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Inhaled nitric oxide as rescue therapy in severe ARDS cases due to COVID-19 pneumonia: a single center experience

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Abstract. – OBJECTIVE: Inhaled NO (iNO) has been recommended as rescue therapy in acute respiratory stress syndrome (ARDS) cases. In this study, we aimed to demonstrate the efficacy of iNO as a rescue therapy in patients with severe ARDS due to COVID-19.

PATIENTS AND METHODS: This retrospective study included patients with ARDS due to COVID-19 who were treated with iNO between March 2020 and January 2022 in the intensive care unit (ICU) of Inonu University. Patients' files were reviewed retrospectively, and demographic data, APACHE II and Sequential Organ Failure Assessment (SOFA) scores, initiation day of iNO and duration of iNO treatment, length of stay in hospital/ICU, blood biochemistry values, complete blood counts, inflammatory parameters, arterial blood gas values, lactate, PaO_2/FiO_2 ratios, anti-inflammatory drugs and outcome were recorded.

RESULTS: Data from 16 patients were reached. iNO was given at a dose of 20 ppm continuously. The mean duration of treatment with iNO was 3.5 days. All patients took the prone position except a single patient. While all patients received steroid therapy, four patients received anti-cytokine therapy, and five patients received intravenous immunoglobulin therapy. All patients were in severe ARDS with a mean PaO_2/FiO_2 ratio of 58 before iNO therapy. A significant increase in PaO_2/FiO_2 values was detected with the use of iNO ($p<0.05$). While three patients (19%) were discharged from the ICU, thirteen patients died.

CONCLUSIONS: In our study, it was determined that iNO applied as a rescue treatment in patients with severe ARDS improved oxygenation. Although the effect of iNO on survival was low, it may be interpreted as clinically significant considering the severity of the general clinical condition of the patients.

Key Words:
Acute respiratory distress syndrome, Inhaled nitric oxide, COVID-19, Intensive care, Mortality.

Introduction

In December 2019, an outbreak of acute community-acquired atypical pneumonia of unknown etiology was reported in Wuhan, the capital of Hubei province in central China. A pandemic was declared by the World Health Organization on March 11, 2020[1]. As of June 1, 2022, there have been 533,070,966 cases of COVID-19 recorded worldwide, with 504,125,013 recovery cases documented, while 6,314,392 cases ended in mortality[2]. Inhaled nitric oxide (iNO) is a pulmonary vasodilator used as a rescue therapy in patients with severe hypoxemia. iNO improves ventilation-perfusion rate and reduces pulmonary vascular resistance[3,4]. iNO is a gaseous free radical produced from the breakdown of arginine by enzymes (neuronal, endothelial, and inducible nitric oxide synthase) that control vasodilation. iNO is important in maintaining the vascular system. It stimulates pulmonary vasodilation through both pathological and physiological processes, including antimicrobial activities to increase the relaxation of smooth muscle cells, immune response, and blood flow[5]. iNO plays a role in processes such as cell communication, vasodilation, blood pressure control, and wound healing, and has antimicrobial and anti-tumoral properties, especially at high doses[6]. iNO was used during the 2003 severe acute respiratory syndrome (SARS) epidemic in respiratory failure patients with severe hypoxemia. By looking at the similarities between the SARS epidemic and the Coronavirus disease-2019 (COVID-19) pandemic, it is conceivable to use iNO therapy in COVID-19 patients[7].

In our study, we aimed to examine the effects of iNO on oxygenation and mortality in patients who developed severe respiratory failure due to COVID-19 and received iNO.

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Patients and Methods

Patients who were intubated in our intensive care unit (ICU) and received iNO treatment for ARDS due to COVID-19 between March 2020 and January 2022 were included in this retrospective study. After obtaining approval from the Inonu University Health Sciences Non-Interventional Clinical Research Ethics Committee, the files and electronic records of COVID patients using iNO were reviewed (2022/3112). Demographic data of patients, acute physiology and chronic health evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores, duration and timing of iNO treatment, as well as white blood cells, hemoglobin, platelet, neutrophil and lymphocyte counts, C-reactive protein (CRP), interleukin 6 (IL-6), procalcitonin (PCT), fibrinogen, ferritin, D-dimer and arterial blood gas values, were recorded. The PaO2/FiO2 ratios of the patients were calculated and recorded before and after iNO administration. Any anti-inflammatory drugs [steroid, tocilizumab, anakinra, intravenous immune globulin (IVIG)] administered to the patients were recorded.

