Should inhaled Nitric Oxide be used as an adjunct treatment for COVID-19?

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KEY FINDINGS

There is no current evidence to support the use of inhaled nitric oxide for patients with COVID-19.

- Inhaled nitric oxide is a pulmonary vasodilator used in conditions with pulmonary hypertension or hypoxemia but may also have antimicrobial properties against some bacteria, viruses and fungi [1,2].
- In vitro, the organic nitric oxide donor, *S*-nitroso-*N*-acetylpenicillamine, significantly inhibited the replication cycle of SARS-CoV in a concentration-dependent manner [1,8]. Nitric oxide also inhibited viral protein and RNA synthesis [1,2].
- There is no current evidence to support the use of inhaled nitric oxide for patients with COVID-19 but there are four ongoing clinical trials.
- Indirect evidence from the systematic review and meta-analysis showed no clear evidence for improved survival among patients with ARDS [4]. There was no clear benefit among patients with MERS-CoV infection [5,6]. Although there were favorable results for SARS infection [13], the study is of very low quality.
- Inhaled nitric oxide significantly increased risk for renal impairment [4]. Other additional adverse events identified include methemoglobinemia, inhibition of platelet aggregation, formation of nitrogen dioxide [9-12].
- Surviving Sepsis Campaign (2020) recommends against the routine use of inhaled nitric oxide in mechanically ventilated adults with COVID-19 ARDS (*Strong recommendation, weak quality of evidence*) [14].

RESULTS

There are currently no studies on the use of inhaled nitric oxide (iNO) as treatment of patients with COVID 19 infections. There are indirect evidences on the use of iNO for acute respiratory distress syndrome (ARDS), severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome coronavirus Infection (MERS-CoV).

A Cochrane systematic review was conducted in 2016 which included 14 trials of moderate quality with 1275 participants on inhaled nitric oxide for ARDS. Results showed no statistically significant effect on mortality for adults (RR 1.04, 95% CI 0.9 to 1.19; I^2 statistic = 0%) and children (RR 0.78, 95% CI 0.51 to 1.18; I^2 statistic = 22%). However, it showed transient improvement in oxygenation index at 24 hours with a MD of -2.31 (95% CI -2.73 to -1.89; I^2 statistic = 0%) and improvement on PaO2/FiO2 at 24 hours with a mean difference (MD) of 15.91 (95% CI 8.25 to 23.56, I^2 statistic = 25%). There was no significant difference for ventilator-free days. There was a statistically significant increase in the incidence of renal failure for patients on inhaled nitric oxide (RR 1.59, 95% CI 1.17 to 2.16; I^2 statistic = 0%) [4].

A non-randomized trial was done on 14 patients treated in the ICUs of two Beijing hospitals on iNO as treatment for SARS in 2004. Compared to no treatment, iNO significantly improved arterial oxygen saturation (SpO2) from 93% to a mean level of 99% ($p < 0.05$); reduced the need for supplemental oxygen ($p < 0.05$) and reduced the need and led to discontinuation of CPAP and BiPAP ventilation ($p < 0.05$). Chest Xray improved in 5 of the 6 patients who received iNO [13]. However due to serious validity issues from the small sample size of 14 (iNO = 6, control = 8), non-randomization, lack of allocation concealment and non-blinding, the study was of very low quality.

In a multicenter retrospective cohort of critically ill MERS patients in Saudi Arabia with 330 participants showed that management with noninvasive ventilation (NIV) were more likely to require nitric oxide compared to patients on invasive mechanical ventilation (20.0% vs 11.7%, $P = 0.05$) [6]. In a case series involving 12 patients with confirmed or probable MERS-CoV infection, 6 patients received NO due to refractory hypoxemia. Five patients were alive at day 90 of illness [5]. The studies on MERS-CoV were limited to a case series and a retrospective cohort with low quality of evidence. For both studies, the patients also received other oxygen rescue therapies (i.e. neuromuscular blockade, high-frequency oscillation ventilation, extracorporeal membrane oxygenation, and prone positioning), hence the clinical therapeutic effect of iNO alone for MERS-CoV infection is unknown.

There are four clinical trials on the role of inhaled nitric oxide, three of which are conducted in the United States of America for mild/moderate COVID-19, severe COVID-19 and as prophylaxis for COVID-19 health workers respectively. The results are expected between March to April 2020. A fourth ongoing study in Canada on the role of inhaled gaseous nitric oxide (gNO) as antimicrobial treatment for difficult bacterial infections created a sub-study for COVID-19. Result of the study is expected by December 2020. The details of the clinical trials are presented in Table 1.

