Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Impact of HFNC application on mortality and intensive care length of stay in acute respiratory failure secondary to COVID-19 pneumonia

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SUMMARY

Background: In Covid-19 pneumonia, high mortality rates reported in intubated patients have raised non-invasive methods of respiratory support.
Objective: We aimed to evaluate the impact of HFNC application on intubation requirement, intensive care length of stay, and short-term mortality in patients with COVID-19 pneumonia.
Material-method: Patients receiving oxygen by reservoir mask or HFNC therapy in our intensive care units due to COVID-19 pneumonia were included in the study. Group H consisted of patients who received HFNC, and Group K consisted of patients who received conventional oxygen therapy (COT). The number of patients intubated, duration of intensive care stay and short-term mortality were recorded.
Results: 43 patients were included. The short-term mortality and the number of patients with intubation need was lower in Group H. There was no significant difference between the Groups in the length of intensive care stay.
Conclusion: Administration of HFNC in respiratory failure secondary to COVID-19 pneumonia decreases the need for intubation and mortality.

Introduction

Coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) prompts a wide range of clinical courses, from asymptomatic to the need for intensive care. Approximately 5–10% of the population affected by this virus require intensive care due to acute respiratory failure secondary to COVID-19 pneumonia.[1] Numerous randomized studies are available on medical treatments; however, respiratory support is the basis of treatment in acute respiratory failure. Non-Invasive Ventilation (NIMV), High Flow Nasal Cannula (HFNC) and Invasive Mechanical Ventilation (IMV) options are available for providing this respiratory support based on the patient's clinical condition, and these applications are known to provide clinical benefits in SARS-CoV and MERS-CoV.[2,3]

NHF is the nasal delivery of heated and humidified air to the patient with high flow (20–70 lt / min) and more stable oxygen support (fio2: 21–100%). Physiologically; It provides improvement in acute respiratory failure such as mild and moderate ards by increasing airway pressure, end-expiratory lung volume, oxygenation, and the rate of carbondioxide clearance of gas content in the dead space.[4] Patient self-inflicted lung injury, which may develop as a result of excessive breathing effort of the patient, is prevented by decreasing respiratory work and rate.[5] In addition, NHF has been shown to reduce the need for intubation when compared to conventional methods such as nasal cannula or mask.[6] Consequently, by preventing intubation, the complications caused by sedation, long intensive care unit(ICU) stay or invasive mechanical ventilation will decrease.

In all patients admitted to the Intensive Care Unit (ICU) due to acute respiratory failure secondary to COVID-19 pneumonia, HFNC was initially avoided due to the concern of high aerosolization-related contamination.[7] In addition, due to the scarcity of studies on this subject, NHF application was recommended with weak

Abbreviations: COVID-19, Coronavirus disease 2019; HFNC, High flow nasal cannula; COT, Conventional oxygen therapy; SARS-CoV-2, Severe acute respiratory syndrome Coronavirus 2; MERS-CoV, Middle east respiratory syndrome coronavirus; WHO, World Health Organization; NIMV, Non-invasive mechanical ventilation (NIV); IMV, Invasive mechanical ventilation; P/F, Partial oxygen pressure/Fraction of oxygen saturation; ICU, Intensive care unit; ARDS, Adult respiratory distress syndromes; GCS, Glascow coma score; PCR, Polymerase chain reaction; BMI, Body mass index; RR, Respiratory rate

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recommendations and low level of evidence in The Surviving Sepsis Campaign Covid-19 Guidelines.[8] However, over time, it has been observed that there is a limited supply of respiratory support devices in ICU, and that NHF application has a similar risk of contamination among aerosol-generating procedures with conventional oxygen masks.[9] In addition, compared with typical ARDS, it was observed that respiratory mechanics are more protected and lung compliance is higher in acute respiratory failure due to covid-19, but there is a pulmonary thrombotic damage associated with increased d-dimer levels.[10] Considering all these factors HFNC assumes a pivotal role in clinical practice, but a randomized, controlled study of HFNC application has not yet been published.

