Original Research

Impact of Inhaled Epoprostenol in Patients on COVID-19 Acute Respiratory Distress Syndrome (ARDS)

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Abstract

Background
Coronavirus disease 2019 (COVID-19), a novel respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), can progress to critical illness and the development of acute respiratory distress syndrome (ARDS). Variability in clinical presentation has led to 2 distinct theoretical classifications of COVID-19 ARDS based on different phenotypical presentations. The first of which follows closely to traditional ARDS presenting as severe hypoxemia with markedly reduced lung compliance, whereas the second presents as severe hypoxemia with preserved to high lung compliance. With uncertainty surrounding the specific pathological and mechanistic nature of COVID-19, we designed this study to elucidate the potential benefits of inhaled epoprostenol in COVID-19 ARDS.

Methods
This was a retrospective, observational, cohort study conducted at a 425-bed teaching hospital. Chart reviews of patients' electronic medical records were conducted and the following data were documented on a password-protected spreadsheet: patient demographics, administration of intravenous fluids and/or corticosteroids, rate and duration of inhaled epoprostenol (0.01-0.05 mcg/kg/min over 7 mL/hr per dose), and ventilator settings while on inhaled epoprostenol, mortality, and intensive care unit (ICU) length of stay (LOS). The primary objective was to evaluate the effect of inhaled epoprostenol on the number of ventilator-free days in COVID-19 patients. Secondary objectives included assessing the effects on ventilator settings, mortality, and ICU LOS.

Results
Over the span of 8 months, the charts of 848 patients diagnosed with COVID-19 were reviewed for inclusion in the study. Of those patients, 40 patients (intervention arm) who received at least 1 dose of inhaled epoprostenol (0.01-0.05 mcg/kg/min over 7 mL/hr per dose) were randomly selected for entry into the study. In the control arm, 40 patients with a diagnosis of COVID-19 who did not receive epoprostenol were randomly selected. There were no statistically significant differences in outcomes between the epoprostenol and control arms, in regard to ventilator-free days, ICU LOS, hospital LOS, and in-hospital mortality. Based on maximum ventilator settings during the first 3 days of inhaled epoprostenol use, there were no statistically significant differences between the 2 groups except for an unexpectedly lower oxygen saturation in the epoprostenol group.

Conclusion
The use of inhaled epoprostenol did not have a statistically significant effect on ventilator-free days, ventilator settings, hospital and ICU LOS, and overall in-hospital mortality.

Keywords
COVID-19; vasodilators; SARS-CoV-2; respiratory distress syndrome; vasodilator agents; treatment outcome

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Background

Coronavirus disease 2019 (COVID-19) resulted in a worldwide pandemic, which has involved approximately 220 countries.[1] This disease can cause a range of clinical manifestations, which range from an asymptomatic presentation or mild symptoms to critical illness and the development of acute respiratory distress syndrome (ARDS) requiring ventilator support.[2] Variability in clinical presentation has led to 2 distinct theoretical classifications of COVID-19 ARDS based on different phenotypical presentations.[2] The first of which follows closely to traditional ARDS presenting as severe hypoxemia with markedly reduced lung compliance, whereas the other presents as severe hypoxemia with preserved to high lung compliance.[2,3]

COVID-19 that leads to severe respiratory compromise is hypothesized to be due to significant inappropriate right to left pulmonary shunt leading to severe hypoxemia.[2-5] Mechanistically, this shunt is proposed to occur secondary to pulmonary vasculature vasoplegia and microthrombi deposition in COVID-19 ARDS.[2,3] Inhaled epoprostenol, a synthetic analogue of prostacyclin, is a strong vasodilator of pulmonary vascular beds and a potent endogenous inhibitor of platelet aggregation.[6] Its theoretical benefit in patients with severe respiratory compromise is hypothesized to be reduced pulmonary shunting, improved ventilation-perfusion matching, and reduced microthrombi deposition.[2,4,6] Inhaled epoprostenol has also been identified as a potential inhibitor of SARS-COV-2 viral replication due to epoprostenol's unique biochemical structure.[7]

