ORIGINAL RESEARCH

Real-world use of inhaled nitric oxide therapy in patients with COVID-19 and mild-to-moderate acute respiratory distress syndrome

Steven H Abman[1], Nicholas R Fox[2], M Ibrahim Malik[2], Sneha S Kelkar[3], Shelby L Corman[3], Sanika Rege[3], Jenna Bhaloo[3], Rachel Shah[3], Ren-Jay Shei[4], Dana Saporito[4], Nisreen Shamseddine[4], Erik DeBoer[4], George J Wan[4], on behalf of the NOTICE Study Investigators

[1]Department of Pediatrics, University of Colorado Anschutz School of Medicine and Children's Hospital Colorado, Aurora, CO, USA; [2]Piedmont Athens Regional, Athens Pulmonary, Athens, GA, USA; [3]OPEN Health, Bethesda, MD, USA; [4]Mallinckrodt Pharmaceuticals, Hampton, NJ, USA

Abstract

Background: Inhaled nitric oxide (iNO) has been studied in patients with severe acute respiratory distress syndrome (ARDS) due to COVID-19 when it may be too late to impact disease course. This article aims to describe real-world iNO use and outcomes in patients with COVID-19 with mild-to-moderate ARDS in the United States.

Methods: This was a retrospective medical chart review study that included patients who were ≥18 years old, hospitalized for COVID-19, met the Berlin ARDS definition, received iNO for ≥24 hours continuously during hospitalization, and had a partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ratio (P/F ratio) of >100 to ≤300 mmHg at iNO initiation. Outcomes included oxygenation parameters, physician-rated Clinical Global Impression–Improvement (CGI-I) scale scores, and adverse events. Response to iNO was defined as >20% improvement in P/F ratio.

Results: Thirty-seven patients at six sites were included. A P/F ratio of ≤100 was the most common reason for exclusion (*n*=146; 83% of excluded patients). The mean P/F ratio (SD) increased from 136.7 (34.4) at baseline to 140.3 (53.2) at 48 hours and 151.8 (50.0) at 72 hours after iNO initiation. The response rate was 62% (*n*=23). During hospitalization, no patient experienced adverse events, including methemoglobinaemia, airway injury, or worsening pulmonary oedema associated with iNO. At discharge, 54.0% (*n*=20) of patients improved or remained stable according to the CGI-I.

Conclusion: In patients hospitalized with COVID-19 and mild-to-moderate ARDS, iNO was associated with improvement in the P/F ratio with no reported toxicity. This study provides additional evidence supporting a favourable benefit–risk profile for iNO in the treatment of mild-to-moderate ARDS in patients with COVID-19 infection.

Keywords: acute respiratory distress syndrome (ARDS), COVID-19, inhaled nitric oxide, P/F ratio, real-world.

Introduction

Acute respiratory distress syndrome (ARDS) is a major cause of morbidity and mortality in patients with COVID-19, which is caused by the SARS-CoV-2 virus.[1] Up to 20% of patients with COVID-19 develop critical illness characterized by ARDS, with progressive hypoxaemia often leading to the need for mechanical ventilation;[2–6] mortality in these patients is as high as 74%.[7] Patients with refractory hypoxaemia despite ventilatory support and prone positioning may require extracorporeal membrane oxygenation (ECMO), which may have limited availability and is associated with high cost and risk of complications.[8,9]

Inhaled nitric oxide (iNO) stimulates soluble guanylyl cyclase, which results in increased levels of cyclic 3'–5'-guanosine monophosphate (cGMP) in lung smooth muscle cells, leading to pulmonary vasodilation.[10] Due to its mechanism of action, iNO has been proposed as a potential therapeutic option for ARDS in patients with COVID-19. iNO has potent and selective vasodilator effects on pulmonary circulation without affecting systemic vascular tone. iNO also exhibits micro-selective

properties that enhance perfusion only in well-recruited areas of the lung, thereby reducing intrapulmonary shunting.[10] Additionally, in large multicentre randomized trials, iNO has been shown to reduce the need for ECMO therapy in neonates with profound hypoxaemia despite mechanical ventilation.[11,12] Previous studies have shown that iNO can improve the oxygenation index (OI) in paediatric and adult patients with ARDS with a favourable benefit–risk profile.[13–15] While the only FDA-approved use of iNO (INOmax®, INO Therapeutics LLC, Hampton, NJ, USA) is for the treatment of term and near-term neonates with severe hypoxaemic respiratory failure with pulmonary hypertension,[16] it has been recommended by medical guidelines as a means of avoiding ECMO in adult patients with ARDS with hypoxaemia despite protective ventilation and prone positioning prior to consideration of ECMO.[17]

In addition, some evidence suggests that nitric oxide has antiviral activity, including direct inhibition of viral replication,[18,19] activation of ciliary movement[20] and increased mucus secretion.[21] Moreover, in a small observational study conducted during the SARS outbreak of 2002, iNO therapy improved oxygenation and reduced the need for mechanical ventilation in patients compared with a matched control group.[22]

Previous observational studies in patients with COVID-19 treated with iNO have yielded mixed results,[23–27] potentially owing to small sample sizes and heterogeneity in study design, patient populations, iNO regimens, and duration of follow-up. Of note, most of these studies included patients with severe ARDS; when hypoxaemia is deeply entrenched, very few treatments are effective and clinical complications with ARDS begin to mount, including multiorgan failure.[28] Therefore, the objective of this study was to describe real-world iNO use and clinical outcomes, including the ability to sustain oxygenation, in hospitalized patients with COVID-19 and mild-to-moderate ARDS in the United States.

