

The Outcomes of COVID-19 Patients with ARDS Who Received High Flow Nasal Oxygen in Medical Wards Outside Intensive Care Units Under Supervision of Non-intensivists.

YOĞUN BAKIM ÜNİTELERİ DIŞINDAKİ SERVİSLERDE YOĞUN BAKIM UZMANI OLMAYAN HEKİM GÖZETİMİ ALTINDA YÜKSEK AKIŞLI NAZAL OKSİJEN ALAN COVID-19 ARDS HASTALARININ SONUÇLARI

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ABSTRACT

Objective: Efficacy of high-flow nasal oxygen (HFNO) use in COVID-19 patients who developed ARDS in medical wards is poorly studied. We aimed to investigate whether use of HFNO in wards outside intensive care unit under supervision of non-intensivists has clinical effects on acute respiratory failure and whether it reduces ICU workload.

Methods: COVID 19 patients who received HFNO therapy for ARDS in medical wards of an academic hospital were analyzed retrospectively. Primary outcome was the proportion of patients who were successfully weaned from HFNO.

Results: 43 patients (32 male, median age 61 [54-70] years) were investigated. 14 (33 %) patients weaned from HFNO and 29 (67%) patients failed HFNO and were transferred to ICU. HFNO was applied in the group of HFNO with success with a median duration of 7 days (4-9) and in the failed group with median 3 days (2-5), $p=0.002$. Median SpO₂ after HFNO was higher in patients with HFNO success compared to with HFNO failure [95 (94-97) vs 93 (92-95), $p=0.015$]. In the group of HFNO with success, there were more hypocapnic patients than in the group of HFNO with failure [19/29 (66 %) vs 3/14 (21%); $p=0.015$]. Logistic regression analysis indicated that patients with hypocapnia had 9.8 times the odds of having HFNO failure compared with patients with normocapnia. No patient died among the patients succeeded HFNO however 90% of patients who transferred to ICU died.

Conclusion: Use of HFNO for COVID-19 patients with ARDS at a non-critical

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setting seemed to be beneficial in avoiding intubation and reducing workload of ICU. However due to high mortality rate among the HFNO failed group, it would be better to be used undersupervision of intensivists and by skilled team.

Key words: COVID-19, High Flow Nasal Oxygenation, ARDS, medical ward, ICU workload

ÖZ

Amaç: Servislerde Akut Solunum Sıkıntısı Sendromu (ARDS) gelişen COVID-19 hastalarında yüksek akışlı nazal oksijen (YANO) kullanımının etkinliği yeterince araştırılmamıştır. YANO'nun yoğun bakım dışı servislerde yoğun bakım uzmanı olmayan gözetiminde kullanımının akut solunum yetmezliği üzerine klinik etkisinin olup olmadığını ve Yoğun Bakım Ünitesinin (YBÜ) iş yükünü azaltıp azaltmadığını araştırmayı amaçladık.

Yöntem: Bir akademik hastanenin servislerinde ARDS nedeniyle YANO tedavisi alan COVID 19 hastaları retrospektif olarak incelendi. Birincil sonuç, YANO'dan başarıyla ayrılan hastaların oranıydı. YANO'nun başarısızlığı, yoğun bakım ihtiyacının ortaya çıkması olarak tanımlandı.

Bulgular: 43 hasta (32 erkek, medyan yaş 61 [54-70] yıl) incelendi. 14 (%33) hasta YANO'dan ayrıldı. 29 (%67) hasta YANO'da başarısız oldu ve yoğun bakım ünitesine nakledildi. YANO başarılı grupta ortalama 7 gün (4-9), başarısız grupta ortalama 3 gün (2-5) uygulandı, $p=0,002$. YANO sonrası medyan SpO₂, başarılı grupta başarısız olanlara kıyasla daha yüksekti [95 (94-97) ve 93 (92-95), $p=0,015$]. Başarılı YANO grubunda, başarısız YANO grubuna göre daha fazla hipokapnik hasta vardı [19/29 (%66) - 3/14 (%21); $p=0,015$]. Lojistik regresyon analizi, hipokapni olan hastalarda normokapni olan hastalara kıyasla YANO başarısızlığı 9.8 kat daha fazla görüldü. YANO'yu başaran hastalar arasında hiçbir hasta ölmedi, ancak yoğun bakım ünitesine nakledilen hastaların %90'ı öldü.