There are limited scientific data to suggest a clinical benefit of inhaled epoprostenol in the setting of traditional ARDS. There are even fewer studies of inhaled epoprostenol's impact on outcomes in COVID-19 ARDS. Previous literature consists primarily of small retrospective studies and case reports that have resulted in inconsistent findings. Ammar and colleagues found inhaled epoprostenol to be non-inferior to nitric oxide in regard to ventilator-free days, intensive care unit (ICU) length of stay (LOS), PaO2/FiO2 ratio, and in-hospital mortality.[8] In more recent studies, the use of inhaled epoprostenol in patients with COVID-19 ARDS resulted in variable benefits from oxygenation, with the authors suggesting its clinical role may serve as a rescue agent.[8,9] We hypothesized that epoprostenol may have the clinical benefit of improved oxygenation in COVID-19 ARDS through reduced pulmonary shunting, improved ventilation-perfusion matching, and a reduction in microthrombi deposition. The objective of our study was to further evaluate the safety and efficacy of inhaled epoprostenol in critically ill patients diagnosed with COVID-19 ARDS.

Methods

This was a retrospective, observational chart review conducted from February 1, 2020, to September 30, 2020, at a 425-bed acute care, teaching hospital. Eligible patients for inclusion were adults aged 18 years or older with a confirmed diagnosis of COVID-19. COVID-19 status was confirmed using either nucleic acid amplification testing (NAAT) (eg, reverse-transcription polymerase chain reaction [RT-PCR assay]) or antigen testing. Included patients were also mechanically ventilated. A total of 848 patients with a diagnosis of COVID-19 were screened for inclusion. The intervention arm consisted of 40 patients who met the following criteria: diagnosis of COVID-19 ARDS, received at least 1 dose of inhaled epoprostenol (0.01-0.05 mcg/kg/min over 7 mL/hr per dose), and required mechanical ventilation for oxygen support. In the control arm, 40 patients who did not receive epoprostenol were selected using a clinical surveillance program and random number generator to be included in the study. Inclusion criteria for the control arm included the following: a diagnosis of COVID-19 ARDS and mechanical ventilation for oxygen support. Patients who had expired within 24 hours of hospital admission were excluded. Other than a single patient who received 2 doses of tocilizumab, patients included in our analysis did not receive other novel therapies (ie, nitric oxide, tocilizumab, etc) outside of remdesivir for the treatment of severe COVID-19 ARDS. Our primary objective was to evaluate the effect of inhaled epoprostenol on ventilator-free days. The primary safety outcome assessed the frequency of systolic blood pressure (SBP) reduction of 20 mmHg or greater within a 1-hour window, 3 hours following initiation of inhaled epoprostenol. Secondary objectives included maximum ventilator settings, in-hospital mortality, and ICU LOS. This study was approved as exempt by the Institutional Review Board.

Data Collection

A clinical surveillance platform was utilized to retrieve a list of patients who were administered inhaled epoprostenol. Chart reviews of patients' electronic medical records were conducted and the following data were documented on a password-protected spreadsheet: patient demographics, administration of intravenous fluids and/or corticosteroids, rate and duration of inhaled epoprostenol, maximum ventilator settings (Mode, Positive End Expiratory Pressure, FiO2, SpO2, Plateau Pressure) on days 1, 2, and 3 while on inhaled epoprostenol (or first 3 days while on the ventilator, if in the control group), in-hospital mortality, hospice admission, hospital LOS, ICU LOS, and the frequency of SBP reduction following initiation of inhaled epoprostenol.

Data Analysis

A power analysis calculation concluded that 40 patients would be required in each group to achieve 80% power and an alpha level of 0.05. An independent t-test was performed to compare days of receiving mechanical ventilation between the intervention and control arms, specify the differences in patient outcomes between groups based on maximum ventilator settings on days 1, 2, and 3, and evaluate both hospital and ICU LOS. Evaluation of in-hospital mortality was assessed using logistic regression. Data analysis was conducted using SPSS statistical software.