In our study, we aimed to evaluate the impact of HFNC administration on oxygenation, intubation requirement, length of stay in intensive care, and mortality in patients with acute respiratory failure due to COVID-19 pneumonia.

Materials & methods

Our study was planned retrospectively in five cohort intensive care units for COVID-19 located in our hospital. The study began after obtaining the approval from the local ethics committee of our hospital (12.05.2020/2789) and registration in Clinical Trials (NCT04424836). Written and oral consent was obtained from the patients themselves and/or their legal successors.

Data of patients over 18 years of age who were followed-up and treated in intensive care unit for acute respiratory failure due to Covid 19 pneumonia between March 15th, 2020, and May 30th, 2020, were retroactively reviewed. The study included patients admitted to the intensive care unit with acute respiratory failure due to Covid-19 pneumonia who underwent conventional oxygen therapy (COT) by reservoir mask or HFNC. Covid-19 was diagnosed with PCR (Polymerase Chain Reaction) test. The diagnosis of pneumonia was made through clinical findings and the appearance of multifocal ground-glass opacities that had consolidated on computed tomography. Acute respiratory failure was defined as having a P/F (Partial oxygen pressure/Fraction of oxygen saturation) ratio of less than 300 despite conventional oxygen therapy with a reservoir mask of 6 lt/min.

The data of patients who had respiratory acidosis (Ph < 7,30 and PaCO2 > 50 mmhg) in the arterial blood gas assessment taken immediately after being admitted to the intensive care unit, Glascow Coma Score (GCS) < 12 and, therefore, who underwent NIMV or were intubated from the beginning of their intensive care stay, and patients with primary pulmonary pathologies other than pneumonia (lung cancer, cardiopulmonary edema, Kartagener's syndrome, etc.) were not included in the study. In addition to all these, patient data on self prone were not included in the study in order to reduce variables and create more homogeneous groups. Data of patients who could not applied self-prone positioning due to treatment refusal or noncompliance were included in the study.

Although all patients with acute respiratory failure who were admitted to the hospital were candidates for NHF treatment, the number of applications in the same period was well above the capacity of both beds and devices. Due to our ethical concerns, no selection criteria were applied and only the order of application was considered in patient selection. For this reason, in cases where there were not enough devices, patients were supported with conventional mask oxygen.

The study was divided into two groups. The data of patients who underwent HFNC were included in the first group (Group H), and the data of patients who underwent COT with reservoir mask were included in group 2 (Group K).

In Group H, during HFNC treatment, the flow air temperature was 31–37 degrees, the flow rate was 30–60 lt/min, and the FiO2 delivered was in the range of 40–90% with target SpO2 range of > 93%. Treatment was applied continuously at the beginning; intermittent application was started after P/F > 250 and clinical well-being occurred.

In Group K, COT was applied with reservoir mask with a flow rate of 6–15 lt/min with SpO_2 value of > 93%. FiO2 (%) = 21 + 4*flow rate (liter/min) formulation was used for the calculation in patients receiving COT.

The Surviving Sepsis Campaign Covid-19 Guideline was taken into consideration in the fluid management of patients in both groups.[8] Anticoagulant therapi was administered in prophylactic dose to all patients.

Patient data was taken from our hospital's electronic information system and nurse observation records. Age, gender, body mass index (BMI), demographic data, and additional diseases (Diabetus Mellitus, hypertension, coronary artery disease, chronic obstructive pulmonary disease, congestive heart failure, chronic renal failure, etc....) of all patients were recorded. Respiratory Rate (RR), SpO_2 values at the beginning and at 24th hour, P/F calculated by pH, $paCO_2$, paO_2 measured in arterial blood gas rates were recorded.