Sonuç: ARDS'li COVID-19 hastalarında servis ortamında YANO kullanımı, entübasyondan kaçınma ve yoğun bakım ünitesinin iş yükünü azaltmada faydalı görünüyordu. Ancak YANO başarısızlığı olan grupta mortalite oranının yüksek olması nedeniyle yoğun bakım uzmanlarının gözetiminde ve yetenekli ekipler tarafından kullanılması daha doğru olacaktır.

Anahtar kelimeler: COVID-19, Yüksek Akışlı Nazal Oksijenasyon, ARDS, yoğun bakım ünitesi dışı servis, yoğun bakım iş yükü

HFNO (High-flow nasal oxygen therapy) treatment has traditionally only been used in intensive care unit (ICU) settings. The new Covid-19 pandemic is one of the worst and most pervasive in modern history, affecting millions of people. Managing hospital space and expanding the capacity of intensive care units to keep up with the growing demand is a challenge (1). However, it is currently being used more frequently in medical wards, intermediate care units, and emergency departments (EDs). Previous research has demonstrated that HFNO has allowed patients with COVID-19 pneumonia to avoid ICU while

also providing better results than conventional oxygen therapy (2-4). HFNO is a method that uses prongs to provide heated and humidified oxygen to the nose. HFNO generates positive pressure in the upper airways, which allows a higher fraction of minute ventilation to participate in alveolar gas exchange and reduces physiological dead space by flushing expired carbon dioxide from the upper airway, which may lessen the work of breathing and improve oxygenation in acute respiratory distress syndrome (ARDS) patients (2,5,6). A small number of those research documented HFNC (High-flow nasal cannula)

use outside the ICU, despite certain studies focusing on its emergency department use showing that HFNC is safe and effective in the emergency department compared with non-invasive ventilation and traditional oxygen therapy (5,7-9). The purpose of the study is to examine the effectiveness of HFNO in COVID-19 patients with ARDS in medical wards and its contribution to ICU offloading.

METHODS

Patients and Study Design

The study was conducted with the approval of the Turkish Republic Health Ministry General Directorate of Health Services, COVID-19 Scientific Research Evaluation Commission, and Ondokuz Mayıs University Ethics Committee. As this was a retrospective study, the informed consent was waived.

Patients who underwent HFNO in the medical wards outside the intensive care units between 01.12.2020 and 31.05.2021 in Ondokuz Mayıs University Hospital were included. This time period was the 2nd wave of the COVID 19 pandemic, and HFNO was started to be implemented in the wards for the first time as the intensive care capacities were exceeded during this time. Patients who were applied HFNO as primary usage (which is called "step-up" therapy before initiating ICU care) for ARDS due to COVID 19 pneumonia were included in the study. Patients who received HFNO as step down therapy which means after ICU care were excluded. Other exclusion criteria were as follows: Being under the age of 18, patients with multi-organ failure or hemodynamically unstable patients, patients with metabolic acidosis and terminally ill patients

Patients were divided into two groups as patients with HFNO success and patients with HFNO failure. A patient was considered to have received successful HFNO treatment if they were discharged from the hospital alive, had better oxygenation after HFNO was stopped, and did not require invasive mechanical ventilation (IMV) or non-invasive ventilation (NIV). HFNO failure, on the other hand, was described as the requirement for NIV and/or IMV and death while receiving HFNO therapy (10).

Data Collection

Demographic, clinical, laboratory and radiologic information at admission were collected and analysed retrospectively. Age, gender, chronic diseases including hypertension (HT), diabetes mellitus (DM), obstructive lung disease, cardiovascular disease, chronic renal disease and malignancy were recorded. Laboratory markers recorded for each patient at admission were white blood cell count (WBC), hemoglobin (Hb), neutrophil (N), lymphocyte (L), neutrophil to lymphocyte ratio (NLR), D-dimer, ferritin, C-reactive protein (CRP) and procalcitonine.