CONCLUSION

There is no current evidence to support the use of inhaled nitric oxide for patients with COVID-19. The results of the ongoing trials as well as high quality randomized controlled trials are needed to support its use. Only a methodologically flawed indirect evidence for nitric oxide on SARS patients showed improved arterial oxygenation, reduced need for supplemental oxygen and improved chest x-ray results. For patients with ARDS and MERs-CoV, it did not show clear benefit and even showed increased risk for renal impairment.

Declaration of Conflict of Interest

No conflict of interest

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Table 1. Characteristics of clinical trials

No.	Clinical Trial ID / Title	Status	Start and estimated primary completion date	Study design	Country	Population	Intervention Group(s)	Comparison Group(s)	Outcomes
1	NCT04305457 Nitric Oxide Gas Inhalation Therapy for Mild/Moderate COVID-19	Recruiting	3/21/20 – 4/1/21	Open label, Randomized controlled trial	United States of America Massachusetts General Hospital	Laboratory confirmed COVID 19 patients, 18 years old and above, admitted in hospital with spontaneous breathing with or without hypoxia (n = 240) Exclusion: Tracheostomy, high flow nasal cannula, hospitalized and confirmed diagnosis >72 hours	Nitric Oxide inhalation	No intervention	Primary: Reduction in the incidence of mild/moderate COVID-19 requiring intubation and mechanical ventilation in 28 days Secondary: - Mortality - Time to clinical recovery Other: Negative conversion of COVID-19 RT-PCR from upper respiratory tract in 7 days
2	NCT04306393 Nitric Oxide Gas Inhalation in Severe Acute Respiratory Syndrome in COVID-19 (NOSARSCOVID)	Recruiting	3/21/20 – 3/21/21	Multicenter, single blind, Randomized controlled trial	United States of America - University of Alabama - Louisiana State University Health Shreveport - Massachusetts General Hospital	Laboratory confirmed COVID 19 patients, 18 to 99 years old and above, admitted to the ICU who are intubated and mechanically ventilated (n = 200) Exclusion: Patients intubated >72 hours from initiation of treatment gas	Inhaled Nitric Oxide until PaO2/FiO2 ≥ 300 mmHg Nitric oxide gas - 80 ppm of inhaled nitric oxide for 48 hours, followed by 40 ppm, followed by weaning before stop. Weaning criteria: maintenance of a PaO2/FiO2 ratio ≥ 300 for at least 24 hours consecutively.	No intervention	Primary: Change of arterial oxygenation at 48 hours Secondary: - Time to reach normoxemia during the first 28 days - Proportion of SARS-nCoV-2 free patients during the first 28 days - Survival at 28 days - Survival at 90 days
3	NCT04312243	Not yet recruiting	4/2/20 – 3/20/21	Open label, Randomized controlled trial	United States of America	Health care workers aged 18-99 years old, scheduled to work with SARS-CoV-2	Inhaled nitric oxide gas	No intervention	Primary: COVID 19 diagnosis in 14 days

	NO Prevention of COVID-19 for Healthcare Providers (NOpreventCOVID)				Massachusetts General Hospital	infected patients for at least 3 days in a week (n = 470) ExclusionL previous SARS-COV 2 infection, pregnancy, hemoglobinopathies, anemia	Inhaled NO (160 ppm) before and after the work shift.		Secondary: Positive SARS-CoV-2 rt-PCR test
4	NCT03331445 Inhaled Gaseous Nitric Oxide (gNO) Antimicrobial Treatment of Difficult Bacterial and Viral Lung (COVID-19) Infections (NONTM)	Active, not recruiting	10/24/17 – 12/31/20	Open label safety study (COVID-19 Sub-study)	Canada Diamond Centre, Vancouver	Adults & Adolescents (≥ 14 years old) With Non-Tuberculous Mycobacteria, Burkholderia Spp, Aspergillus Spp and Corona-like Viral (Sub-Study) Infections with Oxygen saturation on room air >92% at screening (n = 20)	Nitric Oxide 0.5 % / Nitrogen 99.5 % Gas for Inhalation - Inhaled Nitric Oxide 160ppm balance air Other Name: Thiolanox	No comparator group	COVID 19 Substudy Primary: Reduction in the incidence of mechanical assistance of BIPAP, CPAP, intubation and mechanical ventilation Secondary: - Proportion of patients with mild COVID 19 who deteriorate to severe form requiring BIPAP/CPAP, intubation and mechanical ventilation - Mortality - Negative conversion of COVID-19 RT-PCR from upper respiratory tract - Time to clinical recovery - Alleviation of symptoms (Modified Jackson Cols score)