In our clinic, when the desired response was not obtained although appropriate mechanical ventilation strategies, recruitment maneuvers, and prone position were applied for ARDS, iNO treatment was started.

Statistical Analysis

IBM SPSS Statistics Software version 26 (IBM Corp., Armonk, NY, USA) was used in the analysis. Data were given as median (min-max), mean (standard deviation), and number (percent). Conformity to the normal distribution was done using the Shapiro-Wilk test. Dependent samples *t*-test and Wilcoxon test were used where appropriate in statistical analyses. A *p*-value lower than 0.05 was considered statistically significant.

Results

The records of 16 patients receiving iNO ARDS treatment due to COVID pneumonia were analyzed. The mechanical ventilation settings of all patients were adjusted to be 4-8 ml/kg (according to predicted body weight) and the plateau pressure was below 30 according to the protective ventilation strategy. The optimum positive end-expiratory pressure (PEEP) was adjusted with a decremental PEEP approach, and peak inspiratory pressure (Pinsp) was adjusted so that the driving pressure would be less than 15. With the exception of one patient, it was determined that all the patients were placed in the prone position. It was observed that iNO was applied to patients with a PaO_2/FiO_2 ratio less than 100 despite all these applications (Table I). All patients received steroid treatment (1 mg/kg methylprednisolone), but 11 patients were given high-dose steroids. Anti-cytokine therapy was given to four patients, and intravenous immunoglobulin therapy was given to 5 patients, while 5 patients required renal replacement therapy (Table I).

It was observed that the patients were intubated approximately 5 days after admission to ICU, iNO treatment was started 9 days later, and the treatment lasted approximately 3.5 days (Table II). It was found to be a statistically significant improvement in PaO_2/FiO_2 ratio and a worsening in Sequential Organ Failure Assessment (SOFA) score, IL-6, and platelet values with iNO treatment ($p<0.05$). When the outcome patterns of the patients were examined, 3 patients (19%) were transferred from the ICU to the ward, whereas 13 patients died (Table III).

Discussion

Lung protective ventilation strategy and high PEEP applications are recommended in ARDS treatment. Prone position, recruitment maneuvers, and the use of short-term neuromuscular blockers are recommended in cases where these strategies are insufficient, such as a PaO_2/FiO_2 ratio below 150. If hypoxemia persists despite all these applications, rescue treatment methods such as iNO or extracorporeal membrane oxygenation (ECMO) are recommended. However, ECMO is an expensive treatment method that is not available at all centers or is limited in number. ECMO is recommended by Extracorporeal Life Support Organization (ELSO) in experienced centers, and it has some complications (i.e., serious bleeding and vascular issues). Increasing ARDS cases and the limited ECMO resource led to the use of iNO as a rescue therapy during the COVID pandemic in our clinic. Although we estimated that we used iNO in more patients, we were only able to access the data of 16 patients.

iNO improves ventilation-perfusion rate by vasodilation in pulmonary vessels. It also relieves right ventricular outflow by reducing pulmonary vascular resistance. There is no clear recommendation

Table I. Patients' demographic and clinic data.