The severity of COVID 19 disease according to radiological involvement on pulmonary computed tomography (CT) was determined by a semi-quantitative scoring system (10). A visual score between 0 and 5 was assigned to the percentage of radiological involvement area for each lung lobe. Scoring: 0 points, 0 points for no involvement, 1 point for <5% involvement, 2 points for 5-25% involvement, 3 points for 26-49% involvement, 4 points for 50-75% involvement, and 5 points for > 75% involvement. The total score obtained by summing the scores calculated for the 5 lobes of the lung including right lung upper, middle and lower lobes and the left lung upper and lower lobes was defined as the CT severity score (CT-SS). CT-SS was qualitatively classified as mild (score 1-5), moderate (score 6-14), or severe (score 15-25) (11). We also assessed the medications including steroid, pulse steroid, and anti-cytokine therapy if available.

High Flow Nasal Oxygen Therapy and monitoring

HFNO therapy (AIRVO2, Fisher & Paykel Health Care Ltd., Auckland, New Zealand) was applied to patient with ARDS due to COVID 19 pneumonia who were desaturated ($SpO_2 < 90$) despite oxygen via non-rebreather mask at flow of 10 L/min which equates a FiO_2 of 0.60. HFNO was initiated at flow of 60 L/min flow, 0.1 FiO_2 and with the temperature set at 31 to 37 C. Since most of the samples taken for blood gas analysis in the medical wards were venous, the diagnosis of ARDS was defined as $SpO_2/FiO_2 < 315$ according to the Kigali modification of Berlin criteria (12). SpO_2/FiO_2 was measured under conventional oxygen just before HFNO. After HFNO, SPO_2

was followed up and FiO₂ was adjusted to maintain SpO₂ at 90%. The maximum SPO₂ within first 24 hours was recorded. The Fio₂ was estimated as follows: $FiO_2 (\%) = 21 + 4 \times \text{flow (L/min)}$ (13). HFNO was stopped based on improvement of clinical signs of respiratory distress and ability to maintain SPO₂ >90 with less than 6 L/min of conventional oxygen. Those with oxygen saturation below 90 or developing respiratory distress despite HFNO with 100% FiO₂ were transferred to the intensive care unit. Presence of hypocapnia or hypercapnia, heart rate and respiratory rate before and after HFNO were recorded. However, since FIO₂ follow-up was not recorded in the patient files, SpO₂/FiO₂ could not be calculated. Patients who underwent prone ventilation were noted, if any. Use of HFNO in wards outside of ICUs was under supervision of non-intensivists including pulmonologist and infectious diseases and clinical microbiology specialist.

Outcomes

We aimed to evaluate the efficacy of HFNO therapy based on the effect of HFNO on respiratory rate, SpO₂ and on the need for respiratory support escalation including noninvasive or invasive mechanical ventilation. Thus, we tried to reveal whether HFNO reduces the workload of intensive care units. We also investigated the factors predicting HFNO failure.

Statistical Analysis

Statistical analyses were performed using the SPSS software version 22. Continuous variables were reported as median value and interquartile range (IQR). The differences between two groups were analyzed by Mann–Whitney U test. Categorical variables were reported as number and percentage. Comparisons between categorical variables were made with Chi-square test or Fisher's exact test. The significant factors within univariable analysis were analyzed by binary logistic regression analysis to identify the independent predictors of HFNO failure. P value less than 0.05 was accepted for statistical significance.

RESULTS

We screened 79 patients who received HFNO for ARDS due to COVID 19 pneumonia in the medical wards. 43 out of 79 patients were eligible for the study. Median age

(IQR) of the study population was 61 (54-70), 32 out of 43 (74%) were male. Among 43 patients, 14 (33%) patients weaned from HFNO successfully whereas 29 (67%) patients deteriorated on HFNO and they were transferred to ICU where they were mechanically ventilated (Table 1).

