FEASIBILITY OF NON-REBREATHER MASKS AND NASAL CANNULA AS A SUBSTITUTE FOR HIGH FLOW NASAL OXYGEN IN PATIENTS WITH SEVERE COVID-19 INFECTION

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ABSTRACT

Objective: *Severe pneumonia and respiratory failure may develop in patients with coronavirus (COVID-19) infection, placing a very significant burden on healthcare systems due to the need for both emergency and intensive care treatment. Therefore, treatment of hypoxemia is a clinical priority in the treatment of such patients. In this regard, new strategies such as High Flow Nasal Oxygen (HFNO) and Non-Rebreather Masks and Nasal Cannula (NRMs+NC) that can provide non-invasive high fraction of inspired oxygen are gaining clinical significance.*

Our objective was to compare oxygen supply by HFNO with NRMs + NC in terms of treatment costs and mortality in a group of COVID-19 patients requiring intensive care unit admission.

Material and methods*: This was a retrospective and single-center study involving 54 patients who were admitted to an Intensive Care Unit with a diagnosis of COVID-19 infection between July 2020 and August 2020.*

Results*: HFNO was compared with NMRs + NC in terms of mortality and duration of hospital stay. The two groups were comparable in age (p=0.45), gender (p=0.33), and mortality (p=0.43). Also, there was no significant difference in oxygen saturation at admission (p=0.63), duration of intensive care (p=0.35), total length of hospital stay (p=0.057), and need for invasive mechanical ventilator (p=0.39) between the study groups.*

The levels of WBC (p=0.36), platelets (p=0.12), lymphocytes (p=0.98), CRP (p=0.11), pro-calcitonin (p=0.20), D-dimer (p=0.74), ferritin (p=0.14), urea (p=0.74), and creatinine (p=0.35) were also similar between the two groups.

Conclusion*: Oxygen support by NRMs + NC was comparable to HFNO in terms of mortality, need for invasive mechanic ventilation, length of intensive care, and length of hospital stay. We believe that NRMs + NC may represent an inexpensive and easily accessible therapeutic substitute for HFNO, particularly when the risk of transmission and costs related with HFNO use are considered.*

Keywords: *High Flow Nasal Oxygen, Non-Rebreathing Mask, Mortality.*

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Introduction

COVID-19 infection has become a major global public health problem in the past year[1]. In particular, patients with acute respiratory distress syndrome (ARDS) may develop severe respiratory failure and need intensive care unit admission. In these patients, hypoxemia is associated with more rapid disease progression and increased mortality. Obviously, a more severe disease course is associated with a major healthcare burden as a result of the need for both emergency and intensive care.

Therefore, strategies aimed at correcting the hypoxemia have gained clinical significance[2]. In this regard, new approaches such as High Flow Nasal Oxygen (HFNO) and NRMs+NC that can deliver non-invasive high fraction of inspired oxygen have become increasingly important.

HFNO provides nasal oxygen support of up to 40-60 L/min, at appropriate temperature and humidity. The air is exhaled, since the mouth of the patient remains open. HFNO leads to high oxygenation, reducing the respiratory difficulty and need for oxygen[3].

On the other hand, the approximate cost of HFNO per patient is around 140-150 US$, resulting in a high cumulative cost due to increasing number of COVID-19 patients admitted for intensive care[4].

Non-rebreathing masks (NRMs) are very safe in prevention of the spread of droplets and they can provide oxygen support up to 90% at a flow rate of up to 15 L/min. In order to maintain the reservoir bag inflated, the minimum oxygen flow rate should be 8 to 10 L/min so that t hypercapnia can be prevented by blocking entry of exhaled air into the bag[3]. Nasal cannula (NC) can provide oxygen at 40-45% at flow rates of 5 to 6 L/minute and represents a very important means of oxygen support for patients with mild hypoxia. FiO2 varies between 0.24-0.45. It is possible to administer near 100% oxygen at a flow rate of 20 L/min, when NRM and nasal cannula are used in combination, providing a high level of nasal and oral oxygen support. The approximate cost of combined use of NRM and nasal cannula (NRMs + NC) is 1-2 US$ per patient, representing a widely available and practical method for oxygen support. Since we cannot provide the oxygen support we want to give with HFNO alone with NRMs, we gave oxygen support with a second oxygen support, nasal cannula, together with NRMs. Thus, maximum oxygen support was provided both through the nose and mouth.

Based on the above-mentioned data, our objective was to compare HFNO with NRMs + NC in terms of cost ant mortality in a group of COVID-19 patients admitted to our intensive care unit.

