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Efficacy and safety of inhaled nitric oxide in the treatment of severe/critical COVID-19 patients: A systematic review

Ajay Prakash, Sukhmeet Kaur, Charanjeet Kaur, Praisy K. Prabha, Anusuya Bhatacharya,[1] Phulen Sarma, and Bikash Medhi

Department of Pharmacology, Experimental Pharmacology Laboratory, Postgraduate Institute of Medical Education and Research, Chandigarh, India

[1]*Department of Ophthalmology, GMCH, Chandigarh, India*

Address for correspondence: Prof. Bikash Medhi, Research Block B, 4th Floor, Room No. 4043, Postgraduate Institute of Medical Education and Research, Chandigarh - 160 012, India. E-mail: drbikashus@yahoo.com

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Abstract

OBJECTIVE:

Present systematic review aimed to analyze the effect of inhaled nitric oxide (iNO) in the treatment of severe COVID-19 and to compare it to standard of care (SOC), antiviral medications, and other medicines.

MATERIALS AND METHODS:

Medline (PubMed), Scopus, Embase, Ovid, Web of Science, Science Direct, Wiley Online Library, BioRxiv and MedRxiv, and Cochrane (up to April 20, 2021) were the search databases. Two reviewers (SK and CK) independently selected the electronic published literature that studied the effect of nitric oxide with SOC or control. The clinical and physiological outcomes such as prevention of progressive systemic deoxygenation/clinical improvement, mortality, duration of mechanical ventilation, improvement in pulmonary arterial pressure, and adverse events were assessed.

RESULTS:

The 14 retrospective/protective studies randomly assigning 423 patients met the inclusion criteria. Cumulative study of the selected articles showed that iNO has a mild impact on ventilation time or ventilator-free days. iNO has increased the partial pressure of oxygen/fraction of inspired oxygen ratio of fraction of in-

spired oxygen in a few patients as compared to baseline. However, in most of the studies, it does not have better outcome when compared to the baseline improvement.

CONCLUSIONS:

In patients with COVID-19 with acute respiratory distress syndrome, nitric oxide is linked to a slight increase in oxygenation but has no effect on mortality.

Keywords: Coronavirus, COVID-19, inhaled nitric oxide, nitric oxide, oxygenation, ventilation

Introduction

COVID-19 has developed as a global challenge to the global health system and its stakeholders as its first and second waves continue to spread. As of May 11, 2021, there were 159,699,271 COVID-19 cases recorded worldwide, with 137,399,547 (86.04%) recovered and 3,319,919 (2.08%) deaths.[1] Acute respiratory distress syndrome (ARDS) is the main characteristic of COVID-19–positive patients which identified by pulmonary hypertension and increased intrapulmonary shunting of blood through hypoventilated regions.[2] As pandemic spreading rapidly, we need fast and accurate treatment for COVID 19, which is essential to limit the further spread of the virus or there must be some agent which fulfill the demand of oxygenation in the case of severe hypoxia, the major cause of death. Currently, there are no specific antiviral therapies for COVID-19 available for human use. COVID-19 is primarily managed by mechanical ventilation with antiviral therapy and steroids in the severe cases.[3,4]

Inhaled nitric oxide (iNO) is a gaseous free radical which is produced from arginine with the help of enzymes (neuronal, endothelial, and inducible nitric oxide synthase) that controls vasodilation. The iNO plays a specific role in maintaining the vascular system and has the unique capability to produce pulmonary vasodilation by involving in the pathological and physiological process, which includes relaxation of smooth muscle cells, immune response, and antimicrobial activities to increase the blood flow.[2,5,6] US FDA approved iNO for the probable treatment in the emergency of hypoxic respiratory failure to the neonates/pediatric population and fulfill immediate requirement of extracorporeal membrane oxygenation,[7] whereas iNO is already being used for a wide range of cardiopulmonary conditions. It is a well-known neurotransmitter, vasodilator, coagulation mediator, antimicrobial agent, or SARS-CoV replication inhibitor.[8,9]

