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Safety and practicality of high dose inhaled nitric oxide in emergency department COVID-19 patients

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ABSTRACT

Background: Inhaled nitric oxide (iNO) is a selective pulmonary vasodilator and mild bronchodilator that has been shown to improve systemic oxygenation, but has rarely been administered in the Emergency Department (ED). In addition to its favorable pulmonary vascular effects, in-vitro studies report that NO donors can inhibit replication of viruses, including SARS Coronavirus 2 (SARS-CoV-2). This study evaluated the administration of high-dose iNO by mask in spontaneously breathing emergency department (ED) patients with respiratory symptoms attributed to Coronavirus disease 2019 (COVID-19).

Methods: We designed a randomized clinical trial to determine whether 30 min of high dose iNO (250 ppm) could be safely and practically administered by emergency physicians in the ED to spontaneously-breathing patients with respiratory symptoms attributed to COVID-19. Our secondary goal was to learn if iNO could prevent the progression of mild COVID-19 to a more severe state.

Findings: We enrolled 47 ED patients with acute respiratory symptoms most likely due to COVID-19: 25 of 47 (53%) were randomized to the iNO treatment group; 22 of 47 (46%) to the control group (supportive care only). All patients tolerated the administration of high-dose iNO in the ED without significant complications or symptoms. Five patients receiving iNO (16%) experienced asymptomatic methemoglobinemia (MetHb) > 5%. Thirty-four of 47 (72%) subjects tested positive for SARS-CoV-2: 19 of 34 were randomized to the iNO treatment group and 15 of 34 subjects to the control group. Seven of 19 (38%) iNO patients returned to the ED, while 4 of 15 (27%) control patients did. One patient in each study arm was hospitalized: 5% in iNO treatment and 7% in controls. One patient was intubated in the iNO group. No patients in either group died. The differences between these groups were not significant.

Conclusion: A single dose of iNO at 250 ppm was practical and not associated with any significant adverse effects when administered in the ED by emergency physicians. Local disease control led to early study closure and prevented complete testing of COVID-19 safety and treatment outcomes measures.

1. Introduction

Nitric oxide (NO) is a selective pulmonary vasodilator which interacts with the pulmonary vasculature to induce smooth muscle relaxation [1,2]. When given by inhalation (iNO), it dilates pulmonary vasculature, reduces ventilation/perfusion (V/Q) mismatch, and decreases both pulmonary arterial pressure and pulmonary vascular resistance [1-3]. Additionally, iNO causes bronchodilation and decreases platelet aggregation, preventing intra-pulmonary thrombosis [3,4]. For these reasons, iNO can improve oxygenation in mechanically ventilated patients [4-6]. Data also suggests that iNO has antiviral activity [7,8]. A 2003 study of patients with SARS-CoV-1 infection reported that iNO improved oxygenation with benefits extending beyond the treatment period [9]. Additionally, in-vitro studies have demonstrated that the NO-donor compound S-nitroso-*N*-acetylpenicillamine (SNAP) increased survival of in-vitro cells infected with SARS-CoV-1 and SARS-CoV-2 [8,10,11].

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Prior studies have tested iNO concentrations ranging from 80 to 200 ppm (ppm). A dose of 160 ppm has been found to be bactericidal and safe when administered under close observation [12,13]. No studies investigating iNO use solely within the emergency department (ED) have been previously reported [14-16].

In the early stages of the COVID-19 pandemic, when few therapeutic options were available, we used a face-mask device [17-19] to administer high-dose iNO (at 250 ppm) for 30 min as a one-time treatment for adult ED patients with COVID-19. This high concentration was chosen to maximize the known virucidal and vasoactive effects of iNO. Our goal was to establish the safety and practicality of administering this novel treatment within the ED to patients with acute respiratory symptoms of COVID-19, and to determine its effectiveness in decreasing disease progression.

2. Methods

We conducted a randomized clinical trial in patients presenting to the Massachusetts General Hospital (MGH) ED with respiratory symptoms most likely due to COVID-19. Subjects were spontaneously breathing adult patients who had been cleared for discharge to home by the attending emergency physician. All subjects were assayed by nasal swab for COVID-19 prior to enrollment using polymerase chain reaction (PCR) testing. To accurately address treatment outcomes specific to COVID-19 progression, we designed an a priori subgroup analysis of subjects who eventually tested positive for COVID-19. This study was reviewed and approved by Partners Human Research Committees and registered at ClinicalTrials.gov. Patients provided informed consent prior to study procedures being performed.