Materials and methods

This retrospective single-center study involved a total of 54 patients admitted to our intensive care unit due to COVID-19 infection between July 2020 and August 2020. The study protocol was approved by the Scientific Research Commission of the Turkish Ministry of Health. The study was approved by the Ethics Committee of the Harran University. All subjects provided written informed consent documents, all methods were carried out in accordance with the Declaration of Helsinki before enrollment". Patient related data such as age, gender, comorbid conditions, saturation at the time of presentation, length of intensive care unit admission (days), total length of hospital stay (days), type of oxygen support administered, discharge status, use of invasive mechanical ventilation, Sepsis-related Organ Failure Assessment (SOFA) score, Acute Physiology and Chronic Health Evaluation (APACHE) score, PaO2/FiO2 (Partial Oxygen /Fractionel inspired oxygen) and certain laboratory parameters (urea, creatinine, C-Reactive Protein (CRP), D-dimer, ferritin, and pro-calcitonin) were recorded and analyzed. After admission, nasopharyngeal samples for PCR analysis were obtained by a physician. The amplification and analysis of the DNA and RNA were performed using a CFX96 real-time PCR detection system (CFX96; Bio-Rad, USA).

Inclusion criteria were as follows: Bilateral diffuse infiltration or ≥ 50% involvement of the total lung area in Computed Tomography, no need for invaziv mechanical ventilation support at presentation, SpO2 of < 88% despite maximum nasal oxygen support, mild and moderate ARDS, COVID-19 PCR (polymerase chain reaction) test positivity, D-dimer > 500 and ferritin > 500, or presence of cytokine storm.

Exclusion criteria were as follows: Presence of invasive mechanical ventilator support at presentation, CT involvement of < 50% in lungs,Requirement only for nasal oxygen,COVID-19 PCR test negativity,Absence of cytokine storm, patients who were referred to another healthcare facility after presentation, pregnant women.

ARDS was defined in 1994 by the American-European Consensus Conference (AECC); since then, issues regarding the reliability and validity of this definition have emerged. Using a consensus process, a panel of experts convened in 2011 (an initiative of the European Society of Intensive Care Medicine endorsed by the American Thoracic Society and the Society of Critical Care Medicine) developed the Berlin Definition, focusing on feasibility, reliability, validity, and objective evaluation of its performance. A draft definition proposed 3 mutually exclusive categories of ARDS based on degree of hypoxemia: mild (200 mm HgPaO2/FIO2 300 mm Hg), moderate (100 mm Hg PaO2/FIO2 200 mm Hg), and severe (PaO2/ FIO2100 mm Hg) and 4 ancillary variables for severe ARDS: radiographic severity, respiratory system compliance (<40 mL/cm H2O), positive endexpiratory pressure (>10 cm H2O), and corrected expired volume per minute (>10 L/min)[5].

A cytokine storm, also called hypercytokinemia, is a physiological reaction in humans and other animals in which the innate immune system causes an uncontrolled and excessive release of pro-inflammatory signaling molecules called cytokines. Normally, cytokines are part of the body's immune response to infection, but their sudden release in large quantities can cause multisystem organ failure and death[6]. Cytokine storms can be caused by a number of infectious and non-infectious etiologies, especially viral respiratory infections such as H5N1 influenza, SARS-CoV-1 and SARS-CoV-2[7-9].

Patients with an oxygen saturation of <88%, respiratory rate of >30 per minute, pulse rate of >110 beats per minute, blood pressure of <90/60 mmHg, and bilateral pneumonia were admitted to the intensive care unit, whereas other patients were treated in the normal ward. All patients had diffuse ARDS and received oxygen support by HFNO or NRMs + NC. They also received wide spectrum antibiotics, low molecular weight heparin, low dose steroids, high dose vitamin C, vitamin D, and tocilizumab or anakinra . Both groups received similar treatments.

First developed in 1981 by Knaus et al., APACHE is the most frequently used model in estimating surveillance.The score range that can be obtained for the APACHE score, which gives an idea about the severity of the disease and the expected mortality risk in the ICU, is between 0 and 71[10].

The SOFA score was first defined as the organ failure assessment score associated with sepsis in 1994. It is organized on the basis of six organ systems: respiratory, coagulation, hepatic, cardiovascular, central nervous system and renal system. While the minimum SOFA score is 0, the maximum SOFA score is 24[11].

The radiological assessment and classification of the patients were based on the criteria proposed by the Radiological Society of North America Expert Consensus[12]. Thus, bilateral ground-glass and reverse halo appearance were considered typical radiological findings; unilateral ground-glass or consolidation or nonperipheral perihilar ground-glass appearance were considered possible radiological findings; isolated consolidation, cavitary lung lesions, or pleural effusions were considered atypical radiological findings; and absence of any pathological findings suggestive of pneumonia was considered a negative radiological finding.