Despite NHF or COT treatment, patients with P / F ratio below 150, SpO2 <93%, respiratory acidosis (pH<7.30 and PaCO2>50 mmhg) or tachypnea were supported with NIV primarily. In NIV application, the device was set at PEEP: 5, pressure above PEEP: 5–15 cmH2O, and FiO2 value was between 40 and 90% (targeting SpO2> 93%). P / F ratio below 150, SpO2 <93%, respiratory acidosis (Ph<7.30 and PaCO2>50 mmhg) or tachypnea were considered to be the failure of NIV therapy. In case of NIV treatment failure or patient noncompliance, the patient was intubated orotracheally and IMV was administered. Patients who had reduced GCS during follow-up were also intubated orotracheally and IMV was applied. This was considered a failure of treatment. The number of patients in need of intubation and the number of ventilator-free days were recorded. In addition, orotracheal intubation times, intensive care hospitalization periods, short-term mortality were recorded in all patients. Short-term mortality was defined as death during intensive care hospitalization, during post-intensive care stay, or after being discharged to home for up to 28 days. In addition, patient data were reviewed for thrombotic complications and right ventricular dysfunction.

Statistical analysis

The data was evaluated using the Windows SPSS 22 program. Descriptive findings are given as number and percentage distributions for categorical variables and mean and standard deviation for numerical variables. In statistical analysis, chi-square test was performed for categorical variables, normal distribution for numerical variables was evaluated according to Kolmogorov–Smirnov, histogram and QQ Plots, and Mann–Whitney U test was used for comparisons. Significance level was considered $p < 0.05$.

Results

A total of 170 patients' data were examined. 57 patients were admitted to the intensive care unit as intubated, Niv or intubated imv was applied to 27 patients within 24 h after admission, self-prone position were applied to 40 patients and 3 patients had lung cancer among their comorbidities. For all these reasons, 127 patients were excluded from the study. The data of 43 patients that fulfilled our study criteria were included in the study. 24 patients participated in Group H and 19 patients in Group K. Demographic data and comorbidities were illustrated in Table 1. There was no statistically significant difference between the groups in terms of gender and BMI. The comorbid conditions in Group K were significantly higher than Group H ($p = 0.006$), and this difference is due to the fact that hypertensive patients were higher in Group K ($p = 0.012$).

Table 1
Characteristics of the Participants at Inclusion in the Study*.

	Group H (*N* = 24) Mean±SD min-max	Group K (*N* = 19) Mean±SD min-max	p
Age(year)	63,3 ± 12,1 (38–81)	69,5 ± 12,3 (50–89)	0,10
BMI(kg/m^2)	26,5 ± 2,6 (21,4–31,0)	26,5 ± 3,2 (21,6- 36,7)	0,84
	n (%)	**n (%)**	
SEX			0,8
Female	7 (29,2)	6 (31,6)	
Male	17(70,8)	13(68,4)	
Comorbidity	12 (50)	17 (92,5)	**0,006**
DM	3 (12,5)	5 (26,3)	–
HT	6 (25,0)	12 (63,2)	**0,012**
CAD	2 (8,3)	3 (15,8)	–
COPD	2 (8,3)	0	–
CHF	1 (4,2)	1 (5,3)	–
CRF	1 (4,2)	1 (5,3)	–
Cancer	0	1 (5,3)	–
Other	0	7 (36,8)	–

* Plus–minus values are means ±SD. BMI:Body Mass Index, DM:Diabetus Mellitus, HT:Hypertension, CAD:Coroner Artery Disease, COPD: Chronic obstructive pulmonary disease, CHF:Congestive Heart Failure, CRF:chronic renal failure.

There were no statistically significant differences between the groups in baseline SpO_2 values, pH, $paCO_2$, paO2, and P/F ratios. (Table 2). There was no statistically significant difference between groups in pH, $paCO_2$, and P/F ratios at 24th hour. SpO_2 and paO2 of Group H at 24 h were higher than Group K (p = 0.014, p = 0.018) (Table 3).