Table 1. Characteristics of the study population

Variable	All patient N=43	Patient with HFNO success N=14	Patients with HFNO failure N=29	Uni-variate P Value	Multi-variate P value
Age, median (IQR)	61 (54, 70)	56 (49-66)	63 (58-71)	0.105	
Male, n (%)	32 (74)	10 (71)	22 (76)	0.515	
Chronic disease n(%)					
Hypertension	20 (47)	7 (50%)	13 (45)	0.751	
Cardiovascular Disease	11 (26)	3 (21)	8 (28)	0.485	
Diabetes Mellitus	10 (23)	5 (36%)	5 (17)	0.136	
Obstructiv Lung Disease	3 (7)	0 (0%)	3 (10)	0.296	
Chronic renal disease	6 (14)	1 (7%)	5 (17)	0.255	
Malignancy	7(16)	2 (14%)	5 (17)	0.590	
Laboratory, median (IQR)					
ProCT, ng/mL	0.12 (0.07-0.25)	0.19 (0.09-0.25)	0.09 (0.06-0.25)	0.604	
CRP, mg/L	91 (57-164)	104 (51-163)	90 (60-173)	0.784	
Dimer, ng/mL	909 (519-2561)	578 (423-1080)	1251 (522-2811)	0.100	
Ferritin, ng/mL	645 (348-1501)	579 (321-1604)	645 (356-1506)	0.856	
Hb, g/dL	13.5 (10.9-14.4)	13.7 (11.0-14.5)	13.5 (10.9-14.6)	0.890	
WBC, x10 ³ /uL	5.9 (3.7-9.9)	7.6 (5.6-10.4)	5.4 (3.6-9.2)	0.154	
N, x10 ³ /uL	4.9 (2.6-8.1)	6.3 (4.1-8.8)	3.8 (2.5 -7.9)	0.195	
L, x10 ³ /uL	0.8 (0.6-1.1)	1.1 (0.6-1.4)	1.0 (0.5-1.2)	0.149	
N/L	4.9 (3.4-12.6)	5.0 (3.5-12.9)	4.7 (3.4-12.9)	0.836	
CTSS	10 (7-14)	10 (8-12)	11 (7-15)	0.532	
S _P O ₂ /FiO ₂ preHFNO	142 (135-147)	146 (137-147)	141 (134-147)	0.189	
SpO ₂ preHFNO	88 (81-88)	88 (82-89)	85 (81-88)	0.259	
SpO ₂ postHFNO	94 (92-95)	95 (94-97)	93 (92-95)	0.015	0.012
RR before HFNO	28 (24-30)	25 (20-28)	28 (26-32)	0.024	NS
RR after HFNO	26 (22-28)	22 (18-26)	26 (24-30)	0.023	NS
Hypocapnia	22 (51)	3 (21)	19 (66)	0.015	0.020
Hypercapnia	0 (0)	0 (0)	0 (0)	NA	
Median time (IQR) from admission to HFNO initiation, day	5 (4-7)	5 (4-7)	5 (4-8)	0.683	
HFNO duration	4 (2-7)	7 (4-9)	3 (2-5)	0.002	NA
HLOS	21 (17-33)	17 (14-22)	24 (19-39)	0.004	NA
Pulse Steroid	33 (77)	11 (79)	22 (76)	0.584	
Prone position	7 (16)	1 (7)	6 (21)	0.287	
Antisitokin therapy	14 (33)	4 (29)	10 (35)	0.620	
Mortality	26 (61)	0 (0)	26 (90)	NA	

IQR= Interquartile ratio, ProCT= Procalcitonin CRP=C-reactive protein, WBC= White blood count, Hb=Hemoglobin, N=Neutrophile, L=Lymphocyte, CTSS= Computed tomography severity score, RR= Respiratory rate, SpO₂=Oxygen saturation on pulse oxymeter HFNO= High flow nasal oxygen, HLOS= Hospital length of stay

The median time from admission to the start of HFNO therapy was 5 (4-7) days, without difference between patients who succeeded and failed HFNO, [5 days (4-7) vs 5 days (4-8), p=0.683]. HFNO duration was median 4 (2-7) days. Patients with HFNO success remained on HFNO longer than patients with HFNO failure [7 days (4-9) vs 3 days (2-5), p=0.002]. The patients had moderate radiologic severity [median CTSS= 10 points (7-14)]. The median CTSS upon admission did not differ between patients weaned from HFNO and those transferred to the ICU [10 points (8-12) vs 11 points (7-15), p=0.532] (Table 1).

