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The Evaluation of COVID-19 Patients Treated with HFNC in ICU

Yoğun Bakımda HFNO ile tedavi edilen COVID-19 Hastalarının Değerlendirilmesi

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ABSTRACT *Objective:* Since the COVID-19 pandemic caused respiratory failure in many patients, oxygen delivery methods had to be diversified, and their numbers increased. High flow nasal cannula (HFNC), which has been shown beneficial in acute respiratory failure previously, also came to the fore. We investigated the efficacy of HFNC on patients hospitalized in intensive care units due to COVID-19.
Materials and Methods: We retrospectively screened the patients followed up in the intensive care unit due to COVID-19. Patients treated with HFNC performed the study group. We analyzed the relationships among demographics, laboratory results, treatment modalities, complications, and outcomes.
Results: Among the 330 patients including mean ventilation duration with HFNC was 7,84 days. 170 (51.5%) patients were intubated during HFNC treatment. Only 5 of them were extubated. Intubated patients had higher mean HFNC duration (9,74 days – min:2, max:49) compared to non-intubated patients (6,05 days- min:1, max: 30). There was a significant relationship between mortality and age (OR: 1.04), APACHE II score (OR: 1.35), having cancer (OR:3.89), receiving NIV (OR:5.94), and presence of secondary bacterial infection (OR:44.6)
Conclusion: HFNC, whose benefit in acute respiratory failure has been proven, is also widely and successfully used in COVID-19 patients. Comprehensive randomized studies are required to demonstrate the effect of HFNC use on intubation requirement and mortality.
Keywords: Ventilation, mortality, COVID-19, respiratory failure, pneumonia, oxygen therapy

ÖZ *Amaç:* COVID-19 pandemisi nedeniyle solunum yetmezliği gelişen hastalarda oksijen desteği için farklı cihazlar ve yöntemler kullanılmıştır. Bu yöntemlerden birisi de daha önce akut solunum yetmezliğinde faydalı olduğu gösterilen yüksek akımlı nazal kanül (HFNO)'dur. Bu çalışmada, COVID-19 nedeniyle yoğun bakım ünitelerinde yatan hastalarda HFNO'nun etkinliğini araştırmayı amaçlanmıştır.
Gereç ve Yöntemler: COVID-19 nedeniyle yoğun bakımda takip edilen hastalar geriye dönük olarak tarandı. Yoğun bakım yatışı sırasında HFNC ile tedavi edilen hastalar çalışma grubunu oluşturdu. Demografik veriler, laboratuvar sonuçları, tedavi modaliteleri, komplikasyonlar ve klinik sonuçlar arasındaki ilişkiyi incelenmiştir.
Bulgular: Dahil edilen 330 hasta arasında HFNC ile ortalama ventilasyon süresi 7,84 gündü. 170 (%51,5) hasta HFNC tedavisi sırasında entübe edilmişti. Bunlardan sadece 5'i ekstübe olabilmişti. Entübe edilen hastaların ortalama HFNO alma süresi (9,74 gün – min:2, maks:49) entübe olmayan hastalara (6,05 gün- dak:1, maks: 30) göre daha yüksekti. Mortalite ile yaş (OR: 1.04), APACHE II skoru (OR: 1.35), kanser öyküsü (OR:3.89), NIV uygulanması (OR:5.94) ve sekonder bakteriyel enfeksiyon varlığı (OR:44.6) arasında anlamlı bir ilişki vardı.
Sonuç: Akut solunum yetmezliğinde faydası kanıtlanmış olan HFNC, COVID-19 hastalarında da yaygın ve başarılı bir şekilde kullanıldığı görülmüştür. HFNC kullanımının entübasyon gereksinimi ve mortalite üzerindeki etkisini göstermek için kapsamlı randomize çalışmalara ihtiyaç vardır.
Anahtar Kelimeler: Ventilasyon, mortalite, koronavirüs, solunum yetmezliği, pnömoni, oksijen tedavisi

Introduction

High flow nasal cannula oxygen therapy (HFNC) is a relatively new oxygen delivery system for adults. It allows the delivery of oxygen at the desired level reliably. It also provides heated and humidified gas, enhancing patients' comfort, decreasing breathing work, and preventing airway epithelium injury. Nasal usage and its soft and flexible prongs allow a more tolerable procedure for patients. An easy-adjust and straightforward interface makes it –user-friendly- for doctors.