When the changes in values between the Group H and Group K compared to baseline at the 24th hour were evaluated, paO2 values increased in Group H and decreased in Group K, and the difference between these two groups was statistically significant (p = 0.001). P/F values increased in Group H, whereas decreased in Group K, and the difference between these two groups was statistically significant (p = 0.03). Spo2 values increased in both groups, while the increase in Group H was significantly higher than Group K (p = 0.04). There was no significant difference between the baseline and 24th hour pH and $paCO_2$ values of the two groups (Table 4).

There was no statistically significant difference between the groups in length of stay in intensive care and the number of ventilator-free days (Table 5). The short-term mortality and the number of patients in need of intubation in Group H was lower (p < 0.019, p = 0.037) (Table 5).

Thrombotic complications and right ventricular dysfunction were not observed in the patients. However, some patients were consulted by cardiology due to increased cardiac enzymes. In the evaluations, this enzyme increase was not associated with myocardial infarction or cardiac dysfunction, and it was thought to be secondary to hypoxia.

Table 2
Initial Respiratory Rate, SpO_2 and Arterial Blood Gas Values*.

	Group H(*N* = 24) Mean±SD min-max	Group K(*N* = 19) Mean±SD min-max	p
Respiratory Rate (Rate/min)	33,4 ± 4,5 (26–40)	32,8 ± 4,3 (28–40)	0,40
SpO_2 (%)	89,5 ± 3,9(78–97)	89,4 ± 5,9 (80–98)	0,9
pH	7,4 ± 0,04 (7,35–7,58)	7,4 ± 0,07 (7,3–7,6)	0,7
$paCO_2$	32,4 ± 6,9 (19–51)	32,5 ± 7,9 (21–46)	0,8
paO_2	63,1 ± 7,0 (56–86)	68,0 ± 14,9 (56–113)	0,7
P/F	170,7 ± 19,1 (151–232)	183,9 ± 40,3 (151,3–305,4)	0,7

* Plus–minus values are means ±SD. SpO_2: Saturation Pulse Oxygen, P/F: PaO_2/FiO_2(Partial Oxygen Pressure/Fraction of Inspired Oxygen), PaO_2: Partial Oxygen Pressure, $PaCO_2$:Partial Carbon Dyoxid Pressure.

Table 3
24th Hour SpO2 and Arterial Blood Gas Values.

	Group H(*N* = 24) Mean±SD min-max	Group K(*N* = 19) Mean±SD min-max	p
SpO_2 (%)	93,4 ± 4,2(81–99)	90,3 ± 5,2(73–97)	**0,014**
pH	7,4 ± 0,05(7,31–7,55)	6,8 ± 1,7(4,47–7,59)	0,08
$paCO_2$	34,2 ± 7,2(22–57)	38,9 ± 17,3(21–99)	0,5
paO_2	81,7 ± 26,7(54–169)	68,1 ± 18,3(39–120)	**0,018**
P/F	198,5 ± 51,3(135–382)	184,2 ± 49,5(105,4–324,3)	0,9

*Plus–minus values are means ±SD. SpO_2: Saturation Pulse Oxygen, P/F:PaO_2/FiO_2(Partial Oxygen Pressure/Fraction of Inspired Oxygen), PaO_2: Partial Oxygen Pressure, $PaCO_2$:Partial Carbon Dyoxid Pressure.

Discussion

Covid-19 disease shows a wide clinical spectrum from asymptomatic to ARDS and multiorgan failure. While 41% of patients requiring hospitalization require oxygen therapy, this ratio was recorded as 70% in the presence of comorbidity among these patients.[11] It is also known that hypoxia in the group of patients with high comorbidities may cause poor outcomes.[12] In the initial period of the disease, hypoxic respiratory failure was evaluated as typical ARDS and similar mechanical ventilation approaches were proposed.[13] Therefore, benefits from COT, NHF, NIV, and IMV approaches were based on prior studies.[2,3] Initial data directed to early intubation and IMV in respiratory failure due to COVID-19 pneumonia. Especially in March 2020, the WHO's release of contact measures on aerosolization-forming processes has raised concerns about the use of NHF.[7] Over time, intensive care resource limitation, increased labor force, increased need for neuromuscular blockers, and high mortality in intubated patients brought new quests.[11,14] Again, although the guides initially for the respiratory support to be applied lead us to our experience on ARDS, with the fact that pulmonary pathologies caused by the virus are better understood, a different respiratory failure preserved by respiratory mechanics in the foreground suggests that NHF can benefit more than expected.[14,15]