The ARDS has different clinical presentations in COVID-19 and non-COVID-19 patients; higher rate of endothelial damage (vascular) and microthrombi (pulmonary) was seen in ARDS with nCoV-2019–infected patient as compared to the non-COVID-19 patients.[10,11] Longobardo *et al*., 2020 explored the hypothesis of an increase in partial pressure of oxygen/fraction of inspired oxygen (PaO_2/FiO_2) ratio after therapy with iNO in patients with ARDS not caused by COVID-19.[12] Literature showed that in well-ventilated lung tissue, iNO only dilates the pulmonary arteries with no effect on breath perfusion, but it can decrease intrapulmonary shunt and can increase arterial oxygenation throughout the body.[13,14,15,16,17] There are several studies registered at www. clinicaltrial.gov, which suggests the importance of the intervention in COVID-19 [Table 1].[18] Therefore, the present systematic review aimed to establish the efficacy and safety of iNO in the treatment of nCoV-2019–infected patients.

Materials and Methods

The systematic review aimed to establish the efficacy and safety as per following outcomes:

1. Improvement in PaO_2/FiO_2 ratio

2. Need of mechanical ventilation and frequency of intubation

3. Length of hospital stay

4. Change of level of IL-6, TNF-α, fibrinogen, C-reactive protein (CRP), ferritin, and dimer after iNO

5. Mortality.

Database search and data extraction

The data was screened at 11 medical literature databases (PubMed, Cinahl Plus, Scopus, Embase, Ovid, Web of Science, Science Direct, Wiley online library, BioRxiv and MedRxiv, and Cochrane) performed up to April 20, 2021, without any language restriction. Apart from these, the references of the included studies were also screened for possible inclusion criteria. The search was conducted using the keywords: "((COVID-19 OR NO" OR "SARS coronavirus-2" OR COVID or SARS)) AND ((”Nitric oxide OR "NO" or "iNO" or "inhaled nitric oxide OR inhalational NO") AND "nCoV").

Screening of articles

After searching the databases with appropriate keywords, duplicates were removed, and three reviewers (SK, PKP, and YS) screened the studies using title and abstract as predefined inclusion/exclusion criteria. Full text of relevant studies was further evaluated for possible inclusion in the systematic review using inclusion/exclusion criteria. Any discrepancies among investigators were resolved by consulting with BM and AP.

Eligibility criteria

Inclusion/exclusion criteria

The studies were included in the systematic review with any of the above-mentioned outcomes described in the article following iNO treatment in COVID-19–positive patients. There are no restrictions on geographical site selection; therefore, any location studies, whether open level/retrospective or prospective or cross-sectional, will be included in the study.

However, articles not related to the treatment of iNO or have iNO efficacy in other disease from COVID-19 or not an original article/report, review letter, or full text with no outcome as described were excluded from the study.

Results and Discussion

Study (data) selection

Data were extracted by three reviewers (HS, CK, and PKP) independently extracted from the included articles using a pretested data extraction form. After screening of 11 medical literature databases (PubMed, Cinahl Plus, Scopus, Embase, Ovid, Web of Science, Science Direct, Wiley online library, BioRxiv and MedRxiv, and Cochrane) till 20 April 2021 without any language restriction, 369 studies were selected, of which 172 from PubMed and 221 from other sources. The studies were screened based on inclusion and exclusion criteria. Finally, 14 retrospective/prospective studies were selected with the 423 patients with COVID-19–positive patients treated with iNO [Figure 1].[20]

Improvement in partial pressure of oxygen/fraction of inspired oxygen ratio

In the 24 h after starting iNO, Longobardo *et al*., 2020[12] observed that the COVID-19 group had more males with ARDS and that there were no changes between groups in mode of mean airway pressure, ventilation, volume (tidal), positive end-expiratory pressures (PEEP), fluid balance, or use of other drugs. However, iNO treatment improved PaO_2/FiO_2 ratio significantly less than in COVID-19–associated ARDS patients compared to ARDS patients who were not associated to COVID-19 (3% vs. 47%) [Table 2], while Bagate *et al*., 2020 indicated that a combination of iNO and almitrine improved blood oxygenation by more than 50% in severe COVID-19 patients as compared to the iNO-alone group. They observed that the improvement in the ratio of PaO_2/FiO_2 was significantly better, i.e., 102–180 mmHg when treated with combination of iNO and almitrine [Table 2].[21]

