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Letter to the Editor: “Use of inhaled epoprostenol with high flow nasal oxygen in non-intubated patients with severe COVID-19”

Joe W. Chiles III, MD^{a,*}, Kadambari Vijaykumar, MBBS^{a,1}, Adrienne Darby, PharmD^f, Ryan L. Goetz, MD^c, Lauren E. Kane, PharmD^f, Abhishek R. Methukupally, MD^d, Sheetal Gandotra, MD^a, Derek W. Russell, MD^{a,b}, Micah R. Whitson, MD^{a,e,1}, Daniel Kelmenson, MD^{a,1}

^a Division of Pulmonary, Allergy & Critical Care Medicine, University of Alabama at Birmingham, Birmingham, AL, United States of America

^b Birmingham Veterans Affairs Medical Center, Birmingham, AL, United States of America

^c Department of Medicine, Tinsley Harrison Internal Medicine Residency Program, University of Alabama at Birmingham, Birmingham, AL, United States of America

^d Division of Nephrology, University of Alabama at Birmingham, Birmingham, AL, United States of America

^e Department of Emergency Medicine, University of Alabama at Birmingham, Birmingham, AL, United States of America

^f Department of Pharmacy, University of Alabama at Birmingham, Birmingham, AL, United States of America

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ABSTRACT

Purpose: Acute lung injury associated with COVID-19 contributes significantly to its morbidity and mortality. Though invasive mechanical ventilation is sometimes necessary, the use of high flow nasal oxygen may avoid the need for mechanical ventilation in some patients. For patients approaching the limits of high flow nasal oxygen support, addition of inhaled pulmonary vasodilators is becoming more common but little is known about its effects. This is the first descriptive study of a cohort of patients receiving inhaled epoprostenol with high flow nasal oxygen for COVID-19.

Materials and methods: We collected clinical data from the first fifty patients to receive inhaled epoprostenol while on high flow nasal oxygen at our institution. We compared the characteristics of patients who did and did not respond to epoprostenol addition.

Results: The 18 patients that did not stabilize or improve following initiation of inhaled epoprostenol had similar rates of invasive mechanical ventilation as those who improved or stabilized (50% vs 56%). Rates of mortality were not significantly different between the two groups (17% and 31%).

Conclusions: In patients with COVID-19 induced hypoxemic respiratory failure, the use of inhaled epoprostenol with high flow nasal oxygen is feasible, but physiologic signs of response were not related to clinical outcomes.

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1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic has now caused more than 4.2 million deaths worldwide. [1] Acute lung injury (ALI) and acute respiratory distress syndrome may occur in as many as 33% of hospitalized patients with COVID-19, directly contributing to the high rates of mortality. [2] High flow nasal cannula (HFNC) has been utilized for the treatment of COVID-19 associated respiratory failure [3,4] and may be associated with reduced rates of invasive mechanical ventilation (IMV) in this population. [3] The lung pathophysiology associated with COVID-19 is multifaceted and includes airway

inflammation, micro- and macrothrombi in the pulmonary vasculature, and diffuse alveolar damage and hyaline membrane formation in the alveolar spaces. [5] Pulmonary vasodilators, such as inhaled epoprostenol (iEpo), offer putative benefits that may specifically target this pathophysiology by improving ventilation and perfusion matching, reducing pulmonary artery pressures, and supporting right heart function. Preliminary studies of iEpo in those receiving IMV for COVID-19 demonstrated heterogeneous response to iEpo with some patients showing improved oxygenation and others with little response or worsening oxygenation, [6-8] but little is known about iEpo efficacy in patients not receiving IMV. Despite this dearth of evidence, a recent survey of critical care providers in a national COVID-19 clinical trial network found that 11/20 sites were routinely using inhaled vasodilators for patients on HFNC or non-invasive positive pressure ventilation (NIPPV). [9] We performed this study to provide the first description of the use of iEpo with HFNC in the COVID-19 population as well as to determine whether

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* Corresponding author at: 1900 University Blvd, THH 422, Birmingham, AL 35294, United States of America.

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evidence of physiologic response (improved oxygenation) was related to clinical outcomes.

2. Materials and methods

After IRB approval with waiver of informed consent, and excluding four patients with do not intubate orders at the time of iEpo initiation, we performed a retrospective cohort study of the first 50 consecutive patients at our institution who received oxygen supplementation via HFNC with concomitant use of iEpo for COVID-19 associated ALI. All patients were admitted to the medical intensive care unit between June and August 2020 and tested positive for Severe Acute Respiratory Syndrome-Coronavirus-2 by RT-PCR. In addition to HFNC, two patients were receiving NIPPV at time of iEpo initiation and five other patients received NIPPV at some point while on iEpo. All clinical decisions including timing and titration of iEpo, as well as decision to intubate, were at the discretion of the clinical team.

