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ARTICLE **SHORT COMMUNICATION**

Inhaled Epoprostenol Use in Patients with SARS-CoV2-Related Severe Hypoxemic Respiratory Failure

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Inhaled epoprostenol (iEPO) is an aerosolized synthetic prostacyclin that enhances pulmonary artery vasodilation. It is used off-label as a salvage therapy in moderate-severe acute respiratory distress syndrome (ARDS) refractory to conventional therapies such as positive pressure ventilation. Despite showing improved hemodynamics and oxygenation in multiple studies, to our knowledge, studies evaluating the use of iEPO in ARDS patients did not show any mortality or morbidity benefits. This might be explained by the scarcity of studies on it and the small sample size involved in each study[1-3]. Prior to the onset of the COVID-19 pandemic, one retrospective single-center study evaluated the use of iEPO in non-intubated patients through noninvasive routes of ventilation. In this study of 36 patients, administering iEPO through HFNC and NIPPV resulted in an improvement in oxygenation parameters [4]. On the other side after the COVID pandemic, a recently published multicenter randomized single-blinded controlled trial conducted in Germany compared iEPO with placebo for ARDS and showed that iEPO significantly improved oxygenation in the subgroup of ARDS who were COVID-19 positive only. Mortality, secondary organ failure, and adverse events were similar in the intervention and the control group for both COVID-19 and non-COVID-19 ARDS patients [5]. In the era of SARS-CoV2, iEPO has presented itself as an option to theoretically delay or even prevent the need for intubation in this critically ill population. To date, two retrospective studies evaluated the use of iEPO to delay or prevent mechanical ventilation In patients on High Flow Nasal Cannula (HFNC) were published [6,7]. In one study, patients receiving iEPO had a significantly prolonged time from HFNC initiation to mechanical ventilation compared to those who did not. However, there was no statistically significant difference in mortality or length of hospital stay between the two groups [6].

In our study, we aim to see if a small population of patients treated for severe COVID-19 at a single, tertiary, academic medical center with iEPO through non-invasive devices prior to mechanical ventilation would improve oxygenation parameters.

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METHODS

We present a retrospective series of patients from a single tertiary academic medical center who exhibited acute hypoxemic respiratory failure due to SARS-CoV2. These patients required non-invasive oxygenation methods, encompassing both continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BIPAP) modes of non-invasive positive pressure ventilation (NIPPV), as well as high-flow nasal cannula (HFNC). Inhaled epoprostenol was initiated for these patients before the commencement of mechanical ventilation.

At this institution, inhaled epoprostenol is sometimes used in in non-intubated patients with severe refractory COVID-19-related hypoxemia who met the following criteria: PaO2/FiO2 ratio less than 200, FiO2 greater than or equal to 60% on high flow nasal cannula or non-invasive ventilation. The decision to use is at the discretion of the treating pulmonologist/intensivist. The initial dose administered was 50ng/kg of ideal body weight/minute, and no other inhaled medications were administered concurrently with nebulized epoprostenol. If the decision is made to wean patient off iEPO, the dose is titrated down by 10 ng/kg of ideal body weight/minute every 4 hours based on clinical response, defined as an increase in SpO2 by 5%, an increase in PaO2 by 10 mmHg, or an improvement in PaO2/FiO2 ratio by 10%. Once the patient reached the lowest dose of 10ng/kg of ideal body weight/min, the medication could be discontinued after 2 hours of the latest dose adjustment.

Respiratory therapists are responsible for setting up the aerosolized epoprostenol, which involves providing tubing for the system. In non-ventilated patients, the medication is nebulized in a system connected to a heated high-flow nasal cannula. The duration of therapy is dependent on clinical response and at the discretion of the treating provider. The administration of inhaled epoprostenol in this circuit is considered an aerosol generating procedure necessitating airborne precautions when needed.

Patient encounters were screened using electronic medical records from January 1, 2020 through April 30, 2021. The diagnosis of SARS-CoV2 was confirmed using nasal polymerase chain reaction (PCR) testing. Patients were monitored for fraction of inspired oxygen (FiO2-%), oxygen saturation (SO2%), S/F ratio, partial pressure of oxygen (PO2%), PaO2/FiO2 ratio, and PCO2 and pH from the time of iEPO initiation for 48 hours.

DATA ANALYSIS - Descriptive statistics were reported for the study variables. A paired t-test was conducted to compare FiO2-%, SO2%, S/F ratio, PaO2/FiO2 ratio, PCO2, and pH at the time of iEPO initiation to values obtained 48 hours after initiation. Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp).

The study was approved by the University of Florida office of research, the number for this IRB is IRB20210100.

RESULTS

Our study examined a cohort of 18 patients with SARS-CoV2-related hypoxemic respiratory failure who required either high-flow nasal cannula (HFNC) or non-invasive positive pressure ventilation (NIPPV). The patients were evenly distributed by gender, with a racial distribution of seven identified as black (38.9%), and one as Hispanic (5.6%). The mean body mass index (BMI) was 30.8kg/m2 (SD = 8.0). Of note, 76.5% of patients were on vasoactive agents at the time of iEPO initiation. Furthermore, thirteen patients (72.0%) had either an even or negative fluid balance 24 hours before and after iEPO initiation. Four patients had diastolic dysfunction (22.2%), six had a reduced left ventricular ejection fraction < 55% (33.3%), and five had either right atrial or right ventricular dilatation or a reduced tricuspid annular plane systolic excursion (TAPSE).