The positive impact of HFNC in acute respiratory failure patients was shown previously in various studies [1-3]. SARS-CoV-2 pandemic (COVID-19), as a disease causing acute respiratory failure, resulted in increased need for intensive care units and depletion of medical supplies such as mechanic ventilators, ventilation sets, and oxygen masks. Although early intubation was preferred at first, this approach was abandoned, and higher intubation thresholds were used [4]. So HFNC became a vital tool for oxygen delivery. Despite previous studies reporting usage rates up to 65 percent, the benefits of HFNC in preventing intubation were not shown [5-7]. Nevertheless, higher intubation thresholds and high usage rates of HFNC in the literature suggest it may decrease the intubation rates in case of appropriate use.

In this study, we aimed to investigate the clinical features, and outcomes of COVID-19 patients treated with HFNC in intensive care units. The primary outcome of the study is the determine the clinical, laboratory, and radiological findings and outcomes of COVID-19 patients treated with HFNC. The secondary outcome was to identify factors associated with death.

Materials and Methods

We included the adult patients followed in the COVID-19 intensive care units of the tertiary health center between 01.08.2020 and 01.01.2021. We gathered the medical information of the patients retrospectively by evaluating their records. We collected the basal demographic data, comorbidities, previous history of long-term oxygen therapy (LTOT), and continuous positive airway pressure (CPAP), APACHE-II scores, length of hospitalization, polymerase-chain-reaction(PCR) test results, computerized thorax tomography (TCT) findings, and laboratory results. Complications including secondary bacterial pneumonia, pneumothorax, pulmonary thromboembolism were recorded. Concomitant non-invasive ventilation (NIV) use, intubation, and extubation information data were collected. We obtained the data from the computerized database of the hospital.

HFNC was performed with *Fisher&Paykel HealthCare, Airvo™ 2, and Inspired O2FLO™. GE Healthcare Carescape R860 mechanic ventilator* was used for non-invasive and invasive mechanical ventilation

The study protocol was approved by the Institutional Ethical Committee of Ankara City Hospital (decision no: E1/1463/2021, date: 20.01.2021).

Statistical Analysis

SPSS software version 23.0 was used for statistical analysis. Descriptive analyses were presented using mean and standard deviation (mean ± SD) for normally distributed variables and median and minimum-maximum values for skew distributed variables. Categorical variables were expressed as numbers and percentages (%). For comparison between groups, Mann–Whitney ***U*** test and ***t***-test were used for continuous variables, and the chi-square test was used for categorical variables. Logistic regression analysis will be used to evaluate the relationship between independent variables.

Selection of Patients

We retrospectively reviewed 987 patients followed in the intensive care unit between 01.08.2020 and 01.01.2021. We excluded 115 patients because they stayed in ICU lower than 48 hours. 266 patients received nasal or mask oxygen. 127 patients were admitted as intubated and 5 patients with tracheostomy to the ICU. 144 patients were intubated in ICU while they were receiving nasal or mask oxygen. The remaining 330 patients treated with HFNC constituted the study group (Figure 1).

Results

We included 330 patients with a mean age of 66,7 (min 27-max: 95). 227 (68.8%) patients were male 103 (31.2%) were female. The mean APACHE II score was 11.6 (min: 3, max: 28). The most common comorbidities were hypertension and diabetes mellitus (DM), and coronary artery diseases (CAD) (55.2%, 34.8%, and 20.9%) respectively). Median PaO2/FiO2 was 101.6 (40-223). Baseline characteristics of patients are depicted in Table 1.

The primary laboratory abnormalities were Lactate dehydrogenase (LDH), Interleukin-6 (IL-6), and C-reactive protein (CRP) levels were increased in 330 (100%), 324 (97.3%), and 319 (97.3%) individuals, respectively. 284 (86.1%) had lymphopenia. Laboratory results are summarized in Table 2.