Patient	Age, gender	Co-morbidity	APACHE II	SOFA	Anti-inflamatory/ anti-cytokine therapy	PaO_2/FiO_2	Prone position/ recruitment	iNO treatment duration	Entubation duration	iNO therapy duration	Lenght of ICU	Outcome
1	76, F		7	4	250 mg methyl-prednisolone/3 days	51	+	3	2	11	32	Exitus
2	83, M	Renal transplation	12	4	-	51.0	+	2	4	20	13	Exitus
3	71, M	CAD, Coroner Bypass surgery	10	4	250 mg metil-prednisolone/3 days	60.0	+	1	8	10	10	Exitus
4	68, M	COPD, gastro-intestinal hemorrhage	9	7	250 mg metil-prednisolone/3 days	69.0	+	4	7	10	21	Exitus
5	65, M	COPD, tuberculosis	13	5	250 mg methyl-prednisolone/3 days +400 mg tocilizumab/2 days	67	+	3	4	9	15	Exitus
6	70, M	COPD	18	5	250 mg methyl-prednisolone/3 days +400 mg tocilizumab/2 days	60.0	+	4	2	5	8	Exitus
7	52, M	DM, myocardial ischemia	7	7	250 mg methyl-prednisolone/3 days	55.0	+	5	2	17	40	Exitus
8	50, M	-	3	6	250 mg methyl-prednisolone/3 days +400 mg tocilizumab/2 days	50.0	+	3	18	19	23	Exitus
9	61, F		35	8	250 mg methyl-prednisolone/3 days	50.0	+	2	1	2	3	Exitus
10	68, M	Parkinsonism	24	6	250 mg methyl-prednisolone/3 days +IVIG 0.4 g/kg/5 days	60	+	4	4	7	21	Exitus
11	73, M	-	14	6	-	70.0	+	5	10	11	19	Exitus
12	83, F	HT, COPD	10	4	-	50.0	+	1	2	3	3	Exitus
13	71, M	CAD	12	3	250 mg methylprednisolone /3 days +400mg tocilizumab/ 2 days+IVIG 0.4 g/kg/5 days	65	+	5	4	6	25	Survival
14	87, F	CHF, AF	13	6	IVIG 0.4 g/kg/5 days	45.0	+	4	3	4	7	Exitus
15	51, F	Malignency	5	9	IVIG 0.4 g/kg/5 days	85.0	-	3	5	8	23	Survival
16	62, M	-	15	8	250 mg methyl-prednisolone/3 days	52	+	3	1	7	35	Survival

AF: atrial fibrillation; CAD: coronary arterial disease; CHF: chronic heart failure; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; F: female; HT: hypertension; iNO: inhaled nitric oxide; IVIG: intravenous immunoglobulin; M: male; PaO_2/FiO_2 ratio: partial arterial oxygen pressure to fractional inspired oxygen; SOFA: Sequential Organ Failure Assessment.

for the dose of iNO in reports, it has been applied at different doses and times in different studies[8-10]. In our clinic, on the other hand, continuous treatment was applied with a dose of 20 ppm/hour, followed by a reduction after the desired response was obtained. Before applying iNO, optimal PEEP was measured with decremental PEEP maneuvers as recommended by ARDS guidelines. Recruitment maneuvers were performed, steroids were given, and all patients were placed in a prone position (except one).

Abman et al[8] used iNO as a starting median dose of 30 (9-40) ppm and a median termination dose of 5 (0.5-15) ppm in mild-moderate ARDS patients undergoing high flow, noninvasive or invasive ventilation. A 20% increase in PaO_2/FiO_2 was considered significant, and the median response time to iNO was determined to be 3 days. The time from hospitalization to the onset of iNO was 7.2 days. The median iNO treatment time was indicated as 6 days. Unlike this study, all of our patients in our study had severe ARDS. Our patients were intubated approximately 5 days after admission to the ICU, iNO treatment was started approximately on the 9th day, and the treatment lasted an average of 3.5 days.

In a study[9] investigating the use of iNO and almitrine bismesylate alone or in combination in patients with moderate ARDS with COVID-19, authors demonstrated that oxygenation did not improve. Longobardo et al[10], in their study comparing COVID-19 and non-COVID-19 ARDS patients, showed that iNO did not improve oxygenation in patients with COVID-19. Ferrari et al[11] did not observe a significant improvement in oxygenation after the administration of 20 ppm iNO in ten patients receiving mechanical ventilation support due to COVID-19. In the study of Chen et al[7], patients with ARDS who underwent non-invasive mechanical ventilation were administered iNO at a dose of 30 ppm and gradually decreasing doses. As a result, they observed that the oxygenation of the patients increased. In the study of Abou-Arab et al[4] iNO was administered at a dose of 10 ppm to 34 of 80 patients followed up with severe COVID-19 pneumonia in the ICU. They observed

Table II. Patients' demographic data.

Age (year)	67.69±11.39
Female	6 (40%)
Presence of comorbidity	11 (73.3%)
Time to start treatment (days)	9.06±5.60
NO treatment time (days)	3.50±1.59
Intubation day	4.81±4.34
APACHE II	12.94±7.78
Intensive care duration (days)	18.63±11.10
Length of hospital stay (days)	24.19±15.62

APACHE II: acute physiology and chronic health evaluation score II.