Methods

Study design

This retrospective, observational study used patient-level data abstracted from medical charts of patients hospitalized with confirmed COVID-19 and treated with iNO (INOmax®) in the United States. A convenience sample of physicians in pulmonary and critical care medicine, internal medicine, and/or infectious diseases specialties were recruited as study investigators and were responsible for patient selection and data collection from patient charts. Physicians were recruited from hospitals using a targeted list provided by the study sponsor and the Society of Critical Care Medicine's Discovery VIRUS COVID-19 Registry. More than half of the centres were unable to participate due to reasons such as no response, insufficient time or personnel to help with the study, or unavailability of eligible patients. Data were collected from six centres that agreed to participate between 1 October 2020 and 31 March 2021. Central ethics approval was granted by the Western Copernicus Group institutional review board, with site-level approval granted as required by each participating institution.

Study population

The study included patients who were at least 18 years old at the time of hospitalization, met the Berlin definition of ARDS,[29] received iNO for at least 24 hours continuously at any time during hospital stay, and had a partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ratio (P/F ratio) of >100 when iNO was initiated. Patients were required to have had serial P/F ratios recorded for at least two values prior to iNO initiation, with the most recent at 12 hours before iNO initiation, to have had clear documentation of the exact time of iNO and mechanical ventilation initiation and discontinuation, and to have been discharged from the hospital at least 30 days prior to data collection. Exclusion criteria were previous hospitalization for COVID-19, previous or concurrent use of any other pulmonary vasodilator therapy within 24 hours prior to administration of iNO, use of nitric oxide donors (e.g. sodium nitroprusside, triglycerol nitrate), insufficient clinical history and information from admission to discharge or death available to the admitting institution, or enrolment in an iNO-related interventional clinical trial during the COVID-19 hospitalization. Participating physicians provided de-identified data from eligible patients' medical records. All eligible patients were enrolled at each site to avoid selection bias.

Study outcomes

Patients were followed from COVID-19-related hospitalization up to 30 days post discharge or until loss to follow-up. Data collected included patients' demographic characteristics, comorbidities, presence of COVID-19 symptoms, laboratory tests, type and duration of mechanical ventilation, and inpatient treatments administered. Study outcomes included oxygenation parameters, physician-rated Clinical Global Impression–Improvement (CGI-I) scale scores, length of stay, discharge destination, readmission, mortality, adverse events, and complications.

The oxygenation parameters consisted of serially measured P/F ratio, positive end-expiratory pressure (PEEP), and mean airway pressure (MAP) from 24 hours prior to initiation of iNO until 24 hours after discontinuation of iNO. For sites that did not routinely collect PaO_2 measures, SpO_2 was converted to PaO_2 using the Severinghaus–Ellis equation and conversion tables.[30] OI was calculated as $MAP \times FiO_2 \times 100/PaO_2$. Response to iNO was defined as a >20% improvement in P/F ratio from the last measurement prior to initiating iNO (i.e. baseline).[23,24,31] In a sensitivity analysis, a definition of >10% improvement in P/F ratio was used to describe response.[26]

Data on iNO doses and dose changes as well as frequency of administration were collected to characterize the weaning process. Successful weaning of iNO was defined as discontinuation of therapy at least 1 day prior to death or hospital discharge. Complications during hospitalization included cardiomyopathy, seizure, kidney failure or replacement therapy, pulmonary embolism, deep vein thrombosis, and evidence of co-infection (bacterial or viral), as defined by the investigator. Selected adverse events of interest (worsening pulmonary oedema, methemoglobinaemia and airway injury) were also observed.

Statistical methods

Descriptive statistics were used with count and percentage in each category for categorical variables, mean and standard deviation (SD) for normally distributed continuous variables, and median and range for non-normally distributed continuous variables. Time-dependent endpoints were analysed in terms of total number of events observed and the proportion of patients experiencing events after accounting for censoring using Kaplan–Meier methods. The P/F ratio trajectory was assessed among patients with available data at each relevant time point (prior to iNO initiation and at 24, 48, and 72 hours post initiation). Missing data were imputed using linear interpolation that assumes a linear relationship between data points and utilizes non-missing values from adjacent data points to compute a value for a missing data point. Statistical analysis was conducted using SAS 9.4.

Results

Site and patient enrolment

The study targeted seven study sites in geographically diverse regions of the USA. Five hospitals were academic tertiary referral centres, and two were other academic/teaching hospitals. ECMO was available at five of the seven study sites. At the time of data collection, six sites had treated more than 250 patients with COVID-19 since 1 January 2020.