Studies evaluating bacterial environmental contamination showed that NHF has a risk of contamination similar to conventional oxygen.[16] In SARS, it has been reported that there was no transmission to healthcare workers exposed to NHF application.[17] In the review published by Agarwal A et al., it has been stated that the use of NHF in COVID-19 patients is uncertain in terms of aerosol formation and contamination; the decision should be made according to benefit/risk ratio expected from the treatment and the use of personal protective equipment should be considered until precise data are obtained.[18]

The application of NHF provides the desired concentration of oxygen by heating and moistening it with high flow. These features are its most important advantages compared to COT. It also has lower transpulmonary pressures compared to NIV and IMV and causes less lung damage.[19] Because transpulmonary pressure, which is the sum of the pressure applied to the airway by the ventilator and the pleural pressure created by the patient's spontaneous respiratory effort, is the main cause of lung stress.[20] According to our current information,

Table 4
Changes in SpO2 and Arterial Blood Gas Values at the Initial and 24th Hour.

	Group H(*N* = 24)	Group K(*N* = 19)	p
SPO2	3,8 ± 4,8(−6 – 14)	0,6 ± 5,3(−8 – 15)	**0,04**
Ph	−0,01±0,03	−0,32±0,82	0,09
PCO2	1,7 ± 5,0	7,5 ± 14,3	0,18
PO2	18,5 ± 26,1	−0,76±14,53	**0,001**
P/F	27,7 ± 48,6(−52,4–166,2)	−1,71±41,0(−56,7–116,2)	**0,03**

SpO_2: Saturation Pulse Oxygen, P/F:PaO_2/FiO_2(Partial Oxygen Pressure/Fraction of Inspired Oxygen), PaO_2: Partial Oxygen Pressure, $PaCO_2$:Partial Carbon Dyoxid Pressure.

Table 5
ICU Stay Period, Ventilator-Free Period, Mortality Rate and Intubation Need.

	Group H(*N* = 24) Mean±SD min-max	Group K(*N* = 19) Mean±SD min-max	p 0.5
ICU Stay Period (Day)	9,8 ± 4,8 (3–22)	9,0 ± 7,9 (3–36)	0,18
Ventilator-Free Period (Day)	4,4 ± 2,2 (2–10)	1,9 ± 0,9 (1–3)	0,9
	n (%)	n (%)	
Mortality Rate	12 (50)	16 (84,2)	**0,019**
Intubation need	13 (54,2)	16 (84,2)	**0,037**

ICU: Intensive Care Unit.

this is the first study comparing NHF and COT treatments within the group of patients with respiratory failure after COVID-19 pneumonia.

In previous studies on the use of oxygen support with NHF in hypoxic respiratory failure, better patient comfort, decreased respiratory distress, regressed tachypnea, better oxygenation, and decreased intubation requirement have been found.[6,21-26] However, significant differences in mortality have not been detected. Only Frat et al.[21] has achieved a favorable outcome on mortality. In our study, it was found that mortality was lower in patients who underwent NHF compared to patients who underwent COT. The similarity of the mortality rates can be related to the patient's p/f rates is between 100 and 200 in both Frat et al.[16] and our study, because in their study, Frat et al. emphasized that mortality decreased especially in the subgroup with p / *f* <200 mmhg. In our study, the mean p / f ratio at the beginning was below 200 mmhg in both patient groups. The inclusion of cases with acute hypoxic respiratory failure caused by COVID-19 pneumonia alone in our study may have led to this result.