2.1. Primary and secondary outcomes

This randomized clinical trial aimed to test practicality, safety, and efficacy of a single, novel high-dose administration of iNO by mask (250 ppm continuously for 30 min) in an ED patient population with respiratory symptoms most likely due to COVID-19.

The first aim of this study was to establish the safety of high-dose iNO in an ED patient population with COVID-19 related respiratory symptoms. Adverse events were defined as a primary endpoint of incidence of methemoglobin level (MetHb) > 5%, hypoxemia (SpO2 < 90%), and systemic hypotension (decrease in mean arterial pressure (MAP) > 50 mmHg).

The second aim was to establish that high-dose iNO could be practically and safely administered by emergency physicians in the ED, and could be well tolerated by ED patients with respiratory symptoms.

The final aim of this study was to determine whether early treatment with high-dose iNO could prevent the progression to a more severe disease state as measured by 1) return rates to the ED with COVID-19-related disease, 2) hospitalization, 3) intubation, and 4) 28-day mortality.

2.2. Inclusion and exclusion criteria

ED patients were eligible for enrollment if they were age 18 years old or older, had at least one respiratory sign or symptom of COVID-19 (cough, respiratory rate > 24 breaths/min, atypical chest pain, dyspnea, resting peripheral oxygen saturation (SpO2) < 97%, or chest radiograph consistent with COVID-19-related airspace disease.) Patients had fewer than 12 days of symptoms, positive or pending SARS-CoV-2 PCR tests, and clearance for discharge from the ED. Potential subjects were excluded if they were judged to have a > 50% likelihood of alternative (non-COVID-19) etiology of their symptoms, had a tracheostomy, required oxygen therapy to maintain SpO2 > 94%, were pregnant, age > 90 years, had participated in other COVID-19 studies, or had a clinical contraindication to the use of iNO.

2.3. Study drug administration

Following informed consent and enrollment, subjects were randomized to either the treatment group (iNO plus standard of care) [20,21] or the control group (consisting of standard of care treatment) at a 1:1 ratio.

All subjects wore a snug-fitting mask attached to a non-rebreathing circuit capable of delivering continuous 250 ppm iNO through a reservoir bag and scavenging chamber to minimize nitrogen dioxide (NO_2) exposure [18]. NO balanced in nitrogen (Airgas; Radnor, Pennsylvania) was blended with medical air and oxygen to obtain the desired mixture based on prior in-vitro measurements. All subjects received 15 l-per-minute (LPM) medical grade air and 2 LPM oxygen for a total of 30 min. Subjects in the iNO treatment group had 5 LPM of iNO (Table 2) added to this circuit to achieve a concentration of 250 ppm (See Table 1).

Vital signs (heart rate, respiratory rate, blood pressure, and SpO_2) and MetHb levels were continuously monitored throughout the duration of treatment. Abnormal oxygen saturation (SpO_2 < 90%), hypotension (a decrease in mean arterial pressure (MAP) > 50 mmHg), were indications for immediate discontinuation of iNO treatment. If MetHb ≥5%, the session was continued but iNO flow was decreased.

All subjects were observed for at least 5 min following administration of iNO or placebo, and discharged if their MetHb <3% and downtrending, had SpO_2 > 94%, and had no new respiratory complaint.

2.4. Data collection and statistical analysis

In our study calculations, we calculated a need for a sample of a total of 236 patients. Patient background information was obtained from interviews and electronic health record review. Historic and prospective data were collected and entered into a HIPPA-compliant, secure hospital computer interface (REDCap). All enrolled patients received continuous MetHb, SpO_2, and physician monitoring throughout the 30-min treatment period.

Active enrollment began in April 2020. All subjects were tracked and medical record review was performed to identify follow-up medical encounters. All subjects were contacted 28 days after enrollment to identify progression of symptoms or any complications. Patients with a negative SARS-CoV-2 PCR result were retroactively excluded.

