and cardiac disorder were compared in both the groups. Mean duration of ICU stay in NIV group was 9±2 days and in HFNC group was 10±3 days. There was significant difference in mean duration of ICU stay between two groups (Table- 1).

Table-1: Demographic Profile

	Groups		p value
	NIV(n = 41)	HFNC (n = 41)	
Age (years) Mean ± SD	49.37±7.73	48.27±7.11	0.505
Gender			
Male	28(68%)	23(56%)	
Female	13(32%)	18(44%)	
Body mass index	25.89±3.05	25.40±2.34	0.418
Co- morbidities			
Diabetes mellitus	14(34%)	9(22%)	
Hypertension	9(22%)	5(12%)	
Chronic respiratory disease	6(15%)	3(7%)	
Cardiac disorder	3(7%)	1(2%)	
ICU stay(days)	9±2	10±3	0.07

Values are presented as Mean ± SD, number of patients (%)**,** *p –value<0.05 statistically significant, NIV-non invasive ventilation, HFNC- high flow nasal cannula, Intensive care unit-ICU.

Mean heart rate and MAP in both the groups did not show any significant difference at all time intervals. In between the groups there was no difference in haemodynamic variations

There was no statistical significant difference with respect to mean respiratory rate between two groups and at all the intervals of follow up (Table-2).

Table-2: Mean Respiratory rate

	Groups		p value
	NIV (n = 41) Mean ± SD	HFNC (n = 41) Mean ± SD	
On Admission	27.71±3.92	27.46±4.32	0.784
1st hour	23.54±3.80	24.46±4.11	0.309
6 hrs	22.67±4.54	23.46±4.32	0.422
12 hrs	23.86±4.32	24.46±5.42	0.580
24 hrs	23.66±4.41	25.37±5.14	0.109
2nd Day	20.63±4.80	22.32±5.05	0.124
4 to 6th day	19.88±4.87	20.41±5.03	0.629
1st Week	18.66±4.82	19.51±4.65	0.418

Values are presented as Mean ± SD, p* –value < 0.05 (statistically significant), NIV- non invasive ventilation, HFNC- high flow nasal cannula.

Table-3: Mean SpO2

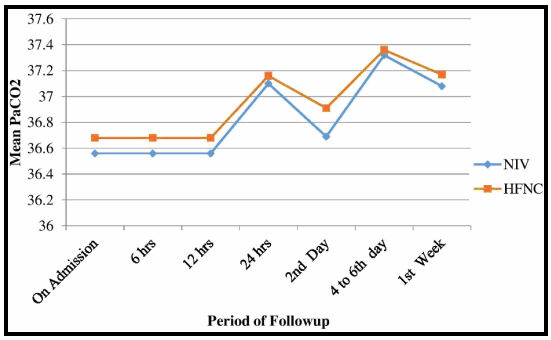
	Groups		p value
	NIV (n = 41) Mean ± SD	HNFC (n = 41) Mean ± SD	
On Admission	86.65±7.74	85.93±9.72	0.711
1st hour	95.56±4.23	94.78±4.64	0.428
6 hrs	97.34±4.68	95.86±4.76	0.159
12 hrs	97.45±1.87	96.64±2.82	0.129
24 hrs	97.56±1.73	96.49±2.04	0.012*
2nd Day	97.36±1.53	96.53±1.86	0.030*
4 to 6th day	98.64±1.45	97.63±2.05	0.011*
1st Week	97.44±1.80	97.48±1.92	0.922

Values are presented as Mean±SD, *p – value < 0.05 statistically significant NIV- non invasive ventilation, HFNC- high flow nasal cannula.

There was no statistical significant difference in oxygen saturation (Spo_2) from admission till 48 hours in between the two groups and there was statistically significant difference from 48 hours of admission to day 6 (Table-3).