According to the current information, mortality in COVID-19 patients with critical illness was 49%, and as high as 50–90% in the presence of IMV. In our study, we found that the need for intubation was less in the patient group who underwent NHF compared to the patient group who underwent COT. Therefore, we think that the cumulative effect of both less intubation need and better oxygenation in patients with NHF has positive results on mortality. However, being over 60 years of age, along with the presence of pre-existing comorbid conditions such as cardiovascular disease, diabetes, chronic respiratory disease, hypertension, and cancer have been associated with a higher risk of death in COVID-19 patients.[8] In our study, the number of comorbidities and, especially the number of hypertensive patients, were higher among patients who underwent COT, though with a slight difference. In addition, the mean age of the group was higher than the NHF group. In this case, it may be the cause of high mortality in the COT group.

In our study, the positive decrease in the need for intubation and mortality with NHF application could not be observed in the duration of the stay in intensive care and the number of ventilator-free days. Although there were no statistically significant differences, the number of ventilator-free days was 4.5 days in patients who underwent NHF and 2.2 days in patients who underwent COT. According to a review and meta-analysis, where Tinelli et al.[27] compare the NHF and COT usage in emergency patients, no difference has been detected in the need for intubation, hospitalization duration, treatment failure, and mortality. Positive outcomes related to the need for oxygenation and intubation in intensive care are more pronounced than in emergency patients. Our data was similar to intensive care data in terms of oxygenation and intubation, while the duration of stay in intensive care was similar to those in emergency patients. The fact that the duration of stay in intensive care was similar in both groups may not only be related to mechanical ventilation but also due to high comorbidity.

In studies[22,23] conducted in intensive care patient groups, improved oxygenation, decreased respiratory rate, improved patient comfort have been observed with NHF, but there was no change in the PaCO2 value. In our study, similarly, we found that oxygenation was better with NHF and PaCO2 value did not change, but we did not find a significant decrease in the respiratory rate. In both groups, the baseline P/F ratio was <200. In the NHF group, P/F increased at the end of the 24th hour, while P/F fell in the COT group. PaO_2 values again increased with NHF application. SpO_2 baseline values increased from 89% in both groups to 94.8% with NHF application and to 90% with COT application. With COT application, our target SpO_2 value of >93% could not be reached, and, in this case, it was associated with increased intubation need.

The peak inspiratory flow rate at a normal and calm breath in humans can reach 30–40 L/min, while the peak inspiratory flow rate in severe exercise conditions, which may be equivalent to acute respiratory failure, can reach above 70 L/min.[28] This improvement in oxygenation is likely due to the better matching of the respiratory support provided by the NHFC with the patient's respiratory needs, coupled with the fact that the oxygen flow with high FiO2 is not diluted with room air and providing a stable FiO2 support.[29]

The limitation of the study was that most of our patients had a P/F ratio between 100 and 200. Therefore, it does not adequately cover patients with mild and severe respiratory failure, and it does not reflect all patients with hypoxic respiratory failure homogeneously. The number of patients with hypertension was higher in the COT treatment group. This can be explained by the fact that when the epidemic started, there were many cases in the city and hospital where we work, and we did not have an NHF device for every patient.

Conclusion

Oxygen therapy with NHF in patients with acute respiratory failure due to COVID-19 pneumonia reduces short-term mortality, the need for intubation, and improves oxygenation compared with COT. NHF is an important and safe alternative treatment for acute hypoxic respiratory failure due to pneumonia secondary to COVID-19.

Disclosure

None

Author's contributions

Mustafa Altinay, Ismet Sayan, Hacer Sebnem Turk and A.Surhan Cinar conceived and designed the study. Nebia Peker, Nurcan Coskun, Kerim Sahin and G.Dilara Demir carriedout the study protocol and retrospectively performed data collection. Mustafa Altinay, Ismet Sayan performed statistical analysis and data interpretation. All authors contributed to the writing of and approved the final manuscript.

Declaration of Competing Interest

This research received no spesific grant from any funding agency in the public, commercial or no-for-profit sectors. The authors declare there are no conflicts of interests.

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