Table 1
Baseline demographics and clinical characteristics. BMI = Body Mass Index; SpO_2 = peripheral saturation of oxygen

	Treatment, $n = 25$	Placebo, $n = 22$
Age, years old	42 [20–63]	40 [22–68]
Gender, Number No. (%) Female	13 (52)	11 (50)
BMI (kg/m^2)	30.7 [22.3–44.6]	29.0 [20.3–38]
Race, No. (%)		
White	12 (48)	9 (40.9)
Black or African American	2 (8)	1 (4.5)
Asian	1 (4)	2 (9.1)
Multiracial	0 (0)	1 (4.5)
Other/Not Specified	10 (40)	9 (40.9)
Ethnicity, No. (%)		
Hispanic or Latino	8 (32)	7 (31.8)
Not Hispanic or Latino	17 (68)	15 (68.2)
Comorbidities, No. (%)		
Hypertension	4 (16)	2 (9.1)
Coronary artery disease	1 (4)	0 (0)
Diabetes	2 (8)	1 (4.5)
Chronic pulmonary disease	5 (20)	2 (9.1)
Immune deficiency	0 (0)	2 (9.1)
Respiratory rate, breaths/min	19 [14–24]	19 [16–26]
Resting SpO_2, %	97 [95–99]	97 [93–100]
Altered chest radiograph, No. (%)	9 (36)	8 (36.4)

Table 2
Nitric oxide gas, oxygen, and air concentration to obtain 250 ppm and desired FiO_2. FiO_2 = Fraction of inspired oxygen

NO = 250 ± 8 ppm			
Target FiO_2 (%)	NO flow (L/min) (*Airgas*)	Air flow (L/min)	O_2 flow (L/min)
21	5	15	2

2.5. Early study termination

After brisk early enrollment in this study, patients meeting enrollment criteria sharply declined in June 2020 due to changing local COVID-19 epidemiology.

3. Results

3.1. Subject identification and exclusion

Forty-seven patients presenting to the MGH ED met inclusion criteria and were enrolled in this study (25 subjects were randomized to the iNO group and 22 to the control group). At enrollment time, 25 subjects (53%) had pending SARS-CoV-2 PCR tests.

Of 47 originally enrolled subjects, 13 (28%) ultimately had negative SARS-CoV-2 tests, and were followed for safety and complications but excluded from treatment analysis. 34 subjects (72%) tested positive by SARS-CoV-2 PCR and were included in the study analysis for COVID-19 treatment efficacy. Nineteen of the 34 had been assigned to the iNO group, while 15 had been assigned to the control group.

Two subjects (3%) were lost to follow-up at 28 days.

3.2. Vital signs, imaging, and symptoms

Prior to enrollment, vital signs were taken, along with an inventory of COVID-19 signs and symptoms. Patients were enrolled if they met entry criteria.

Of the 34 patients with positive SARS-CoV-2 PCR, 2 patients (6%) were noted to have Tmax >37.8C. Fifteen patients (44%) demonstrated chest x-ray findings suspicious for COVID-19. Eight patients (24%) were noted to be tachypneic (RR ≥ 24). Prior to enrollment, 32 patients (92%) complained of an acute cough, 28 patients (82%) complained of new dyspnea, and 15 patients (44%) had $SpO_2 < 97\%$ at rest.

3.3. The safety of inhaled NO treatment at 250 ppm

MetHb levels were continuously monitored using a MetHb-oximeter (Masimo Corporation; Irvine, CA). The maximum MetHb level detected was 5.0%. In 3 of the 25 subjects (12%), as MetHb levels approached 5%, iNO flow was gradually decreased without change in the basal flow of 15 LPM air and 2 LPM O_2. Patients remained asymptomatic and did not incur any vital sign alterations or discomfort. MetHb levels in all subjects rapidly decreased following iNO discontinuation and returned to normal within three minutes.

Table 3
Outcomes for patients treated with nitric oxide versus control group. Due to delay times in Emergency Department SARS-CoV-2 PCR processing, infection status was often pending at the time of study administration. Results for subjects with confirmed COVID-19 (positive SARS-CoV-2 PCR) were evaluated independently from all patients, regardless of PCR result

	Confirmed COVID-19		All Participants	
Events at 28 days	Treatment (iNO) group	Control group	Treatment (iNO) group	Control group
Returned to ED	7/19 (37%)	4/15 (27%)	8/25 (32%)	5/22 (33%)
Hospitalized	1/19 (5%)	1/15 (7%)	1/25 (4%)	1/22 (5%)
Intubated	1/19 (5%)	0/15 (0%)	1/25 (4%)	0/22 (0%)
Expired	0/19 (0%)	0/15 (0%)	0/25 (0%)	0/22 (0%)

No subjects experienced significant adverse events or required ED reassessment. All were safely discharged to home after completion of the treatment session.