HT (47%) cardiovascular illnesses (26%), and DM (23%) were the accompanying comorbid diseases that were most common. Between individuals who experienced HFNO success and those who experienced HFNO failure, there was no difference in the frequency of comorbidities. Both groups shared similar laboratory results for CRP, L, NLR, procalcitonin, ferritin, and D-Dimer (Table.1).

Before receiving HFNO, SpO₂/FiO₂ was at a median of 142 (135-147) and there was no difference between the groups that were successfully weaned off of HFNO and those that were unsuccessful [146 (137-147) and 141 (134-146), p=0.189]. Patients with successful HFNO and those with unsuccessful HFNO did not substantially vary in terms of median SpO₂ before HFNO [88 (82-89) vs. 85 (81-88), p=0.259]. However, the median SpO₂ following HFNO was higher in patients with success compared to failure [95 (94-97) vs 93 (92-95), p=0.015]. In the HFNO failure group, there were more hypocapnic patients than in the HFNO success group: 19/29 (66%) versus 3/14 (21%); p=0.015 (Table 1).

Likewise, the respiratory rate before [28/min (26-32) vs 25 (20-28), p=0.024] and after HFNO [26 (24-30) vs 22 (18-26), p=0.023] was higher in the HFNO failure group than in the HFNO successful group. Logistic regression analysis indicated that patients with hypocapnia had 9.8 times the odds of having HFNO failure compared with patients with normocapnia. No patient had hypercapnia before and after

HFNO therapy in this cohort. Patients with higher SpO₂ values after HFNO had a lower risk of HFNO failure compared with patients with relatively lower SpO₂ values (OR 0.6 [0.4-0.9]); p=0.012] (Table 2).

Table 2- Logistic regression analysis of factors associated with HFNO failure

Factors	OR	95%CI	P
SpO ₂ post HFNO	0.6	0.4-0.9	0.012
RR before HFNO	0.9	0.8-1.1	0.293
RR after HFNO	0.7	0.3-1.6	0.432
Hypocapnia	9.8	1.4-67.3	0.020

OR=Odds ratio, CI=Confidence interval, SpO₂=Oxygen saturation on pulse oxymeter, RR=Respiratory rate, HFNO= High-flow nasal oxygen,

HLOS of patients with HFNO failure was longer than HLOS of patients with HFNO success [24 days (19-39) vs 17 days (14-22), p=0.004]. The number of patients having pulse steroid therapy, prone position and anticytokine therapy did not differ between groups. Of 14 patients weaned from HFNO no patient died. Of 29 patients transferred to ICU just three survived (Table 1).

DISCUSSION

The key finding of our study is that in one-third of COVID-19 patients who developed ARDS in non-ICU services under the care of nonintensivists, the need for transfer to the intensive care unit was avoided by the use of HFNO. Hypocapnic patients in this cohort were more likely to experience HFNO failure. Patients with HFNO success reached higher oxygenation levels than the patients with HFNO failure.

To our knowledge, the use of HFNO for ARDS in general wards first emerged during the COVID-19 pandemic. The few studies that have been done in this area have demonstrated that the use of HFNO outside of intensive care seems practical and safe (14-17). Based on

these data, HFNO was found to be helpful in enhancing respiratory comfort, dyspnea, and respiratory rate but did not significantly affect gas exchange. We showed that HFNO is effective at lowering respiratory rate, but due to the lack of arterial blood gas data and follow-up SpO₂/FiO₂ values, we were unable to assess its impact on oxygenation. However, after HFNO therapy within 24 hours, pulsed oxygen saturation increased up to targeted levels.

Most studies on the variables predicting the efficacy of HFNO were conducted in the intensive care setting. Retrospective studies reported that tachypnea, thoracoabdominal asynchrony, higher SOFA score, advanced age, male gender, lower oxygenation at baseline, higher APACHE score are the factors associated with HFNO failure (18-21). However the only factor that has been prospectively validated is the ROX index which is the ratio of SpO₂/FiO₂ to respiratory rate. Patients who experienced HFNO failure had a much lower ROX index than patients who had success (17, 22, 23). In patients receiving HFNO support, the ROX index has been evaluated as a predictor of the necessity for intubation. A ROX index of 4.88 or higher at the 2nd, 6th, or 12th hours of treatment was linked to a reduction in the need for IMV in patients who had HFNO for pneumonia and respiratory failure (22). In cases of acute respiratory failure associated to COVID-19, the ROX index was also found to be reliable (a,b)24, 25 However, due to variations in clinical practice, time of measurement, and patient demographic variability in known research, the ROX index cut off values (2.7–5.99) fluctuate (24,26,27). With a ROX index cut off value of 5 and above, a meta-analysis comprising 8 trials and 1301 patients with acute respiratory failure connected to COVID-19 demonstrated the higher discriminative accuracy for the higher success rates. However, subgroup analysis revealed that for the first six hours of therapy, no discernible meaningful discriminative difference was found.(25)