Computed thorax tomography revealed multilobar ground- glass infiltration consistent with COVID-19 in 327 (99.1%) patients. 2 patients had simultaneous pulmonary thromboembolism (PTE) at first admission. During follow-up, 3 more patients developed PTE, and 6 patients developed pneumothorax. There may be more concomitant PTE underdiagnosed due to non-contrast CTs.

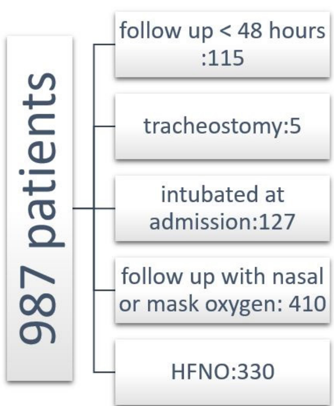

Figure 1. Study design

All patients received favipiravir, 18 patients received remdesivir, and 2 patients received ritonavir-lopinavir as antiviral treatment. We observed that most patients received immunosuppressant therapy due to severe disease. Treatment modalities are presented in Table 3.

The mean ventilation duration with HFNC was 7,84 days. 224 of 330 (67.9%) patients were applied non-invasive mechanic ventilation concomitantly. Intubation was performed in 170 (51.5%) patients during HFNC treatment. Only 5 of them were extubated. Intubated patients had higher mean HFNC duration (9,74 days – min:2, max:49) compared to non-intubated patients (6,05 days- min:1, max: 30) (Figure 2).

The mean length of stay in ICU was 13.9 days for all study group. Patients who received NIV stayed in ICU (14.4 days) longer than those who did not receive NIV(12.7 days) (p=0.019). Similarly, the non-NIV group has a lower intubation rate (36.8%) than the NIV received group (58.5%).

There was documented secondary bacterial pneumonia in 71 (41.7%) intubated patients. The most seen agents are *Acinetobacter spp.* (40), *Clostridium striatum, Staphylococcus Aureus* (8), and *Klebsiella spp* (8). We couldn't obtain a respiratory specimen from non-intubated individuals.

Of the 155 patients who transferred to the COVID general ward, 7 were transferred to another ICU for further

Table 1:. Baseline characteristics

		HFNC (106)	HFNC+ NIV (224)	Total (330)
Age	Median, min-max	68.0 (31-88)	66.6 (27-95)	66.7 (27-95)
Sex	Female/ Male (F/M)	39/67	64/160	103/227
Comorbidities (N, perc)				
Hypertension		55 (51.9%)	127 (56.7%)	182 (55.2%)
Diabetes mellitus		37 (34.9%)	78 (34.8%)	115 (34.8%)
CAD		27 (25.5%)	42 (18.8%)	69 (20.9%)
COPD		12 (11.3%)	17 (7.6%)	29 (8.8%)
Cancer		10 (9.4%)	18 (8.0%)	28 (8.5%)
Heart Failure		7 (6.6%)	20 (8.9%)	27 (8.2%)
Asthma		7 (6.6%)	13 (5.8%)	20 (6.1%)
CKD		7 (6.6%)	10 (4.5%)	17 (5.2%)
CVD		2 (1.9%)	11 (4.9%)	13 (3.9%)
Demans		6 (5.7%)	4 (1.8%)	10 (3%)
PaO_2/FiO_2 median, min-max*		116 (44-223)	92.5 (40-217)	101.7 (40-223)

CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, CKD: Chronic kidney disease, CVD: Cerebrovascular disease, N: number, perc: percentage, *PaO_2/FiO_2 was calculated at the beginning of HFNC follow-up, and 5 were discharged home. During ICU stay, 163 patients (49.4%) died. Examination of the relationship between comorbidities and mortality revealed that there was a statistically significant relationship between the presence of heart failure (p=0.007), hypertension (p=0.04), cerebrovascular disease (p=0.04), and cancer (p=0.01) and mortality. The only treatment modality with a statistically significant relationship with mortality was cytokine filter (p: 0.001). Among laboratory results, increased CRP (p=0.004) and procalcitonin (p= 0.001) levels were associated with mortality. The range of observed mortality was higher than expected mortality in whole group (7.7%-85.2%, 4%-40%, respectively). While mortality observed in patients with an APACHE-2 score below 10 was lower than expected in the HFNC group and slightly higher than expected in the HFNC+NIV group, the mortality rates in patients with an APACHE-2 score of 10 and above were much higher than expected in both groups (Table 4). We made logistic regression analysis to determine independent factors associated with mortality. We found that mortality was increasing with age (OR: 1.04), APACHE II score (OR: 1.35), having cancer (OR:3.89), receiving NIV (OR:5.94), and presence of secondary bacterial infection (OR:44.6).

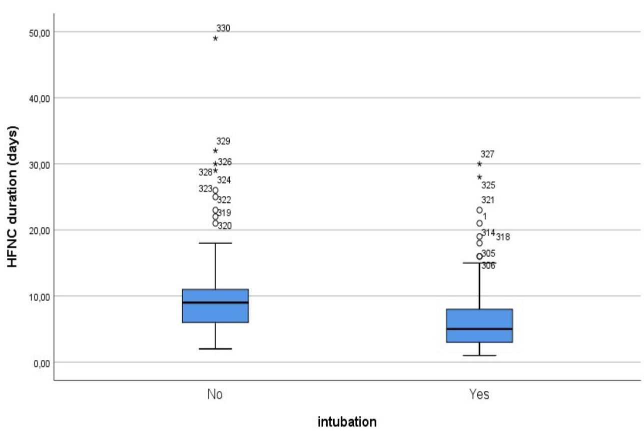

Figure 2. Comparison of HFNC durations between intubated and non-intubated patients

Discussion

In this retrospectively designed study, we investigated clinical, laboratory, and radiological characteristics of COVID-19 patients treated with HFNC hospitalized in the ICU for the primary outcome, and we found that most of the patients were elderly (med: 66.7) and the most common comorbidities were hypertension, DM, and CAD. LDH, IL-6, and CRP were increased in almost all patients, and the most common radiologic finding was multilobar ground-glass infiltration. While the mean ICU stay of the patients was 13.9 days, HFNC was applied for a mean of 7.8 days; approximately two-thirds of patients received NIV concomitantly and half of them were intubated. During ICU stay, 163 patients (49.4%) died, and logistics regression showed that advanced age, higher APACHE II score, cancer, receiving NIV, and secondary bacterial infection were significantly associated with mortality as the secondary outcome.

Most of our patients were elderly and had comorbidities consistent with the literature. In a study on the use of HNFC in severe COVID-19 patients, the median age of the patients was 61, and the most common diseases were HT, DM and CAD [8] A meta-analysis investigating ICU admissions of COVID-19 patients also showed that 85% of patients were

Table 2. Laboratory Rresults

Lab (med, min-max)	HFNC (106)	HFNC+ NIV (224)	Total (330)
Wbc ($x10^9$/L)	9.13 (2.83-108.7)	9.19 (0.12-22.94)	9.17 (0.12-108.7)
Neutrophile ($x10^9$/L)	7.64 (0.82-17.09)	8.03 (0.04-21.27)	7.90 (0.04-21.27)
Lymphocyte ($x10^9$/L)	0.57 (0.05-82.74)	0.54 (0.02-36.0)	0.55
Sedimentation* (mm/h)	47.5 (5.0-140.0)	38 (3-123)	42 (3-140)
CRP (g/L)	0.13 (0.001-0.360)	0.136 (0.001-0.54)	0.134 (0.001-0.540)
Procalcitonin (mcg/L)	0.19 (0.03-78.83)	0.23 (0.02-35.04)	(0.02-78.8)
IL-6 (pg/mL)	51.4 (2.0-2020)	44.15 (1.30-1703.0)	44.95 (1.3-2020)
LDH (u/L)	516 (159-2058)	552 (179-1396)	(159-2058)
Ferritin (mcg/L)	624 (22-33743)	702 (23-10795)	676 (22-33743)