The primary outcome of our study was to determine if the use of inhaled epoprostenol (iEPO) prior to mechanical ventilation in patients with SARS-CoV2-related hypoxemic respiratory failure would improve oxygenation parameters. The mean duration of iEPO usage prior to endotracheal intubation was 50.8 hours (SD = 47.2). After 48 hours of iEPO initiation, a significant improvement was observed in our cohort's fraction of inspired oxygen (FiO2), S/F ratio, and P/F ratio ($P<0.006$, $P<0.04$, and $P<0.03$, respectively) [Figure 1]. However, no significant difference was noted in the cohort's oxygen saturation (SpO2), pH, or pCO2. Of note, 55.6% of patients were eventually intubated, and eight patients (44.4%) ultimately decided to pursue comfort measures only and avoid intubation. All of our patients died by the end of their hospitalization.

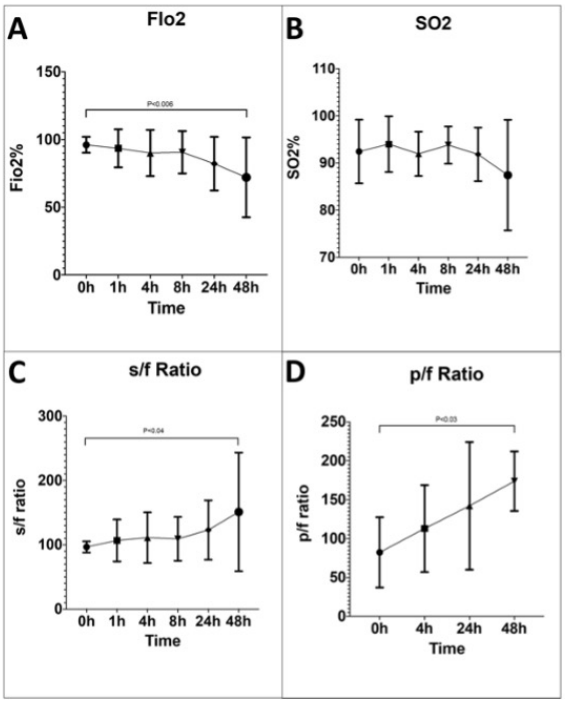
DISCUSSION

In patients with COVID-19-related acute hypoxic respiratory failure on high flow nasal cannula (HFNC) and non-invasive positive pressure ventilation (NIPPV), using iEPO may be an option in cases of refractory hypoxemia to improve oxygenation parameters.

In COVID-19 related ARDS, invasive mechanical ventilation (IMV) is often required. Regarding the use of inhaled epoprostenol in intubated patients with severe COVID-19-related ARDS, there exists a mixed body of evidence. Two retrospective studies suggest that inhaled epoprostenol, especially when combined with prone positioning, can enhance oxygenation parameters [8,9] compared to prone positioning alone. However, it's important to mention that one retrospective study, which involved a subset of 15 mechanically ventilated COVID-19 patients receiving inhaled epoprostenol, reported no significant impact on oxygenation parameters [10].

Various modalities have been explored to prevent mechanical ventilation in these patients. Data on the use of iEPO via non-invasive devices in this patient population is limited. In our cohort of 18 patients, we observed that the P/F ratio, FiO2, and S/F significantly improved 48 hours after iEPO initiation. Although all of our patients eventually required intubation or passed away by the end of their hospital stay, iEPO was used as a bridge to provide additional time for the patients and their families to decide whether to pursue mechanical ventilation or opt for comfort measures.

Figure 1. Patient data 48 hours after iEPO initiation. (a) FiO2 (%), (b) SO2 (%), (c) S/F ratio (SO2/FiO2), (d) P/F ratio (PaO2/FiO2)



We acknowledge that our study has several limitations, including its retrospective nature, lack of a control group, small sample size, and single-center design. In addition, Our study, being a research letter, does not provide specific details regarding patient characteristics and other management strategies employed for the included patients. Given these limitations, the improved oxygenation parameters cannot be confidently attributed solely to the initiation of iEPO vs. other management modalities. To compensate for this, we conducted recurrent measurements of oxygenation parameters as shown in Figure 1. Additionally, none of the patients included in our study had documented results from right heart catheterization or a pre-existing diagnosis of pulmonary hypertension. The absence of this data may have introduced a potential bias and could have influenced the outcomes observed in our study. Despite these limitations, the originality of our methodology and the scarcity of studies addressing this topic give our study significant value.

CONCLUSION

Our study provides evidence of the potential efficacy of iEPO use in COVID-19 patients on either HFNC or NIPPV. Further larger-scale studies with randomized controlled trials are needed to assess the efficacy of iEPO in improving clinical outcomes in this patient population.

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All authors contributed substantially to the study design, data analysis, and interpretation, and the writing of the manuscript. BNA had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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