A total of 213 patients were screened for enrolment; 37 patients at six sites met enrolment criteria and were included in the study (Figure 1). The most common reason for exclusion was severe ARDS with a P/F ratio of ≤100 (n=146; 83% of excluded patients).

Patient and clinical characteristics

Study patients were predominantly men (62.2%) and white (56.8%), with a mean age of 62 years (Table 1). The majority of patients (89.2%) were admitted from home; only 5.4% were admitted from a nursing home. The most common comorbidities among study patients were hypertension (56.8%) and diabetes mellitus (43.2%). Approximately half of patients were receiving at least one pre-admission medication of interest, including oral steroids (21.6%), antibiotics (21.6%), and non-steroidal anti-inflammatory drugs (18.9%), among others (Table 1). During their hospitalization, most patients received concomitant anticoagulants (97.3%), vasopressors (83.8%),

Figure 1.   Patient enrolment.
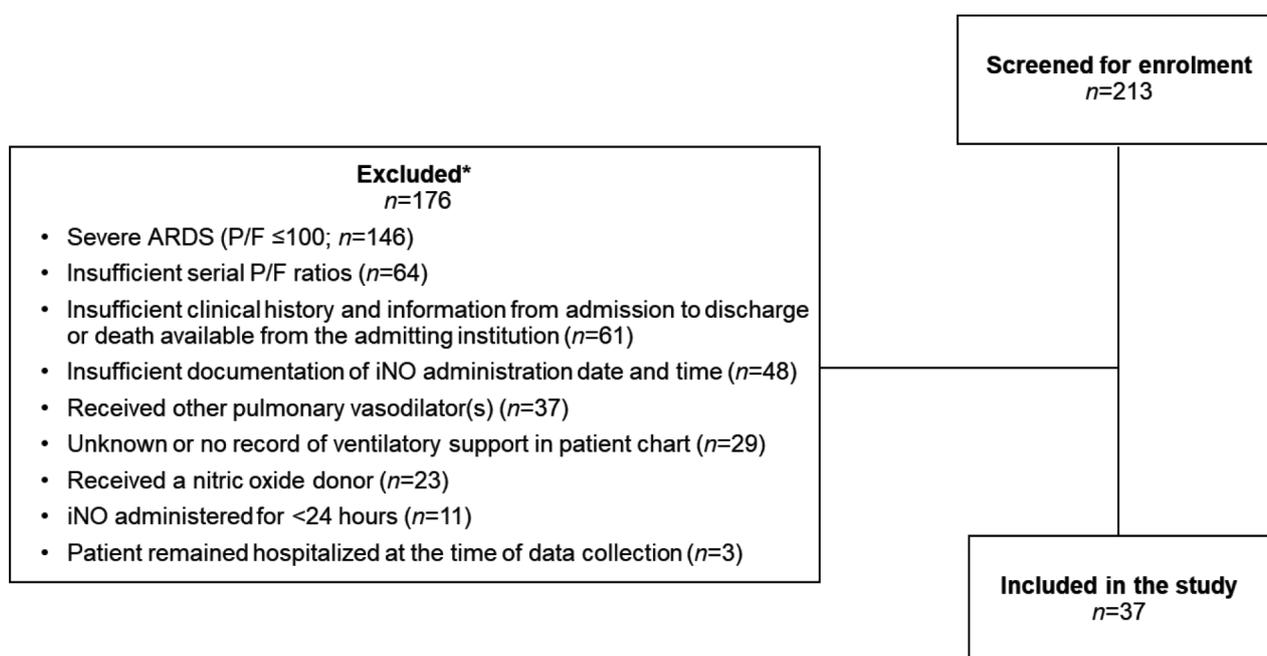
*Reasons for exclusion are not mutually exclusive.

ARDS, acute respiratory distress syndrome; iNO, inhaled nitric oxide; P/F, PaO_2/FiO_2.

dexamethasone (78.4%), and remdesivir (70.3%). Twenty-one patients (56.8%) were prone positioned at any time during hospitalization.

Bilateral reticular nodular opacities were noted on the initial chest radiograph in 75.7% of patients; other findings included ground-glass opacities (16.2%), focal consolidation (13.5%), and pulmonary oedema (8.1%). Two patients (5.4%) had no significant findings on the initial chest radiograph. Thirty-five of the included patients (94.5%) had moderate ARDS (P/F ratio, 101–200 mmHg) and two (5.5%) had mild ARDS (P/F ratio, 200–300 mmHg) at the time of iNO initiation.

iNO administration

Nitric oxide was administered as an inhaled formulation. Mean time from hospitalization to iNO initiation was 7.2 days (SD, 7.0; IQR, 3–12 days). At the time of iNO initiation,

Table 1. Clinical and treatment characteristics of hospitalized patients with COVID-19 and mild-to-moderate ARDS treated with iNO.