*199 patients had sedimentation results.
WBC: White blood cell, CRP: C-reactive protein, IL-6 Interleukin-6, LDH: Lactate dehydrogenase, HFNC: High flow nasal cannula, NIV: Non-invasive ventilation

Table 3. Treatment modalities			
Drugs	**HFNC (106)**	**HFNC+ NIV (224)**	**Total (330)**
Antivirals			
Favipiravir	106 (100%)	220 (100%)	330 (100%)
Remdesivir	2 (1.9%)	16 (7.1%)	18 (5.5%)
Ritonavir-lopinavir	1 (0.9%)	1 (0.4%)	2(0.2%)
Immun-modulators			
Tocilizumab	23 (21.7%)	28 (12.5%)	51 (15.5%)
Anakinra	7 (6.6%)	23 (10.3%)	30 (9.1%)
Steroid	95 (89.6%)	221 (98.7%)	316 (95.8%)
Pulse	42 (39.6%)	120 (53.6%)	162 (49.1%)
Maintenance*	98 (92.5%)	220 (98.2%)	318 (96.4%)
Others			
Hydroxychloroquine	47 (44.3%)	81 (36.2%)	126 (38.2%)
Colchicine	14 (13.2%)	124 (55.4%)	114 (34.5%)
Convalescent plasma	19 (17.9%)	37 (16.5%)	56 (17%)
Cytokine filter	1 (0.9%)	27 (12.1%)	28 (8.5%)
Immune-globulin	1 (0.9%)	3 (1.3%)	4 (1.2%)

*58% of the patients received maintenance steroid treatment as methylprednisolone and 42% as dexamethasone. Pulse steroid has been administered in different dosages (250 mg, 500 mg, 1gr)
High flow nasal cannula, NIV: Non-invasive ventilation

Table 4. APACHE-II scores							
		HFNC (106)		**HFNC+ NIV (224)**		**Total (330)**	
Apache-II (med, min-max)		**10.0 (3-28)**		**11.0 (3-26)**		**11.0 (3-28)**	
Point	**Expected mortality**	**N**	**Observed mortality**	**N**	**Observed mortality**	**N**	**Observed mortality**
0-4 point (N, perc)	4%	8 (7.5%)	0%	5 (2.2%)	20%	13 (3.9%)	7.7%
5-9 point (N, perc)	8%	35 (33.0%)	2.9%	66 (29.5%)	16.7%	101 (30.6%)	11.9%
10-14 point (N, perc)	15%	38 (35.8%)	44.7%	95 (42.4%)	66.3%	133 (40.3%)	79.2%
15-19 point (N, perc)	24%	16 (15.1%)	68.8%	40 (17.9%)	90%	56 (17.0%)	83.9%
20-24 point (N, perc)	40%	9 (8.5%)	88.9%	18 (8.0%)	83.3%	27 (8.2%)	85.2%

HFNC: High flow nasal cannula, NIV: Non-invasive ventilation, med: median, N: number

>70 age years old [9]. Hypertension, DM, and CAD were listed as most common comorbidities in several studies [10, 11]. These findings seem to reflect intensive care patients' general characteristics rather than the use of HFNC. Considering that our patients were also treated with HFNC in the ICU, it is not surprising that the findings were similar.

Though its use is viewed with suspicion as it may cause increased aerosol production initially, NIV has been used in many centers during the COVID-19 period. We also used NIV in many patients with acute respiratory failure due to COVID-19. We found that NIV plus HFNC group had shorter HFNC duration and longer hospitalization time than those receiving HFNC alone. Duan et al. compared HFNC and NIV as first-line therapy. They chose one of these and used the latter as rescue treatment. They stated no difference between groups regarding total HFNC + NIV duration, intubation rate, and mortality [12]. In another study, Wang et al. investigated the sufficiency of HFNC in critically ill COVID-19 patients and used NIV as a rescue therapy as well. They reported HFNC failure at 41% and intubation rate at 29% [13]. A multicenter study examining the mortality rate of patients who underwent intubation after NIV failure also reported a mortality rate of 43% [14]. HFNC and NIV have been applied together or consecutively in various countries. However, this was determined not by evidence or guidelines but by countries' availability to access devices.