3.4. Treatment outcomes

Nineteen subjects with confirmed COVID-19 received iNO, of which 7 subjects (37%) returned to the ED within 28 days complaining of worsening respiratory symptoms. One of these subjects (5%) had extensive pre-existing comorbidities, was subsequently hospitalized, and later required intubation for ventilatory support.

Fifteen subjects with confirmed COVID-19 received control therapy of which 4 subjects (27%) returned to the ED within 28 days due to respiratory symptoms. One subject (7%) was subsequently hospitalized, but was not intubated. No subjects in either arm experienced mortal outcomes at 28 days (Table 3).

Given the premature closure to enrollment, we were not able to test our efficacy hypothesis.

4. Discussion

In this study, we demonstrated safe and practical novel high-dose iNO administration within the ED (250 ppm for 30 min) in spontaneously breathing patients with respiratory symptoms of SARS-CoV-2 infection. While previous studies have described enrolling ED patients (with pulmonary embolism for eventual inpatient low-dose iNO administration (5–50 ppm)), this is the first clinical trial reporting iNO administration within the ED [14-16]. Additionally, this is the first report of high-dose iNO (250 ppm) in a clinical trial. [14-16]. This treatment was found to be safe and well-tolerated.

This study provides evidence that a single high dose of iNO at 250 ppm for 30 min can be safely administered by mask within the ED to patients with symptoms of acute respiratory illness. Patients receiving iNO had a low rate of significant methemoglobinemia, and MetHb levels rapidly normalized within minutes of discontinuing iNO. Patients did not experience significant symptoms, complications, or higher rate of repeat ED visits than those who maintained normal MetHb levels throughout.

Changes in disease prevalence led to premature study closure and prevented adequate testing of the hypothesis that a single high-dose iNO treatment can prevent respiratory decline of COVID-19 patients. Rates of return ED visits were slightly higher among the patients receiving iNO, however due to the small sample size, this was not a significant finding.

This study demonstrates that a single iNO treatment in this novel location (the ED) is well tolerated, can be practically and efficiently administered in the ED by emergency physicians, and poses little risk of hypoxemia, hypotension, or symptomatic methemoglobinemia even in the setting of acute respiratory disease and higher iNO concentrations. Timely access to effective therapy in the ED can be life-saving, and given our findings of safe and practical use of iNO in the ED, further studies to investigate its efficacy in other patients presenting to the ED with acute respiratory illness should be considered. Prior research has demonstrated the promise of iNO for the treatment of hospitalized patients with pulmonary hypertension, acute respiratory distress syndrome (ARDS), asthma, lower respiratory tract infections, and high-altitude pulmonary edema [1,2,4,5,9,22]. These patients could benefit greatly from the expansion of safe, timely, and effective ED treatment options.

4.1. Limitations

A marked decrease in subjects meeting entry criteria prevented this clinical trial from achieving its original treatment enrollment goal to test efficacy in reducing COVID-19 disease progression. Our research group is investigating the timing of therapeutic iNO administration in

populations of intubated ICU patients, spontaneously breathing hospitalized patients, and healthcare workers with a high risk of occupational SARS-CoV-2 exposure. Results of these studies have been independently reported [18,19].

5. Conclusion

This trial provides the first reported clinical experience reporting on iNO therapy given in the ED. Additionally, our novel high-dose administration (250 ppm for 30 min) was administered without adverse events by emergency physicians to patients with acute respiratory symptoms. Early study closure prevents meaningful comment on the efficacy of a single high-dose of iNO in preventing progression of respiratory symptoms of early COVID-19 disease.

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Credit authorship contribution statement

Brian Strickland: Writing – review & editing, Writing – original draft, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Lorenzo Albala:** Project administration, Data curation. **El Centro Coffey:** Investigation, Conceptualization. **Ryan W. Carroll:** Writing – review & editing, Investigation, Conceptualization. **Warren M. Zapol:** Writing – review & editing, Validation, Methodology, Investigation, Conceptualization. **Fumito Ichinose:** Resources, Methodology, Investigation, Conceptualization. **Lorenzo Berra:** Writing – review & editing, Validation, Resources, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **N. Stuart Harris:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

The authors of this study have no conflicts of interest.

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