Study data were analyzed using SPSS (Statistical Package for Social Sciences) for Windows, 23.0. Normal distribution of the parametric data was evaluated by the Shapiro-Wilk test. Non-parametric data were compared using chi-square test, while parametric data were compared by Student's t test. A p value of < 0.05 at 95% confidence interval was considered statistically significant.

Results

A total of 54 patients were included, who were classified into two groups; those who received oxygen by HFNO and by NRMs + NC. The mean age in the HFNO group was 62.30 ± 15.73 years, and 7 (26.9%) of these patients were female, and 19 (73.1%) were male. Hypertension (HT), diabetes mellitus (DM), coronary artery disease (CAD), congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), and chronic renal failure (CRF) were present in 16 (61.5%), 3 (11.5%), 3 (11.5%), 2 (7.7%), 1 (3.8%), and 1 (3.8%) of these patients, respectively. Seventeen patients (64.4%) were discharged, while 9 (34.6%) died.

		HFNO (High Flow Nasal oxygen) (n=26 patients)	NRMS+NC (Non-Re-breathing Masks+Nasal Cannula) (n=28 patients)	P value
Gender	Women	7(26.9%)	11(39.3%)	0,45
	Men	19(73.1%)	17(60.7%)	
Comorbidity	Hypertension	16(61.5%)	16(57.1%)	0,23
	Diabetes Mellitus	3(11.5%)	7(25%)	0,35
	Coronary Artery Disease	3(11.5%)	2(7.1%)	0,42
	Chronic Obstructive Pulmonary Disease	1(3.8%)	4(14.3%)	0,34
	Asthma	0(0%)	2(7.1%)	0,59
	Congestive Heart Failure	2(7.7%)	0(0%)	0,54
	Chronic Renal Failure	1(3.8%)	1(3.8%)	0,74
Discharge status	Discharged	17(65.4%)	21(75%)	0.43
	Died	9(34.6%)	7(25%)	

Table 1: Demographic characteristics of patients.

The mean age in the NRMs + NC group was 65.28 ± 13.32 years, with 11 (39.3%) and 17 (60.7%) being female and male, respectively. HT, DM, CAD, COPD, asthma, and CRF were present in 16 (57.1%), 7 (25%), 2 (7.1%), 4 (14.3%), 2 (7.1%), and 1 (3.8%) of the patients, respectively.

		HFNO (High Flow Nasal Oxygen) (n=26 patients)	NRMS+NC (Non-Rebreathing Masks+Nasal Cannula) (n=28 patients)	P value
Age (year)		62.30+/-15.73	65.28+/-13.32	0.45
Gender	Women	7	11	0.33
	Men	19	17	
Saturation without oxygen at admission		61.34+/-9.82	60.14+/-8.49	0.63
ICU Length of Stay (Days)		10.19+/-6.29	8.70+/-5.20	0.35
Total Length of Stay (Days)		17.88+/-8.28	23.60+/-12.92	0.057
PaO2/FiO2		189.19+/-24.38	189.64+/-28.88	0.20
APACHE score		17.34+/-10.04	20.92+/-11.19	0,46
SOFA score		9.34+/-3.77	10.14+/-4.07	0.22
Patients Needing an Invasive Mechanical Ventilator		11	10	0.39
Comorbidity	Yes	17	22	0.28
	No	9	6	
Discharge status	Discharged	17	21	0.43
	Died	9	7	

Table 2: Clinical characteristics of patients.

Twenty-one patients (75%) were discharged, and 7 (25%) died (Table 1).

The two groups were compared in terms of PaO2 / Fio2 (p = 0.20), APACHE (p = 0.46) and SOFA (p = 0.22) scores. There was no statistically significant difference (Table 2).

No statistically significant difference was found between the two groups in terms of age (p=0.45), gender (p=0.33), and mortality (p=0.43). Also, there were no significant difference in oxygen saturation at admission (p=0.63), duration of intensive care (p=0.35), total length of hospital stay (p=0.057), and need for invasive mechanical ventilator (p=0.39) between the study groups (Table 2).

	HFNO (High Flow Nasal Oxygen) (n=26 patients)	NRMS+NC (Non-Rebreathing Masks+Nasal Cannula) (n=28 patients)	P value
WBCs (White Blood Cells)	10.87+/-5.36	12.18+/-5.02	0.36
Platelets	235.34+/-102.16	279.92+/-108.11	0.12
Lymphocytes	1.00+/-0.80	0.99+/-0.93	0.98
CRP(C-Reactive Protein)	105.23+/-90.30	72.05+/-57.99	0.11
Procalcitonin	2.11+/-3.77	1.00+/-2.41	0.20
D-dimer	2642.61+/-5557.11	2228.07+/-3197.38	0.74
Ferritin	1274.56+/-669.56	980.67+/-798.79	0.14
Urea	60.64+/-36.22	63.68+/-32.81	0.74
Creatinine	1.44+/-0.86	5.32+/-21.51	0.35

Table 3: Comparison of patients' laboratory parameters.