Due to a lack of information on FiO₂ follow-ups, the ROX index could not be calculated in our study. However, using logistic regression analysis, we were unable to show a relationship between HFNO failure and tachypnea, which is a component of the ROX index.

We demonstrated that hypocapnia prior to HFNO could be a sign of HFNO failure. Hypocapnia is probably an expression of one of the pathophysiological mechanisms that make COVID-19 patients' respiratory failure worse. Conceptually, respiratory failure can be divided into two phases according to the level of treatment that is needed. Prior to the patient's presentation to the emergency room, there is an initial period of inflammation without atelectasis (28). The illness may then progress to a phase marked by atelectasis and edema, which coincides with the patient's admission to an intensive care unit or semi-intensive care unit. Eventually, the illness may resolve or progress to a fibrotic phase. Deep and frequent breathing is a characteristic of the initial phase of breathing because of the intact lung compliance (28).

This respiratory pattern, which on the one hand causes hypocapnia, can also produce an excessive swing in transpulmonary pressures, which increases the risk of a patient self-inflicted lung injury (P-SILI) (29,30). This vicious cycle can further advance the disease's progression to a more severe phase. Consequently, we think that the degree of hypocapnia aids in the identification of individuals who are more likely to suffer a self-induced lung injury, which increases the likelihood that their respiratory failure would progress quickly (28-30). According to this study, HFNO failure was 9.8 times more likely to occur in patients with hypocapnia than in individuals with normocapnia.

The COVID-19 patients who failed HFNO had a poor prognosis, with a mortality rate of 90%, according to our study. This is worse than the results of patients who experienced HFNO failure in previous studies, which were about 65% (22, 31). The reason for our discrepancy may be due to delayed intubation originating from the noncritical environment where there is a lack of monitoring and intensive care supervision. In patients receiving HFNO, delayed intubation has previously been found to be associated with increased mortality (24). Patients should be regularly evaluated in terms of clinical measures of respiratory workload along with the ROX index in order to avoid this.

In this cohort, HFNO was initiated on median 5 days after admission, and patients in the HFNO-failed group needed intensive care on median 3 days later. This period of time is compatible with the beginning of a potential cytokine storm (32). However, as prone position, pulse steroid and anticytokine treatment applications exhibited uniform distribution throughout the groups, we could not examine their contribution to HFNO treatments.

Since the characteristics of the patients who succeeded and failed did not differ in terms of age, gender, comorbidities, prognostic laboratory markers, CTSS and oxygenation level before HFNO initiation, we could not demonstrate the impact of these factors on HFNO efficacy.

Our study has a number of limitations. The study had a small sample size and was retrospective, single-centered, and observational. Our findings cannot be generalised. As previously indicated, an accurate assessment of HFNO effectiveness is constrained by the lack of precise data on the oxygenation index. Despite these limitations, we think that these data have roughly and clearly shown that using HFNO in environments other than intensive care, even without the supervision of an intensivist, has a significant advantage in ARDS.

CONCLUSION

This study shows that HFNO therapy in non-critical care environment as a primary therapy for ARDS can be useful in one third of patients for avoiding transfer to ICU. Since the mortality among the patients could not be weaned off HFNO in medical wards is quite high, it should be used by a skilled team under supervision of intensivists in order to prevent delay in intubation. Using HFNO outside the ICU may increase the value of inpatient care for respiratory diseases and may enhance resource use by avoiding unnecessary ICU admission. Future research should concentrate on patient outcome measurements to produce proof for proper HFNC use and the creation of national recommendations.

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