	Patients n=37
Age at hospital admission, mean (SD)	62.0 (10.2)
Men, n (%)	23 (62.2)
Race, n (%)	
White	21 (56.8)
Black/African American	11 (29.7)
Other	2 (5.4)
Unknown	3 (8.1)
Admission source, n (%)	
Home	33 (89.2)
Nursing home	2 (5.4)
Other	1 (2.7)
Unknown	1 (2.7)
Pre-admission medications, n (%)	
Oral steroids	8 (21.6)
Antibiotics	8 (21.6)
Non-steroidal anti-inflammatory drugs	7 (18.9)
Angiotensin-converting enzyme inhibitors	6 (16.2)
Other immunosuppressant agents (not oral steroids)	6 (16.2)
Angiotensin II receptor blockers	4 (10.8)
Antivirals[a]	2 (5.4)
None of the medications listed above	18 (48.6)

	Patients n=37
Comorbidities, n (%)	
Hypertension	21 (56.8)
Diabetes mellitus	16 (43.2)
Morbid obesity (BMI ≥35)	9 (24.3)
Hyperlipidaemia	9 (24.3)
Obesity (BMI ≥30–35)	8 (21.6)
COPD	6 (16.2)
Chronic kidney disease	6 (16.2)
Congestive heart failure	4 (10.8)
Coronary artery disease	4 (10.8)
Asthma	4 (10.8)
History of solid organ transplant	4 (10.8)
Cancer	4 (10.8)
Obstructive sleep apnoea	3 (8.1)
Venous thromboembolism	3 (8.1)
Chest radiograph findings upon hospital admission, n (%)	
Bilateral reticular nodular opacities	28 (75.7)
Ground-glass opacities	6 (16.2)
Focal consolidation	5 (13.5)
Pulmonary oedema	3 (8.1)
Venous congestion	2 (5.4)
Cardiomegaly	2 (5.4)
Atelectasis	1 (2.7)
Pleural effusion	1 (2.7)
Peribronchial thickening	1 (2.7)
Other findings	2 (5.4)
Clear radiograph/no significant findings	2 (5.4)
Concomitant medications during hospitalization, n (%)	
Anticoagulants	36 (97.3)
Vasopressors	31 (83.8)
Dexamethasone	29 (78.4)
Remdesivir	26 (70.3)
Convalescent plasma	7 (18.9)
Hydroxychloroquine/chloroquine	4 (10.8)
Methylprednisolone	4 (10.8)
Lopinavir/ritonavir	3 (8.1)
Ribavirin	2 (5.4)
Interferon alpha	1 (2.7)
Other antivirals[a]	5 (13.5)

[a]All patients received tocilizumab.

ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; iNO, inhaled nitric oxide; SD, standard deviation.

73.0% of patients were receiving invasive ventilatory support (ECMO, 5.4%; other invasive/mechanical ventilation, 67.6%), 21.6% of patients were receiving non-occlusive oxygen support (i.e. via nasal canula or high-flow nasal canula), and 5.4% were receiving non-invasive occlusive ventilation (i.e. bilevel positive airway pressure or continuous positive airway pressure). The median duration of iNO treatment was 6 days (IQR, 3–9 days; range, 1–42 days). The median iNO starting dose was 30 ppm and ranged from 9 to 40 ppm; median dose at iNO discontinuation was 5 ppm (range, 0.5–15 ppm). A total of 25 (67.6%) patients underwent successful iNO weaning before discharge or death, and 14 (56%) of these were weaned without the need to return to the previous dose. During hospitalization, no patient experienced adverse events, including methemoglobinaemia, airway injury, or worsening pulmonary oedema associated with iNO.

Effectiveness outcomes

The mean P/F ratio (SD) increased from 136.7 (34.4) at baseline to 140.3 (53.2) at 48 hours after iNO initiation (n=34) (Figure 2). At 72 hours post initiation, the mean P/F ratio increased to 151.8 (50.0) (n=34). A linear decreasing trend in dose was observed as the P/F ratio continued to increase up to 72 hours post iNO initiation. The OI was available in 24 patients and increased from a mean (SD) of 14.7 (4.4) at baseline to 16.9 (11.3) at 48 hours after iNO initiation. At 72 hours after initiation, the mean OI decreased to 14.1 (9.4). Average PEEP during the 72-hour period following iNO initiation remained relatively constant (mean (SD) baseline 12.3 (3.3); at 48 hours 12.6 (2.9); at 72 hours 12.7 (2.7)).

Nearly two-thirds of patients (n=23; 62.2%) achieved response to iNO, defined as an increase in P/F ratio by >20% at any time after iNO initiation. Median time to response was 3 days (IQR 1–3 days) after initiation of iNO (Figure 3). When response was defined as a >10% increase in P/F ratio, 70.3% (n=26) of patients were categorized as responders. Among the 27 (n=73%) patients receiving invasive mechanical ventilation at the time of iNO initiation, 4 (14.8%) were transitioned to non-invasive ventilation. No patient required ECMO after initiation of iNO.