The levels of White Blood Cells (WBC) (p=0.36), platelets (p=0.12), lymphocytes (p=0.98), CRP (p=0.11), pro-calcitonin (p=0.20), D-dimer (p=0.74), ferritin (p=0.14), urea (p=0.74), and creatinine (p=0.35) were also similar between the two groups (Table 3).

Discussion

Severe hypoxemia may be observed in patients who develop severe ARDS due to COVID-19 pneumonia. Provision of adequate oxygenation has proven to be a major challenge in these patients, and failure to do so may lead to increased need for invasive mechanical ventilation and duration of hospital stay, with consequent increase in mortality rates and treatment costs. The present study comparing oxygen support by HFNO and by NRMs + NC found that both modalities were comparable in mortality, duration of intensive care unit stay, length of hospital stay, and need for invasive mechanical ventilation.

HFNO can deliver a 40 to 60 L/min of oxygen flow via a nasal cannula and has been reported to reduce the need for mechanical ventilation and mortality as well as the duration of intensive care unit stay[13-16]. Also, HFNO was found to be an effective therapeutic modality in subjects with ARDS of mild to moderate severity[17]. On the other hand, it has been suggested that HFNO may not be safer than non-invasive mechanical ventilators and it requires rooms with negative pressure[18]. Pinkham and colleagues observed that the size of the nasal cannula is an important consideration, with narrower cannula increasing the resistance, and thus failing to provide adequate oxygen due to the lack of sufficient pressure and flow rate[19]. Furthermore, others reported that HFNO should be avoided, since it may be associated with viral spread[20,21]. On top of these, the cost of HFNO per patient is approximately 150-160 US$, leading to significant cumulative costs due to the increasing number of patients admitted to intensive care units.

The purpose of oxygen support given to patients in intensive care is to prevent patients from being intubated and to reduce mortality. A review also reported that while the rate of invasive mechanical ventilation requirement decreased in patients who were given HFNO compared to patients who were given conventional oxygen therapy (COT), no difference was observed in terms of mortality[4]. In some studies, they reported that there was no difference in the intubation rate between patients who were given HFNO and COT[22-24].

In studies conducted in China, it was reported that 10% of intensive care patients needed HFNO and it has been reported to decrease intubation rate and decrease mortality[25,26]. In our study, no difference was found between the two groups in terms of intubation rate and mortality.

The aim of the treatment and oxygen support given to patients in intensive care is to ensure that the patient leaves the intensive care unit as soon as possible.Parke et al. showed that there is no difference between COT and HFNO in terms of hospital stay[23]. Other studies have reported similar length of stay in intensive care between HFNO and COT[27,28]. In our study, we found that the hospitalization period was longer in the group using NRMs + NC, but there was no significant difference.

Hypoxemia represents one of the most important determinants of the clinical outcome in patients with COVID-19 pneumonia. Since it may not be possible to utilize HFNO support for each patient due to increased burden in intensive care units, we administered oxygen via NRMs + NC in a group of patients. In the next course, no desaturation or tachypnea was observed in our patients and we observed that HFNO was similarly effective. In addition, we found that the rate of NRMs + NC discharge from the intensive care unit was similar to that of HFNO. Our clinical observations suggest that providing NRMs + NC early in the course of the disease may reduce the need for admission to the intensive care unit. Therefore, we think that NRMs + NC can be used as an alternative in places where HFNO is difficult to reach.It should also be borne in mind that the cost of NRMs + NC per patient is approximately 1-2 US$.

Main limitations of our study include the small sample size and absence of scoring for the thoracic tomography findings. Since there was no negative pressure filter in the intensive care unit reserved for COVID-19 patients, non-invasive mechanical ventilation could not be applied to the patients. Since IL-6 level could not be measured in our hospital, IL-6 level could not be measured.

Conclusion

In conclusion, oxygen support by NRMs + NC was at least as effective as HFNO in COVID-19 patients in terms of mortality, need for invasive mechanic ventilation, duration of intensive care unit stay, and length of hospital stay. We believe that NRMs + NC may represent an inexpensive and more accessible means for oxygen supply as compared to HFNO, particularly when one considers the viral transmission risk and high acquisition cost of the latter. However, further studies are required to confirm our initial observations.

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Abbreviations
COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; HFNO: High Flow Nasal Oxygen NRMs+NC: NonRebreathing Masks +Nasal Cannula

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