Inhaled nitric oxide treatment in spontaneously breathing COVID-19 patients

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To the editor:

Inhaled nitric oxide (iNO) is a pulmonary vasodilator that has been utilized as a rescue therapy in patients with severe hypoxemia by improving ventilation-perfusion matching and decreasing pulmonary vascular pressure.[1,2] iNO was an effective therapy during the severe acute respiratory syndrome (SARS) outbreak in 2003 by improving oxygenation in patients with significant hypoxemia.[3] Given the similarities between the SARS outbreak and the Coronavirus disease-2019 (Covid-19) pandemic, iNO therapy may have a role in Covid-19 patients as well. Here, we describe our experience with utilizing iNO therapy in spontaneously breathing Covid-19 patients.

Methods

We identified non-intubated Covid-19 patients who received iNO therapy. The study was approved by the Institutional Review Board of Boston Medical Center and the requirement for informed consent was waived. The decision to administer iNO was at the discretion of the treating physician and based on institutional clinical guidelines. The starting dose of iNO was 30 parts per million (ppm) for all patients, and the mean duration of therapy was 2.1 days. Estimated SpO_2/FiO_2 (SF) ratio, a surrogate for PaO_2/FiO_2 ratio, was utilized to assess the patient's oxygenation status.[4] Types of respiratory support administered included nasal cannula, nasal pendant with oxymizer, and non-rebreather mask. Descriptive statistics were used to summarize clinical data; categorical variables were reported as counts and percentages. Statistical analysis was performed using SAS v9.4, with $p < 0.05$ considered statistically significant.

Results

There were 39 patients with laboratory-confirmed Covid-19 infection who were treated with iNO therapy while spontaneously breathing. Demographics, clinical characteristics, therapies, and outcomes are summarized in Table 1. Mean age of the patients was 61 years with an average body mass index (BMI) of 33. A total of 22 patients (56.4%) were male, 18 patients (46.2%) identified as Hispanic, and 24 patients (61.5%) had a pre-existing cardiac condition.

Of the 39 patients, 29 (74.4%) were initially admitted to the general medical floor, although 24 of these patients later required transfer to the intensive care unit (ICU). There were 20 hospital discharges, 9 deaths, and the remainder of patients remained hospitalized at the time of analysis. Management of the Covid-19 patients included immunomodulator therapy with an IL6-receptor antagonist (34 patients; 87.2%), hydroxychloroquine (24 patients; 61.5%), azithromycin (21 patients; 53.9%), and self prone (23 patients; 59%).

A total of 21 patients (53.9%) did not require invasive mechanical ventilation after treatment with iNO. Of the 21 patients, 20 were successfully discharged and there was 1 death. Median SF ratio prior to iNO initiation were similar between the 21 non-intubated patients (SF ratio: 108; Table 2) and the 18 patients that eventually required mechanical ventilation (SF ratio: 113). Median Ferritin (intubated: 1002 ng/ml, non-intubated: 625 ng/ml; $p = 0.38$) and D-dimer (intubated: 566 ng/ml, non-intubated: 596 ng/ml; $p = 0.38$) levels were also comparable between both groups, whereas C-reactive protein (CRP) levels assessed prior to iNO therapy were significantly higher in the intubated patients (intubated: 122.9 mg/l, non-intubated: 48.3 mg/l; $p = 0.0108$).

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Table 1. Characteristics of 39 patients with Covid-19 treated with inhaled nitric oxide.

	Total (*n* = 39)
Mean age (SD) - years	61
Male sex - no. (%)	22 (56.4%)
Mean BMI (SD)	33
Race or ethnic group - no. (%)	
Hispanic	18 (46.2%)
African American	14 (35.9%)
White	6 (15.4%)
Asian	1 (2.6%)
Risk factor - no. (%)	
Cardiac (HTN, CAD, CHF)	24 (61.5%)
Diabetes mellitus	13 (33.3%)
Smoking (active or prior)	12 (30.8%)
Pulmonary	4 (10.3%)
Chronic kidney disease	3 (7.7%)
Obstructive sleep apnea on CPAP	2 (5.1%)
Admission floor - no. (%)	
General medical floor	29 (74.4%)
Intensive care unit	10 (25.6%)
Treatment - no. (%)	
Immunomodulator therapy (Sarilumab)	34 (87.2%)
Hydroxychloroquine	24 (61.5%)
Self prone	23 (59%)
Azithromycin	21 (53.9%)
Colchicine	7 (17.9%)
Mechanical ventilation - no. (%)	
Non-intubated	21 (53.9%)
Intubated	18 (46.2%)
Death in the hospital - no. (%)	9 (23.1%)

BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; Covid-19, Covid-19 Coronavirus disease 2019; CPAP, continuous positive airway pressure; HTN, hypertension; IQR, interquartile range; SD, standard deviation.

Following iNO therapy, the SF ratio improved in the 21 non-intubated patients with a median of 54.9 ($p = 0.0078$). CRP and ferritin did not significantly change after iNO treatment though D-dimer levels increased in 25 patients (64.1%) with a median change of 115 ng/ml ($p = 0.0052$).

Discussion

From the 39 spontaneously breathing patients with Covid-19 who underwent therapy with iNO, more than half did not require mechanical ventilation after treatment. These findings suggest that iNO therapy may have a role in preventing progression of hypoxic respiratory failure in Covid-19 patients. During the SARS outbreak, researchers hypothesized that iNO may not simply improve oxygenation, but also potentially have an antiviral mechanism of action.[3,5] The similarities between Covid-19 and SARS are well-documented and our analysis emphasizes the need to further investigate iNO therapy in future Covid-19 studies. Randomized controlled trials are already underway, and findings from such large-scale investigations can ideally reflect upon the role of this therapy in potentially helping avoid mechanical ventilation and improve patient outcomes.[6]

Author contribution(s)

Raj Parikh: Conceptualization; Data curation; Investigation; Methodology; Validation; Writing-original draft; Writing-review & editing.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

Table 2. Comparison of intubated and non-intubated Covid-19 patients.

	Intubated ($n = 18$)	Non-intubated ($n = 21$)	*p* value
Median CRP (IQR) - mg/l	122.9 (68.5–209.9)	48.3 (22.0–108.6)	0.0108
Median ferritin (IQR) - ng/ml	1002 (539–2416)	625 (489–1118)	0.16
Median D-dimer (IQR) - ng/ml	566 (307–656)	596 (419–1004)	0.38
Median SF ratio prior to iNO (IQR)	113 (106–116)	108 (96–118)	0.56
Median change in SF ratio after iNO	–8.6 (–21.8–71)	54.9 (30–86.1)	0.0078

Covid-19, Covid-19 Coronavirus disease 2019; CRP, C-reactive protein; iNO, inhaled nitric oxide; IQR, interquartile range; SF, SpO_2/FiO_2.

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