The findings of another study by Michael *et al*., 2020[22] which found no significant difference between individuals who tested at 10 and 20 ppm of iNO and found a median rise in PaO_2/FiO_2 ratio of 2.2% (95% confidence interval [CI]: 1.3–12) (from 88 [range: 73–110] to 94 [range: 74–116]) were similar. In another study, 10 COVID-19–positive patients had their mean iNO and PaO_2 increased from 62 ± 9 to 64 ± 14 mmHg (P = 0.427) and their mean PaO_2/FiO_2 raised from 81 ± 19 to 84 ± 22 mmHg (P = 0.325), both of which were not significantly different from baseline, while their mean mechanical ventilation duration was 34 ± 21 days.[5] The study by Moni *et al*., 2021[23] demonstrated that iNO treatment raised cycle threshold (Ct) value to normalize to 8.5 or more within 5 days in all patients, whereas viral load was cleared in 72% of patients in the control group (P = 0.04). The same pattern was found by Abou-Arab *et al*., 2020[24] who studied between two groups, i.e. iNO responders versus nonresponders. PaO_2/FiO_2 was considerably lower in the responders' group compared to the nonresponders' group (70 [63–100] vs. 134 [83–173]; P = 0.0001) but was consistent following iNO delivery (P = 0.068). At baseline and after iNO delivery, $PaCO_2$ levels were comparable between groups. They found a response rate of 65% after the treatment of iNO without practicing prone positioning. Feng *et al*., 2020[13] reported that iNO was significantly beneficial to reduce and stabilize the pulmonary artery systolic pressure and decrease the risk of right heart failure in the critically ill COVID-19 patients. They observed that the significant improvement of oxygenation in the COVID-19 patients based on the ratio of PaO_2/FiO_2 and as comparison to baseline. Lotz *et al*., 2021[25] showed beneficial effect of iNO in COVID 19–induced moderate to severe ARDS, by decreasing pulmonary vascular resistance with severe ARDS.

Need of mechanical ventilation

COVID-19 infection induces severe hypoxemia by decreasing ventilation-perfusion matching and increasing pulmonary vascular pressure. Therefore, during the management of COVID-19, maintaining ventilation and oxygenation is a main objective, and if it not maintained, we need mechanical ventilation invasive/noninvasive to fulfill the lung/body requirements. Study by Parikh *et al*., 2020[19] showed that requirements of mechanical ventilation (invasive) were significantly reduced when patients were treated by iNO, i.e., about 53.9% of patients did not require mechanical ventilation, whereas Bagate *et al*., 2020[21] showed that there is no improvement in the oxygenation in iNO treatment alone but got improved when iNO

was given with the almitrine (iNO + almitrine). The similar trends have been finding in the study by Robba *et al*. 2021 which showed the significant improvement in rescue therapies and observed that iNO increased the level of PaO2 from 65 to 72 mmHg, i.e., the oxygenation level.[26,27]

Effect of inhaled nitric oxide in reducing cytokines, fibrinogen, C-reactive protein, ferritin, and dimer level!

There was very less studies found that studied the cytokines, fibrinogen, CRP, ferritin, and dimer level following iNO therapy as a primary or secondary objective. Parikh *et al*., 2020[19] reported that in 21 nonintubated patients, there is no improvement in CRP and ferritin level after iNO treatment, but the level of D-dimer was increased in 64.1% with a median change of 115 ng/ml ($P = 0.0052$), whereas Longobardo *et al*., 2020[12] observed that iNO respondents and nonrespondents have no major differences as compared to the baseline values of D-dimer levels, fluid balance, prone position ventilation and CRP.

Mortality

In most of the screened article, authors have not mentioned about the mortality benefit in the iNO treatment groups. Ferrari *et al*., 2020[5] showed that there was 20% mortality, i.e., out of 10 patients, 8 patients (80%) were discharged, but the reason of 2 deaths were not mentioned in the article. In another article, Parikh *et al*., 2020[19] showed only 1 death out of 21 patients, i.e., 4.76% mortality, was seen and the rest successfully discharged.