Inhaled epoprostenol was initiated at 0.01 µg/kg of ideal body weight per minute for patients requiring high levels of HFNC support, generally ≥30 L/min and ≥90% fraction of inspired oxygen, and was rapidly increased to a maximal dose of 0.1 µg/kg of ideal body weight per minute to maintain peripheral oxygen saturation ≥90%. We utilized a generic formulation of epoprostenol (Sun Pharmaceutical Industries, Inc., Princeton, NJ, USA and Teva Parenteral Medicines, Inc., Irvine, CA, USA) reconstituted with 0.9% sodium chloride to a 30 µg/mL concentration in a 60 mL Aerogen syringe (Aerogen Solo, Aerogen Ltd., Chicago, IL USA) which was administered via BD Alaris smart pump (Becton, Dickinson and Company, Franklin Lakes, NJ, USA) to a vibrating mesh nebulizer. The nebulizer was placed on the dry side of the humidifier on the OptiFlow HFNC system (Fisher & Paykel Healthcare, Inc., Irvine, CA, USA) and oxygen was then passed through the humidifier and flowed through the nasal cannula to the patient. To reduce bio-aerosol dispersion, patients were asked to wear a surgical mask over the nasal cannula.

Demographic and clinical outcomes data were abstracted through electronic medical record review and analyzed with R (version 3.6.2, <https://www.R-project.org/>) and GraphPad Prism (version 9.1.0, GraphPad Software, San Diego, California USA). Data were censored at the time of hospital discharge or death. Response to epoprostenol was defined as either stability or increase in the ratios of partial pressure of arterial oxygen to fraction of inspired oxygen (P/F) or peripheral oxygen saturation to fraction of inspired oxygen (S/F). Comparisons of clinical outcomes between physiologic responders and non-responders were made using the Fisher exact test.

3. Results

A summary of the cohort's demographics, medical history, clinical data at the time of epoprostenol initiation, rates of various treatments and interventions, as well as clinical outcomes can be found in Table 1. A total of 32 patients (64%) had stable or increased S/F ratios after initiation of epoprostenol. Of these 32 patients, 18 required IMV (56%) while 9 (50%) of the 18 patients with worsening S/F ratios required IMV ($p = 0.77$). A total of 10 patients with stable or increasing S/F ratios died (31%) while 3 patients (17%) with decreasing S/F ratios died ($p = 0.33$). Of the 27 patients that required intubation for IMV, 5 (19%) had a desaturation below 80% noted at the time of intubation and no patients lost a pulse in the peri-intubation window. Those patients that received IMV had a median compliance of 30 mL/cm H₂O and a median P/F ratio of 160 after intubation, consistent with moderate acute respiratory distress syndrome. Fig. 1 shows time to death and IMV for the entire cohort.

Table 1
Cohort characteristics, treatments, and outcomes.

	Full Cohort (n = 50)
Demographics	
Age (years)	64 (48–71)
Male sex, n(%)	28 (56%)
Ethnicity	
Black	26 (52%)
Hispanic	3 (6%)
White	19 (38%)
Asian/Other	2 (4%)
BMI (kg/m ²)	34 (28–37)
Medical History	
Hypertension, n (%)	35 (70%)
Diabetes Mellitus, n (%)	26 (52%)
COPD, n (%)	7 (14%)
Chronic Heart Failure, n (%)	6 (12%)
Other Lung Disease, n (%)	3 (6%)
Illness Severity	
APACHE II	11 (8–14)
SOFA	2 (2–3)
WBC (thousands/mm ³)	9.1 (6.6–11.7)
C-reactive Protein (mg/L)	124 (83–181)
ESR (mm/h)	62 (50–70)
D-Dimer (ng/mL)	473 (296–996)
Lactate (mmol/L)	1.4 (1.1–1.8)
HFNC FiO ₂ at iEpo Initiation (%)	100 (80–100)
HFNC Flow Rate at iEpo Initiation (L/min)	40 (30–50)
Medications	
Dexamethasone, n (%)	48 (96%)
Remdesivir, n (%)	48 (96%)
Timing	
Admission to HFNC (days)	1.1 (0.0–3.3)
Admission to iEpo (days)	1.7 (0.5–5.3)
Response	
RR before iEpo	25 (23–29)
RR after iEpo	25 (22–29)
ΔRR	0 (–4–4)
S/F before iEpo	97 (93–120)
S/F after iEpo	98 (94–120)
ΔS/F	0 (–2–3)
P/F before iEpo ^a	81 (68–128)
P/F after iEpo ^b	80 (62–102)
ΔP/F ^c	–14 (–44–3)
Outcomes	
HFNC Duration (days)	3.8 (1.5–6.4)
iEpo Duration (days)	4.3 (2.0–7.3)
Required IMV	27 (54%)
ICU LOS (days)	10.1 (7.1–15.3)
Hospital LOS (days)	17.7 (13.0–24.4)
RRT, n (%)	7 (14%)
Prone Ventilation, n (%)	20 (40%)
Mortality, n (%)	13 (26%)

All data presented as median (interquartile range), except where noted.