We found that 48.5% of patients survived the disease without intubation. Only 2.9% of intubated patients could be extubated, and 49.4% of the patients died in total. In the study mentioned above, Celejewska-Wojcik investigated mortality and intubation rate of COVID patients in ICU receiving HFNC prospectively. They reported that 44% of patients required intubation during follow-up and the overall mortality was 30.2% [8]. The intubation rate is similar to our study, but the mortality rate is lower than ours. It may be because our patients are more severe. Although we know that these results cannot conclude that HFNC avoids or delays intubation, we can say that it is used effectively in a severe patient group in this period. In addition, considering the positive results of the HFNC in non-COVID patients in terms of intubation in literature, we can deduce that it will be beneficial in this group as well [1, 15, 16].

There is a long list of risk factors associated with high mortality, including older age (≥65 years), having obesity, hypertension, diabetes, chronic heart failure, chronic renal disease, chronic liver disease cancer, high d-dimer, high troponin, lymphopenia, neutrophilia, immunosuppression, ARDS, male sex obtained from multiple studies [5, 17, 18]. In terms of risk factors associated with mortality, the results of our study are compatible with the literature. We found that concurrent heart failure, cerebrovascular disease, hypertension, cancer, increased CRP, increased procalcitonin level, and secondary bacterial pneumonia are associated with mortality have been corrected via logistic regression analysis revealed higher age(OR:1.04), APACHE II score (OR:1.35), cancer (OR:3.89), receiving NIV (OR:5.94), and secondary bacterial infection (OR:44.6) independently increased the mortality. Although the APACHE II score, which has been used to predict ICU mortality for many years [19], also reflects COVID-19 mortality in low scores; mortality was much higher than expected in patients with a high APACHE II score of 10 or higher. In two separate studies, it was emphasized that the APACHE II score underestimated mortality in patients hospitalized in ICU due to COVID-19, supporting our findings [20, 21]. This may be related to the more severe and fatal course of COVID-19 in the elderly and the fact that the majority of patients hospitalized in intensive care units are elderly.

Secondary bacterial infections are a relatively less-investigated topic in the literature. Grasselli et al. had stated that gram-negative bacteria and S. aureus were the most common microorganisms cause ventilator-associated pneumonia and doubled the risk of death [22]. Similarly, gram-negative bacteria (especially Acinetobacter spp., Klebsiella) and Staphylococcus Aureus were the most common isolated bacteria. Albeit it seems that there was a greater risk for culture-positive patients in terms of mortality (p: <0.001, OR: 44.7), there may not be a direct relationship since we could collect respiratory samples only in intubated patients.

The high number of patients is one of the strengths of our study. Including the NIV and intubation rates, comorbidities, and treatment data improves the power of reflecting real life. The most important limitation of the study is that it does not include data comparing patients with and without HFNC. However, it should be taken into account that the necessity of providing maximum support to all possible patients during the intensive care patient load is excessive may create an ethical problem in this type of study.

Conclusion

Oxygen support and the delivery route were two of the critical issues of the COVID-19 era. This study showed that HFNC is an essential option for oxygen support as it was used nearly in half of the patients without the need for intubation. Although we couldn't conclude that it decreases the intubation and mortality rates, we believe that further prospectively designed studies may help to determine its contributions.

Ethics

Ethics Committee Approval: The study protocol was approved by the Institutional Ethical Committee of Ankara City Hospital (decision no: E1/1463/2021, date: 20.01.2021).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: I.Ö.T., H.Z.A., Design: A.M.K., O.K., Data Collection and Process: O.K., Analysis or Interpretation: O.K., A.M.K., I.Ö.T., Literature Search: H.Z.A., Writing: A.M.K., O.K., H.Z.A., I.Ö.T.

Conflict of Interest: No conflict of interest was declared by the authors.

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