Limitation of the study

The current systematic review is carried out to interpret the effect of iNO in the COVID-19 patients. Whether administration of iNO improved the outcome/oxygenation status (PaO_2/FiO_2 ratio) to the patients or not or have the better safety profile. Currently, we find that extremely limited number of retrospective/prospective studies were published and lacks randomized clinical trials (RCTs) to ensure the quality of data. As per the current search and analysis, we find that there are specific endpoints/outcomes defined such as improvement in PaO_2/FiO_2 ratio, prevention of progression assessed by an alternate severity scale, length of hospital Stay (death assigned as worst case), need of ventilation and frequency of intubation, effectiveness in reducing cytokines level (IL6/IL10), TNF-alpha, fibrinogen, CRP, ferritin, and dimer levels and finally the morbidity and mortality. There is no concurrent finding in all the selected articles and data found in these articles are sparse and incomplete. However, during the search of articles, we find that the there are many RCTs are registered with "clinicaltrial.gov,"E which in future their result may give us some confirmatory outcome regarding the use of iNO in the COVID-19 patients [Table 1].

Conclusion

In the present systematic review, there is no persistent finding among the studies published. However, few studies have reported its moderate activity in elevating the level of PaO_2/FiO_2 ratio from its baseline, but there is no effect have been seen in the comparative study with almitrine or alone.

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Conflicts of interest

There are no conflicts of interest.

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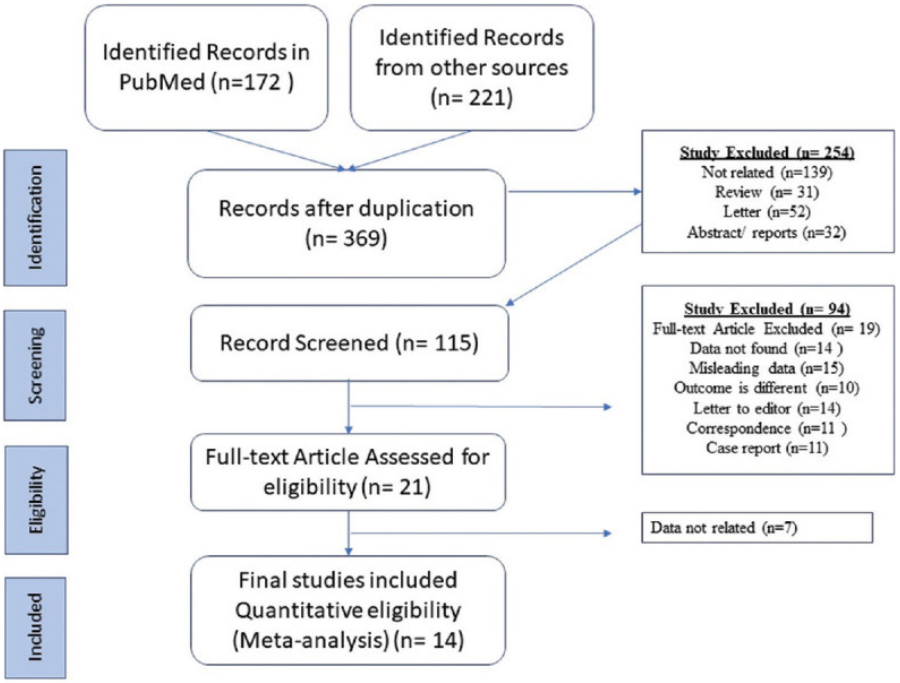
Table 1

Summary of the clinical studies registered in "*clinicaltrial.gov*" for inhaled nitric oxide in the treatment of COVID-19