Table III. Laboratory data before and after iNO treatment (mean±SD).

	Before NO treatment	After NO treatment	*p*
PaO_2/FiO_2 ratio	58.84±10.27	111.38±64.09	0.001
SOFA	5.75±1.73	9.38±4.03	0.004
CRP (mg/dL)	8.10±6.82	7.31±6.05	0.691
PCT (ng/mL)	0.9±1.49	4.28±7.26	0.079
IL-6 (pg/mL)	300.50±621.93	1,587.20±1,982.01	0.031
Fibrinogen (mg/dL)	396.33±178.81	363.07±187.38	0.272
Ferritin (ng/mL)	810.31±507.80	1,425.44±1,414.09	0.293
D-Dimer (mg/L)	6.28±7.70	6.38±6.82	0.470
Leucocyte (10^3 cell/mm^3)	14.00±7.41	12.37±13.02	0.233
Hemoglobin (g/dL)	11.35±1.79	10.99±1.88	0.348
Platelet (10^3 cell/mm^3)	194.19±81.21	134.67±66.94	0.004
Neutrophil (10^3 cell/mm^3)	13.13±6.48	12.91±11.67	0.427
Lymphocyte (10^3 cell/mm^3)	0.91±0.84	1.24±1.86	0.638
BUN (mg/dL)	45.82±28.78	52.17±33.04	0.152
Creatinine (mg/dL)	1.47±0.91	2.04±1.63	0.221
pH	7.31±0.16	7.20±0.22	0.164
$PaCO_2$ (mmHg)	57.10±19.53	74.99±39.55	0.173
HCO_3 (mmol/L)	24.14±6.29	21.41±8.99	0.222
Base excess	0.61±7.23	-1.59±10.66	0.334
Lactate (mmol/L)	1.66±0.97	3.39±3.45	0.065

CRP: C-reaktive protein; HCO_3: bicarbonate; IL-6 interleukin-6; PaO_2/FiO_2 ratio: partial arterial oxygen pressure to fractional inspired oxygen; $PaCO_2$: partial arterial carbondiokside pressure; PCT: procalcitonin; SOFA: Sequential Organ Failure Assessment.

a significant increase in the PaO_2/FiO_2 ratio in 65% of the patients administered iNO. Safaee Fakhr et al[12] applied iNO at a dose of 160 ppm twice a day for up to 14 days in 29 spontaneously breathing patients who did not receive continuous oxygen therapy or high flow oxygen therapy and hospitalized with the diagnosis of COVID-19. They observed that patients with hypoxemia given iNO had improved oxygenation, one patient progressed to mechanical ventilation, and no patients died. There are studies[13-16] supporting that the combination of a specific vasoconstrictor, Almitrin, and iNO increased oxygenation improved compared to iNO alone in COVID-19 patients. There are also publications[17,18] showing that the PaO_2/FiO_2 ratio improved more in non-COVID with ARDS patients. In our study, it was found that PaO_2/FiO_2 values increased significantly after iNO compared to before, and patients regressed from severe ARDS to moderate ARDS. However, it is very difficult to compare the studies on iNO and come to a conclusion. Because the hypoxemia and multi-organ system involvement levels of the patients included in the studies were not similar. The ventilation methods and other treatments, especially the dose and duration of iNO, were also different. The main difference in our study compared with others was that patients had more severe hypoxemia. In fact, all patients in our study had an indication for ECMO, according to ELSO.

The relationship between iNO therapy and mortality was also investigated. In the study of Safaee Fakhr et al[12], it was stated that mortality did not develop in any of the patients who had spontaneous breathing, cough, and tachypnea, who underwent iNO. Taylor et al[19] used a low-dose strategy iNO at a dose of 5 ppm in patients with lung injury due to non-sepsis reasons. A slight improvement in oxygenation was observed, while iNO was shown to be ineffective on disease severity and mortality. Ferrari et al[11] mentioned a 20% mortality rate in their study. Feng et al[20] lost two out of 5 patients in their study. Laghlam et al[21] found the mortality rate to be 50% in patients with moderate ARDS due to COVID-19. Although post-study mortality was given in the study of Longobardo et al[10], 6 (22%) of the 22 COVID-19 ARDS patients included in the study died within the first 24 hours of starting iNO. Buckley et al[22] reported 51% mortality among 100 patients with moderate-to-severe ARDS who underwent iNO.