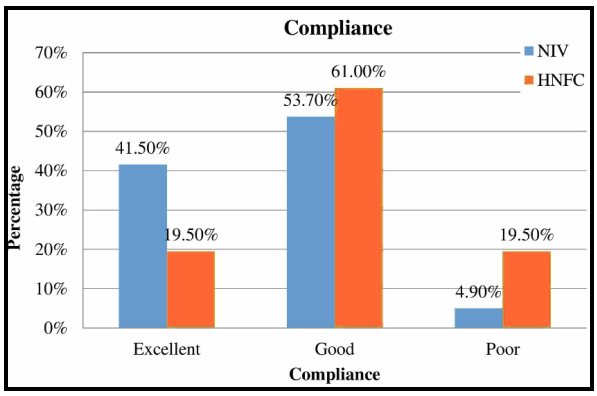
There was no significant difference in mean pH in between the groups. There is no significant statistical difference in PaCo2 between two groups from admission to 1st week (figure-1).

Fig-1: Mean PaCO2



In NIV group, compliance was excellent in 41.5%, good in 53.7% and poor in 4.9% and in HFNC group, compliance was excellent in 19.5%, good in 61% and poor in 19.5%. There was statistically significant difference in compliance between two groups p = 0.03 (figure-2).

Fig-2: Compliance comparison between tow groups



In the study there was no significant difference in mean HRCT score at admission, 24 hrs, 2nd day, 4 to 6th day and 1st week between two groups. Within the NIV group and HFNC group, there was increase in HRCT score at 2nd day, at 4 to 6th day showed significant statistical difference. In 1st week there was decrease in HRCT score and was statistically significant (Table- 4).

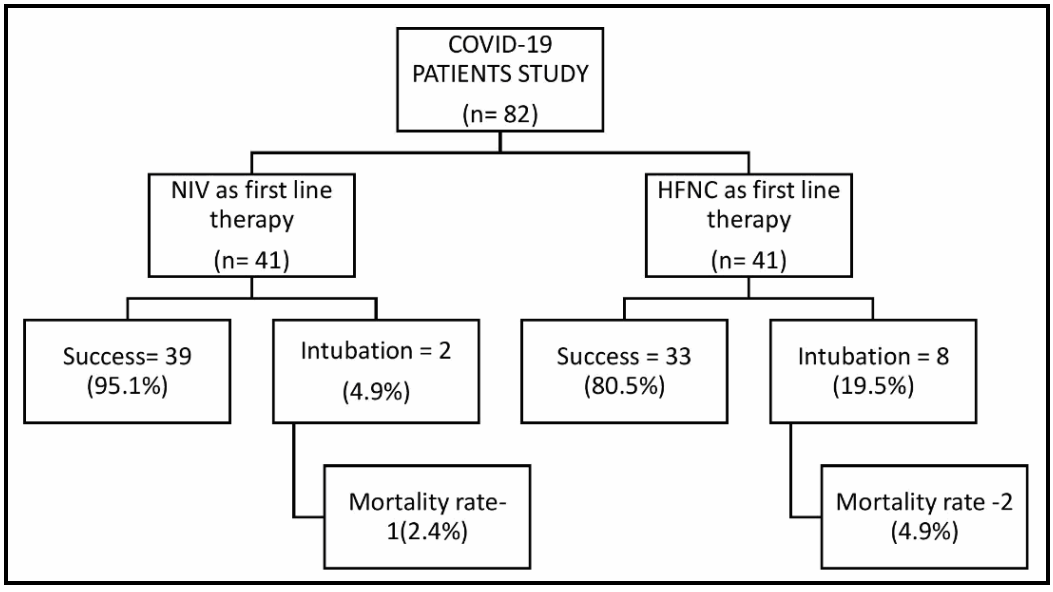
Incidence of failed HFNO and NIV requiring Intubation and outcome: In NIV group 4.9% required intubation i.e 2 patients out of 41 patients and in HFNC group 19.5% required intubation i.e 8 patients out of 41 patients. Intubation required was significantly ± high in HFNC group compared to NIV group (Flow chart- figure-3). In NIV group, 2.4% had mortality and in HFNC group, 4.9% had mortality. There was no significant difference in mortality between two groups.