Other clinical outcomes

Over half of patients (n=20; 54.0%) died during hospitalization, with the majority of deaths (n=16; 80.0%) attributed by the investigator to COVID-19. Of those discharged alive, 58.8%

Figure 2.   Mean PaO$_2$/FiO$_2$ and iNO dosing during COVID-19 hospitalization.
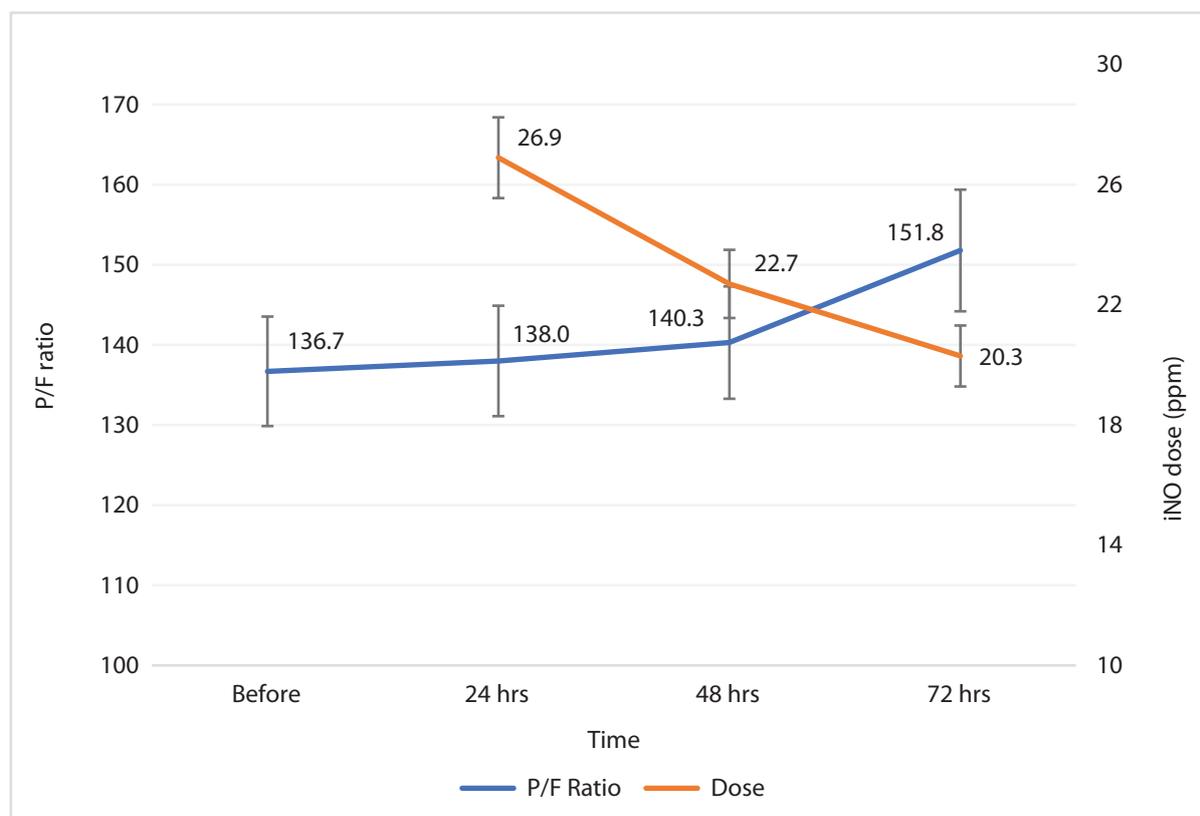
The error bars represent the standard error of each mean. iNO, inhaled nitric oxide; P/F, PaO$_2$/FiO$_2$.

Figure 3. Time to response (improvement in PaO_2/FiO_2 by >20% from pre-iNO).
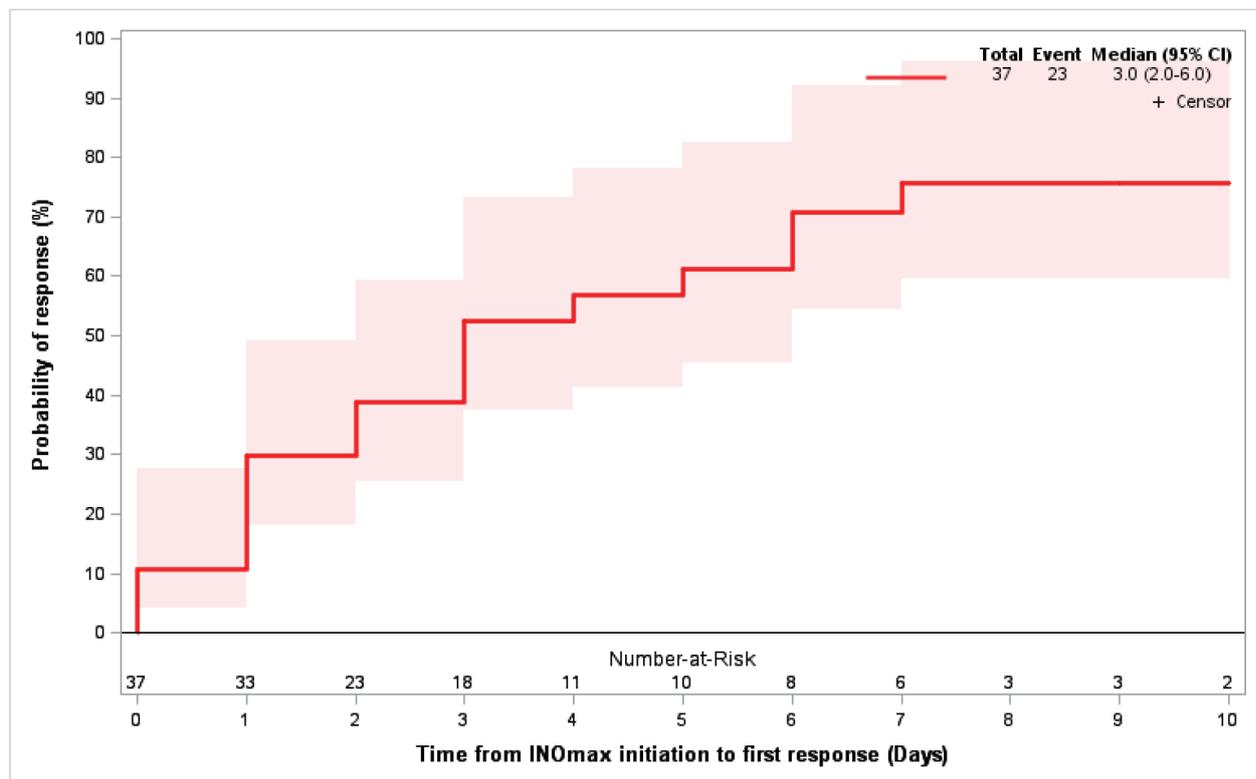
iNO, inhaled nitric oxide.