NCT number	Phases/study design	Country	Enrolment	Interventions	Outcome measures
NCT04388683	Phase 2 RCT	Boston, Massachusetts, United States	42	Nitric oxide	A 7-point Severity Scale was used to assess the prevention of progressive systemic de-oxygenation, with escalation to greater amounts of oxygen and ventilatory support or death Frequency of intubation, ECMO, or need to intubate with "do not resuscitate" order/mortality/IL-6 level/TNF-alpha level/fibrinogen level/CRP level/ferritin level/D-dimer level/IL-6 level/TNF-alpha level/fibrinogen level/CRP level/ferritin level/D-dimer level
NCT04601077	Phase 1/phase 2RCT	Illinois, United States	100	Nitric oxide lozenges, 30 mg versus placebo	Low blood pressure/dizziness Hospitalization, ICU admission, intubation, dialysis, and death are all possible outcomes
NCT04383002	Phase 1/RCT	Toronto, Canada	20	Nitric oxide	COVID-19 PCR status at completion of treatment (day 7) from tracheal aspirate
NCT04338828	Phase 2/RCT	Boston, Massachusetts, United States	47	iNO versus inhaled supplemental oxygen	Rates of return visits to the EDInpatient hospitalizations required Rates of intubation/rates of mortality
NCT04305457	Phase 2/RCT	Louisiana, United States	70	Nitric oxide	Reduction in the incidence of patients with mild/moderate COVID-19 requiring intubation and mechanical ventilation/mortality/time to clinical recovery
NCT04476992	Phase 1 and phase 2/RCT	Russian Federation	20	Nitric oxide-continuous and sessions	At 48 h and 96 outcome in improvement in oxygenation between the groups or at discharge Day 5 and 28: Rate of positive RT-PCR for SARS-CoV-2 between groups in discharge, rate of AKI between

SpO2=Oxygen saturation, NEWS=National early warning score, NORS=Nitric oxide releasing solution, AKI=Acute kidney disease, iNO=Inhaled nitric oxide, NTM=Nontuberculosis mycobacteria, CRISS=Chronic respiratory infection symptom score, RCT=Randomized clinical trials, SARS-CoV-2=Severe acute respiratory syndrome coronavirus 2, rt-PCR=Reverse transcription polymerase chain reaction, SARS-nCoV-2=Severe acute respiratory syndrome novel corona virus 2, NIV=Noninvasive ventilation, HFNC=High-flow nasal cannula, ED=Emergency department, ICU=Intensive care unit, ECMO=Extracorporeal membrane oxygenation, CRP=C-reactive protein, IL-6=Interleukin-6, TNF-α=Tumor necrosis factor-α, NCT=National clinical trial

Figure 1



PRISMA flowchart as per CONSORT statement

Table 2

Summary of the clinical studies included in the systematic review

Author name and year	Place	Type of study	Sample size	Drugs	Route of administration	Day of mechanical ventilator removal/PaO_2:FiO_2 change	Duration of improvement of symptoms	Mo
Longobardo *et al*., 2021[12]	London, UK	Correspondence	*n*=47	Nitric oxide	Nasal	8 (40%) patients with COVID-19 related ARDS had an increment in PaO_2/FiO_2 ratio >10% compared with 10 patients (77%) with ARDS not related to ARDS	No improvements	
Robba *et al*., 2021[26]	Italy	Research	*n*=22	Nitric oxide	Inhalation		Its effect on oxygenation is inconsistent	
Lotz *et al*., 2021[25]		Original article	*n*=7	Nitric oxide	Inhalation	30%-40% can be expected according to the observed median PaO_2/FiO_2 ratio		
Safaee Fakhr *et al*., 2020[27]	Alabama, USA	Case report	*n*=6	Nitric oxide	Nasal	SpO2:FiO2 improved after 1 h	Immediately after NO treatment	
Bagate *et al*., 2020[21]	Créteil, France	Research article	*n*=10	Nitric oxide and almitrine	Nasal	PiO2/FiO2 increased from 102 to 124 mmHg after iNO treatment 102-180 mmHg after treatment with combination of iNO and almitrine	-	
Shekar *et*	Australia	Case report	*n*=19	HFO2 +		Five out of 19 (26%)		

ARDS=Acute respiratory distress syndrome, PaO_2/FiO_2=Partial pressure of oxygen/fraction of inspired oxygen, NO=Nitric oxide, iNO=Inhaled NO, HFO2=Hafnium oxide, IMV=Invasive mechanical ventilation, APACHE-2=Acute physiology and chronic health evaluation, PASP=Pulmonary artery systolic pressure