APACHE II – Acute Physiology and Chronic Health Evaluation. COPD – Chronic Obstructive Pulmonary Disease. ESR – Erythrocyte Sedimentation Rate. HFNC – High Flow Nasal Cannula. iEpo – Inhaled Epoprostenol. IMV – Invasive Mechanical Ventilation. LOS – Length Of Stay. P/F – ratio of arterial partial Pressure of oxygen to Fraction of inspired oxygen. RR – Respiratory Rate. RRT – Renal Replacement Therapy. S/F – ratio of peripheral arterial Saturation to Fraction of inspired oxygen. SOFA – Sequential Organ Failure Assessment. WBC – White Blood Cell.

^a Eight values were missing for this measurement.

^b 12 values were missing for this measurement.

^c 18 values were missing for this measurement.

4. Discussion

In this cohort, we found that, despite requiring a high level of respiratory support at time of iEpo initiation, IMV was avoided in nearly half of patients with severe COVID-19 associated ALI. Other cohorts examining the use of HFNC in COVID-19 have reported rates of IMV between 54

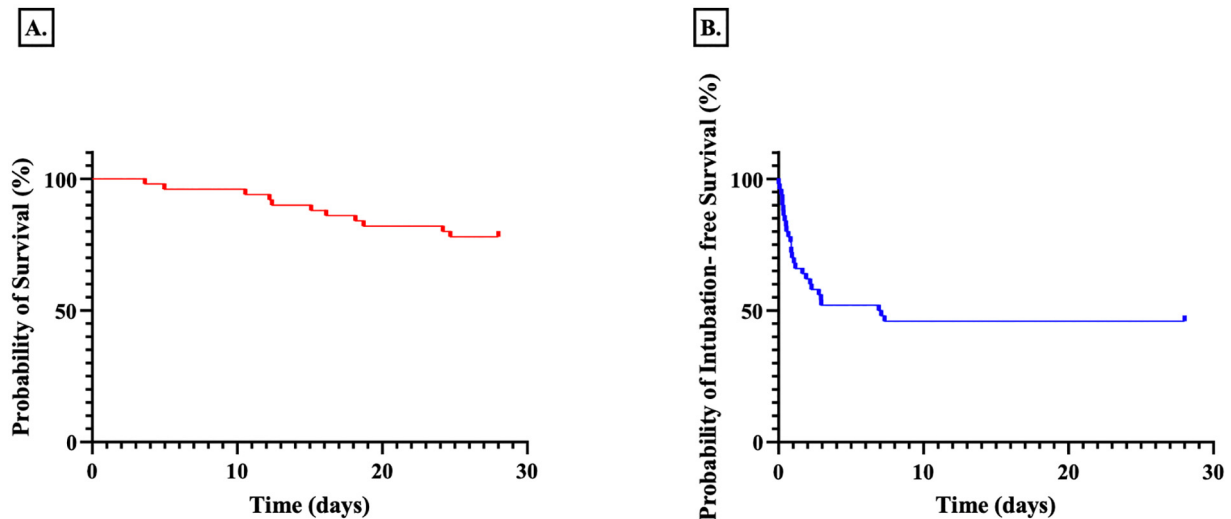


Fig. 1. Kaplan-Meier survival curves with time to death (A) and time to IMV (B) in this cohort of patients with severe COVID-19 ($N = 50$) receiving HFNC and inhaled epoprostenol.

and 75%. [3,4,10] There was no significant difference in the clinical outcomes of IMV requirement or death on the basis of immediate physiologic response to iEpo initiation. This cohort received standard of care therapy per contemporaneous clinical guidelines, including routine use of remdesivir and dexamethasone. We did not find evidence of increased risk that might be caused by delaying intubation manifested as adverse peri-intubation outcomes.

This study's limitations include its retrospective nature, single-center design, and lack of a control group. Patients initiated on iEpo were generally approaching the limits of HFNC support for COVID-19; however, decision to intubate was not standardized. We attempted to minimize the limitations of this study by enrolling a consecutive patient cohort. While changes in P/F ratio before and after initiation of iEpo would have been more granular and sensitive than S/F, these measurements were not routinely collected in many patients.

The use of pulmonary vasodilators with HFNC has been studied previously in pulmonary hypertension, where it has shown improved oxygenation. [11,12] Our study is the first to describe the use of iEpo in patients with COVID-19 associated ALI not receiving IMV. While randomized clinical trial data are needed to investigate the effect of iEpo in this population, our study suggests that the use of inhaled epoprostenol in conjunction with HFNC is feasible. Though this cohort is comprised of patients with COVID-19, iEpo may also have similar effects in a more general population of patients with ALI receiving HFNC support.

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CRediT authorship contribution statement

Joe W. Chiles: Conceptualization, Methodology, Validation, Formal analysis, Writing – original draft, Writing – review & editing. **Kadambari Vijaykumar:** Conceptualization, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Adrienne Darby:** Investigation, Writing – original draft, Writing – review & editing. **Ryan L. Goetz:** Investigation, Writing – review & editing. **Lauren E. Kane:** Investigation, Writing – review & editing. **Abhishek R. Methukupally:** Investigation, Writing – review & editing. **Sheetal Gandotra:** Conceptualization, Methodology, Writing – review & editing.

Derek W. Russell: Conceptualization, Methodology, Writing – review & editing. **Micah R. Whitson:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Daniel Kelmenson:** Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

All authors have no competing interests to disclose.

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