were discharged to home, 23.5% to a rehabilitation facility, 11.8% to another hospital, and 5.9% to a nursing home. Nearly half of those discharged alive had some limitation of activities (47.1%), with fewer patients discharged as non-ambulatory (23.5%), with no limitation of activity (23.5%), or with unknown ambulatory status (5.9%).

Complications of COVID-19 experienced during the hospitalization included renal failure and/or requirement for renal replacement (54.1%), bacterial pneumonia (37.8%), evidence of bacterial or viral co-infection (35.1%), and delirium/encephalopathy (29.7%). Median length of hospital stay was 26 days (range, 6–93 days); a median of 22 days (range, 17–30 days) was spent in an intensive care unit. Median length of stay was longer in patients who survived to discharge (34 days; range, 6–93 days) compared to those who died during hospitalization (22.5 days; range, 8–69 days).

At the time of hospital discharge, 54.0% (n=20) of patients were assessed by the investigator as having improved or having had no change according to the CGI-I (much improved, 24.3%; minimally improved, 16.2%; no change from baseline, 13.5%) and 45.9% were judged to be worse (minimally worse, 5.4%; much worse, 16.2%; very much worse, 24.3%). Five patients (13.5%) were readmitted to hospital within 30 days post discharge, with one additional patient (2.7%) presenting to the emergency department without hospital admission.

Discussion

COVID-19 infection can cause severe and progressive hypoxaemia, often leading to the need for invasive ventilation or even ECMO therapy to sustain cardiopulmonary function. The results of this study suggest that iNO is associated with maintenance or improvement in P/F ratio in patients with COVID-19 and mild-to-moderate ARDS, with nearly two-thirds of patients defined as responders. With no adverse events attributed to iNO treatment, these results support a favourable benefit–risk profile in this population, which has a significant unmet need. Of the 213 patients screened for inclusion in the study, fewer than 20% met study inclusion criteria. Of the excluded patients, the majority had severe ARDS at the time of iNO initiation and one-third had received other pulmonary vasodilators or nitric oxide donors.

These findings provide important information about the use of iNO in real-world practice, suggesting that, during the enrolment period, iNO was typically reserved as a rescue therapy for patients who were critically ill and/or had failed to improve on other medications aimed at improving oxygenation. The design and findings of this study have important differences when compared with previous observational studies of iNO use in patients with COVID-19 and ARDS. Response rates were similar to those seen in a

prospective study including patients who initiated iNO when their P/F ratio decreased to <150 (65%), albeit at a lower dose (10 ppm) than observed in this study.[24] In addition, in a population with primarily moderate and severe ARDS, 64% of patients were defined as responders using a threshold of 10% improvement.[26] In a study designed to evaluate the impact of prone positioning on oxygenation in patients with ARDS due to COVID-19, a subgroup of 12 patients received iNO and 9 (75%) experienced an increase in their P/F ratio of >20%.[32] Conversely, the response rate found in patients with severe ARDS despite high PEEP and prone positioning was only 25%,[23] and initiation of iNO was not associated with significant improvement in the P/F ratio in patients with a baseline ratio of 100 or less,[33] suggesting that treatment with iNO earlier in the ARDS disease course as defined by the P/F ratio may be of benefit to patients with COVID-19.

Further support for early initiation of iNO is evident from several studies where iNO was initiated in patients not yet on mechanical ventilation, of whom up to 96.5% were able to stay off a ventilator until hospital discharge.[34,35] Our study was not able to directly test this hypothesis due to the small number of patients not receiving mechanical ventilation at the time of iNO initiation.