Table-4: Mean HRCT Score

	Groups		
	NIV (n = 41) Mean ± SD	**HFNC (n = 41) Mean ± SD**	**p value**
On Admission	15.17±2.54	15.34±2.44	0.757
24 hrs	15.17±2.54	15.34±2.44	0.757
2nd Day	17.07±2.38	16.71±2.38	0.489
4 to 6th day	11.17±2.54	11.20±2.19	0.963
1st Week	7.12±2.38	7.34±2.44	0.681

Values are presented as Mean±SD,*p –value< 0.05 significant statistically, NIV-non invasive ventilation, HFNC- high flow nasal cannula.

Fig-3: Consort flow diagram of outcome of patients



Discussion

The Asian critical care clinical trials group has suggested that NIV and HFNC can be used in covid-19 patients with mild to moderate acute respiratory distress syndrome (ARDS) [14].The Surviving sepsis campaign covid-19 subcommittee has suggested that the HFNC is superior to NIV in covid-19 patients with acute hypoxemic respiratory failure, and the NIV can be tried with close monitoring if the HFNC is unavailable [15]. The study was conducted to compare the use of NIV and HFNC in patients with covid-19 with hypoxemic respiratory failure as first line of treatment.

In our present study with regard to vital signs like mean heart rate, mean respiratory rate, Spo2, there was statistical significant difference in both the groups. In respect to pH, MAP, $Paco_2$ there was no significant difference in both the groups. Whereas comfort and compliance was better in NIV group compared to HFNC group. Based on the clinical assessment patients were put on either NIV or HFNC, intense monitoring was done to intervene the patients whenever they needed invasive ventilation. According to previous study alternating NIV and HFNC in patients with hypoxemic respiratory failure, they found improvement in oxygen levels with HFNC given in between the sessions of NIV [16]. NIV has been found to improve oxygenation, reduce the rate of invasive ventilation and less mortality in hypoxemic respiratory failure patients [17].

In our study Intubation rate in NIV group was 4.9% and in HFNC group was 19.5%. Intubation rate in NIV group was significantly less compared to HFNC group. In some studies they observed intubation rate was 59% in patients with influenza pneumonia and 30% in patients with severe acute respiratory syndrome when NIV was used as first line of treatment [18-19]. In another study Intubation rate was 36% hypoxemic respiratory failure caused by other causes [20]. In one of the studies they found, the intubation rate was 15% in patients with covid -19 who used NIV and 20% in patients on HFNC as first line of therapy [21], which was similar to our present study.

During non-invasive ventilation, the BiPAP reduces work of breathing by alveolar recruitment. It reduces threshold of inspiratory triggers thereby ensuring optimum tidal volumes. NIV provides adequate inspiratory flows at constant inspired oxygen concentrations. In HFNC, if the patient inspiratory flow rates exceed the fixed set flow rates air entrainment leads to net decreases in FiO_2 delivered compared to set FiO_2 [22]. Mortality was 2.4% in NIV and 4.9% in HFNC group. Mean duration of ICU stay in NIV group was 9 ± 2 days and in HFNC group was 10 ± 3 days.

By taking all safety measures NIV can be used as alternative to invasive method for respiratory support in covid-19 patients. Early detection of intubation in high risk patients and managing with invasive ventilation reduces mortality rate [23]. Delay in invasive ventilation will increase mortality rate in patients who are on NIV and HFNC [24].

Both NIV and HFNC generate aerosols, comparatively NIV generates more aerosol than HFNC due to high pressure in NIV. Spread of infection transmission in our ICU care providers were taken care by proper personal protective measures. Expert committee suggested that NIV should be used carefully in patients who have $PaO2/FiO_2$ between 100 and 150 mmHg [25]. This study has several limitations. Day from covid-19 positivity was not considered in the study. Further studies with larger sample size are required to generalise the results.

Conclusions

Patients diagnosed covid-19 with acutehypoxemic respiratory failure can be treated either with NIV or HFNC as a first line of treatment. NIV is more effective in terms of improvement in saturation, reduced respiratory rate and decrease in ICU stay with good haemodynamic stabilty. NIV group had less intubation rate and more compliance compared to HFNC group.

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Conflicts of interest: There are no conflicts of interest.

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