Evaluating the relationship between iNO treatment and mortality is difficult because there is no standard approach in both the ventilation and iNO treatments of the patients in the studies. However, as it is understood from the previous publication[23], the more severe ARDS, the higher the mortality rate. The patients in our study were in the severe ARDS group due to COVID-19, and our mean PaO_2/FiO_2 value was 58.84±10.27. While a statistically significant increase in mean PaO_2/FiO_2 values was achieved with iNO, 3 (19%) of 16 patients survived, and 13 died. In fact, all of the patients who underwent iNO consisted of patients expected to result in mortality. The survival rate of 19% was considered an improvement. As a result, iNO may be an effective treatment to improve survival.

In a study[24] conducted at an ECMO-specific center in the United Kingdom, it was shown that mortality was reduced by 18% with ECMO, another rescue treatment that can be used as an alternative. In a multicenter study[25] conducted in Poland, the mortality rate of patients admitted to an ECMO-experienced ICU and undergoing ECMO was reported to be 74%. As a result, two studies[24,25] presented by centers with ECMO experience showed that ECMO increased survival by 18% and provided survival by 26%. Therefore, iNO can be interpreted as providing a similar survival rate to ECMO.

Safaee Fakhr et al[12] observed that the IL-6, CRP, ferritin, and D-Dimer levels of the patients were high at the time of hospitalization, but the leukocyte level was normal. There was a slight increase in the platelet count during the hospitalization. In our study, there was no observable increase in platelet counts, but a slight decrease was shown. Parikh et al[3] found no change in CRP and ferritin levels, but an increase in D-Dimer levels in their study on non-intubated patients.

In our study, all of our patients were already in severe ARDS, under invasive mechanical ventilation, and had a high SOFA score as a result. CRP, procalcitonin, IL-6, ferritin, D-dimer, BUN, and creatinine levels were high before and after iNO treatment. The patients were acidotic and hypercapnic, as well as hypoxemia. After the administration of iNO, the oxygenation of the patients improved, while SOFA, IL-6, and platelet counts gradually progressed to poor values. This demonstrates that the patients are getting worse. However, this worsening has been thought to be related to the progression of the disease rather than being related to iNO treatment.

Conclusions

As a result, a significant response was observed in the PaO_2/FiO_2 ratio in response to iNO in patients with severe ARDS due to COVID-19 pneumonia. However, the application of iNO as a rescue treatment resulted in an 18% survival rate of patients whom, without iNO, would have died. The inadequacy of the number of patients in our study is one of the limitations of this study, while the advantage is taking a certain patient group and applying the same iNO and other treatment modalities to all patients by the same team. However, we believe that multicenter studies with more patients in which the same protocol was applied to the same patient group are needed to determine the net effects of iNO on oxygenation and mortality.

Conflict of Interest
No conflict of interests.

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Authors' Contributions
Conceptualization, Murat Bicakcioglu and Ayse Belin Ozer; methodology, Murat Yalcinsoy and Ayse Belin Ozer; validation, Serkan Kalkan; formal analysis, Deccane Duzenci; investigation, Zafer Dogan; data curation, Serkan Kalkan; writing-original draft preparation, Deccane Duzenci and Zafer Dogan; writing-review and editing, Murat Bicakcioglu and Ayse Belin Ozer; visualization, Zafer Dogan and Murat Yalcinsoy; supervision, Murat Yalcinsoy. All authors have read and agreed to the published version of the manuscript.

Ethics Approval
Ethical approval received from the Inonu University Health Sciences Non-Interventional Clinical Research Ethics Committee (2022/3112). The present clinical study was conducted at the Inonu University, in full accordance with ethical principles, including the World Medical Association Declaration of Helsinki.

Informed Consent
Written informed consent was obtained from the subjects or their guardian.

Data Availability
The datasets generated during and/or analyzed during the current study are not publicly available due privacy of patient data but are available from the corresponding author on reasonable request.

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