Strengths and limitations

This study has a number of strengths. To our knowledge, this is the first multicentre evaluation of iNO use and outcomes in the United States. In addition, the outcomes collected provide a comprehensive view of iNO use, clinical outcomes, adverse events, and healthcare resource use in clinical practice. The study population (who had mild-to-moderate ARDS with a

single, common aetiology) is unique from previous studies that focused on severe ARDS and thus provides valuable data in this understudied population.

Study limitations include the retrospective nature of the study design and the use of data abstracted from medical charts of study patients. The accuracy and completeness of data in this study are limited by the availability and quality of data in each patient's medical chart. Treatment patterns in the study reflect the use of iNO for hospitalized patients with COVID-19 in selected medical centres willing to participate in this retrospective medical chart study and may not be representative of all institutions using iNO. The dosing and duration of iNO treatment was variable across sites and determined at the attending physician's discretion. Criteria for initiation of iNO, iNO weaning, and weaning protocols were not standardized across sites. Finally, we did not collect detailed information about all potential interventions for the acute management of COVID-19 ARDS, including diuretics, vasopressors, and prone positioning. Further research is needed to examine the safety and efficacy of iNO in controlled clinical settings, with randomized controlled trials ongoing.

Conclusion

In patients hospitalized with COVID-19 and mild-to-moderate ARDS, iNO treatment was associated with improvement in the P/F ratio with no reported toxicity. This study provides additional evidence supporting a favourable benefit–risk profile for iNO in the treatment of COVID-19. Future randomized, placebo-controlled studies are needed to determine its potential efficacy and place in therapy.

Correspondence: Sneha S Kelkar, OPEN Health, 4350 East-West Highway, Suite 1100, Bethesda, MA 20814, USA.
Email: snehakelkar@openhealthgroup.com

References

1. Adusumilli NC, Zhang D, Friedman JM, Friedman AJ. Harnessing nitric oxide for preventing, limiting and treating the severe pulmonary consequences of COVID-19. *Nitric Oxide*. 2020;103:4–8. https://doi.org/10.1016/j.niox.2020.07.003
2. Ragab D, Salah Eldin H, Taeimah M, Khattab R, Salem R. The COVID-19 cytokine storm; what we know so far. *Front Immunol*. 2020;11:1446. https://doi.org/10.3389/fimmu.2020.01446
3. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*. 2020;323(13):1239–1242. https://doi.org/10.1001/jama.2020.2648
4. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382(18):1708–1720. https://doi.org/10.1056/NEJMoa2002032
5. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395(10223):507–513. https://doi.org/10.1016/s0140-6736(20)30211-7
6. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497–506. https://doi.org/10.1016/s0140-6736(20)30183-5
7. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. 2020;8(5):475–481. https://doi.org/10.1016/s2213-2600(20)30079-5
8. Kobayashi J, Murata I. Nitric oxide inhalation as an interventional rescue therapy for COVID-19-induced acute respiratory distress syndrome. *Ann Intensive Care*. 2020;10(1):61. https://doi.org/10.1186/s13613-020-00681-9
9. Li L, Li R, Wu Z, et al. Therapeutic strategies for critically ill patients with COVID-19. *Ann Intensive Care*. 2020;10(1):45. https://doi.org/10.1186/s13613-020-00661-z
10. Vanhoutte PM, Zhao Y, Xu A, Leung SW. Thirty years of saying NO: sources, fate, actions, and misfortunes of the endothelium-derived vasodilator mediator. *Circ Res*. 2016;119(2):375–396. https://doi.org/10.1161/circresaha.116.306531
11. Roberts JD, Jr., Fineman JR, Morin FC, 3rd, et al. Inhaled nitric oxide and persistent pulmonary hypertension of the newborn. The Inhaled Nitric Oxide Study Group. *N Engl J Med*. 1997;336(9):605–610. https://doi.org/10.1056/nejm199702273360902
12. Clark RH, Kueser TJ, Walker MW, et al. Low-dose nitric oxide therapy for persistent pulmonary hypertension of the newborn. Clinical Inhaled Nitric Oxide Research Group. *N Engl J Med*. 2000;342(7):469–474. https://doi.org/10.1056/nejm200002173420704
13. Creagh-Brown BC, Griffiths MJ, Evans TW. Bench-to-bedside review: inhaled nitric oxide therapy in adults. *Crit Care*. 2009;13(3):221. https://doi.org/10.1186/cc7734
14. Gebistorf F, Karam O, Wetterslev J, Afshari A. Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) in children and adults. *Cochrane Database Syst Rev*. 2016;2016(6):CD002787. https://doi.org/10.1002/14651858.CD002787.pub3
15. Abman SH, Griebel JL, Parker DK, Schmidt JM, Swanton D, Kinsella JP. Acute effects of inhaled nitric oxide in children with severe hypoxemic respiratory failure. *J Pediatr*. 1994;124(6):881–888. https://doi.org/10.1016/s0022-3476(05)83175-0
16. INO Therapeutics LLC. INOmax® Package Insert. https://www.inomax.com/wp-content/themes/inomax-website/dist/downloads/Inomax-PI.pdf. Accessed June 9, 2021.
17. Papazian L, Aubron C, Brochard L, et al. Formal guidelines: management of acute respiratory distress syndrome. *Ann Intensive Care*. 2019;9(1):69. https://doi.org/10.1186/s13613-019-0540-9
18. Akerström S, Gunalan V, Keng CT, Tan YJ, Mirazimi A. Dual effect of nitric oxide on SARS-CoV replication: viral RNA production and palmitoylation of the S protein are affected. *Virology*. 2009;395(1):1–9. https://doi.org/10.1016/j.virol.2009.09.007
19. Akerstrom S, Mousavi-Jazi M, Klingstrom J, Leijon M, Lundkvist A, Mirazimi A. Nitric oxide inhibits the replication cycle of severe acute respiratory syndrome coronavirus. *J Virol*. 2005;79(3):1966–1969. https://doi.org/10.1128/jvi.79.3.1966-1969.2005

20. Myers EN, Runer T, Cervin A, Lindberg S, Uddman R. Nitric oxide is a regulator of mucociliary activity in the upper respiratory tract. *Otolaryngol Head Neck Surg*. 1998;119(3):278–287. https://doi.org/10.1016/s0194-5998(98)70063-4

21. Antosova M, Mokra D, Pepucha L, et al. Physiology of nitric oxide in the respiratory system. *Physiol Res*. 2017;66(Suppl. 2):S159–S172. https://doi.org/10.33549/physiolres.933673

22. Chen L, Liu P, Gao H, et al. Inhalation of nitric oxide in the treatment of severe acute respiratory syndrome: a rescue trial in Beijing. *Clin Infect Dis*. 2004;39(10):1531–1535. https://doi.org/10.1086/425357

23. Tavazzi G, Pozzi M, Mongodi S, Dammassa V, Romito G, Mojoli F. Inhaled nitric oxide in patients admitted to intensive care unit with COVID-19 pneumonia. *Crit Care*. 2020;24(1):508. https://doi.org/10.1186/s13054-020-03222-9

24. Abou-Arab O, Huette P, Debouvries F, Dupont H, Jounieaux V, Mahjoub Y. Inhaled nitric oxide for critically ill Covid-19 patients: a prospective study. *Crit Care*. 2020;24(1):645. https://doi.org/10.1186/s13054-020-03371-x

25. Lotz C, Muellenbach RM, Meybohm P, et al. Effects of inhaled nitric oxide in COVID-19-induced ARDS—is it worthwhile? *Acta Anaesthesiol Scand*. 2020;65:629–632. https://doi.org/10.1111/aas.13757

26. DeGrado JR, Szumita PM, Schuler BR, et al. Evaluation of the efficacy and safety of inhaled epoprostenol and inhaled nitric oxide for refractory hypoxemia in patients with coronavirus disease 2019. *Crit Care Explor*. 2020;2(10):e0259. https://doi.org/10.1097/cce.0000000000000259

27. Prakash A, Kaur S, Kaur C, et al. Efficacy and safety of inhaled nitric oxide in the treatment of severe/critical COVID-19 patients: a systematic review. *Indian J Pharmacol*. 2021;53(3):236–243. https://doi.org/10.4103/ijp.ijp_382_21

28. Hedenstierna G, Chen L, Hedenstierna M, Scaramuzzo G. Treatment of COVID-19 by inhaled NO to reduce shunt? *Am J Respir Crit Care Med*. 2020;202(4):618. https://doi.org/10.1164/rccm.202004-0940LE

29. Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA*. 2012;307(23):2526–2533. https://doi.org/10.1001/jama.2012.5669

30. Severinghaus JW. Simple, accurate equations for human blood O2 dissociation computations. *J Appl Physiol Respir Environ Exerc Physiol*. 1979;46(3):599–602. https://doi.org/10.1152/jappl.1979.46.3.599

31. Bagate F, Tuffet S, Masi P, et al. Rescue therapy with inhaled nitric oxide and almitrine in COVID-19 patients with severe acute respiratory distress syndrome. *Ann Intensive Care*. 2020;10(1):151. https://doi.org/10.1186/s13613-020-00769-2

32. Ziehr DR, Alladina J, Wolf ME, et al. Respiratory physiology of prone positioning with and without inhaled nitric oxide across the coronavirus disease 2019 acute respiratory distress syndrome severity spectrum. *Crit Care Explor*. 2021;3(6):e0471. https://doi.org/10.1097/cce.0000000000000471

33. Ferrari M, Santini A, Protti A, et al. Inhaled nitric oxide in mechanically ventilated patients with COVID-19. *J Crit Care*. 2020;60:159–160. https://doi.org/10.1016/j.jcrc.2020.08.007

34. Parikh R, Wilson C, Weinberg J, Gavin D, Murphy J, Reardon CC. Inhaled nitric oxide treatment in spontaneously breathing COVID-19 patients. *Ther Adv Respir Dis*. 2020;14:1753466620933510. https://doi.org/10.1177/1753466620933510

35. Safaee Fakhr B, Di Fenza R, Gianni S, et al. Inhaled high dose nitric oxide is a safe and effective respiratory treatment in spontaneous breathing hospitalized patients with COVID-19 pneumonia. *Nitric Oxide*. 2021;116:7–13. https://doi.org/10.1016/j.niox.2021.08.003