Results

The study population was approximately 64% male (n = 51; intervention arm = 26/40, control arm = 25/40), 59% were at least 65 years old (n = 47; control arm = 28/40, intervention arm = 19/40), and 24% were morbidly obese (n = 19; control arm = 9/40, intervention arm = 10/40). As for selected comorbidities, there was a greater percentage of patients in the intervention arm with a past medical history of COPD (20%, n = 8) than in the control arm (5%, n = 2). There was also a higher percentage of intervention arm patients taking an immunosuppression/corticosteroid (15%, defined as dexamethasone 6 mg daily for at least 1 day), compared to the control arm (12.5%). There were more patients in the control arm with a history of heart disease (82.5%, n = 33) compared with the intervention arm (67.5%, n = 27). There were no statistically significant differences in demographic data between the control and intervention arms.

Although the primary efficacy outcome was not statistically significant, there was a higher number of ventilator-free days in the intervention arm versus the control arm (10.26% versus 8.18%; 95% confidence interval (CI), 5.31-2.96; respectively, $P > .05$). There were no clinically significant findings in regard to secondary efficacy outcomes. When assessing maximum ventilator settings on days 1 through 3 while on epoprostenol, a statistically significant result was identified with maximum oxygen saturation between the 2 groups (intervention, 93.70% versus control, 97%; $P = .001$). Logistic regression did not reveal a relationship with the other secondary outcomes ICU LOS (95% CI, 4.930-4.580; $P = .942$), hospital LOS (95% CI, 5.442-5.192; $P = .963$), and in-hospital mortality (95% CI, 0.10-4.91; $P = .74$). The primary safety outcome that examined SBP reduction of at least 20 mmHg or greater occurred in approximately 47.5% (n = 19) of patients in the intervention group (primary safety outcome was assessed in the intervention arm only to assess the impact of epoprostenol on systolic blood pressure).

Discussion

The findings of this study are comparable to previously published literature[6,9] as there were no statistically significant differences from the use of inhaled epoprostenol in patients with COVID-19 ARDS in regard to ventilator-free days, oxygenation, hospital and ICU LOS, and in-hospital mortality.[6] Although one of the secondary outcomes showed a lower oxygen saturation in the epoprostenol group when examining the effect on various ventilator settings, this result was likely due to the types of patients selected to receive inhaled epoprostenol and the difficulty in ensuring similarity between groups in a retrospective study. Overall, we did not confirm the efficacy of inhaled epoprostenol; however, it is frequently used as an option for refractory hypoxemic patients secondary to COVID-19 ARDS in which other traditional interventions (high dose corticosteroids, mechanical ventilator setting optimized, etc) have not provided clinical improvements in oxygenation.[6]

Due to the unfamiliarity with this novel disease, researchers have continued to explore various options for the treatment or prevention of COVID-19 using existing drug therapies. Over 130 different investigational drugs have been trialed and evaluated to date.[10] Despite the negative results of this study, the information collected is important in assessing the potential role, or lack thereof, for inhaled epoprostenol in the treatment of COVID-19. Studies such as this will aid in guiding our understanding and management of this disease.

Limitations

There were a few limitations in this study. First, patients were selected from a single-center institution with a relatively small sample size, which may have led to higher variability and bias despite achieving a sufficient study population determined by the power analysis. Secondly, due to the abrupt onset of this novel disease, the duration of observation was limited. The retrospective nature of this study was subject to potential sources of bias and confounding variables. However, a few pre-specified medications were accounted for at the beginning of the study to take into consideration potential confounders, such as the administration of corticosteroids. We did not gather information on interleukin-6 receptor antagonists, which have consistently shown mortality benefits in severe COVID-19 patients. Population-level immunity, for vaccines and/or prior illness, has made severe disease less common, thus the need for the information in our study may be less relevant. Furthermore, evidence shows that the Omicron variant exhibits decreased lung infectivity, making pneumonia a less likely manifestation of the disease. We did not gather information on proning, PaO_2/FiO_2 ratio (to show the severity of ARDS between groups), or information on the use of paralytics, a standard of care for ARDS. There was a statistically significant difference in the maximum oxygen saturation between the epoprostenol and control groups (93.70% versus 97%; $P = .001$), but with no differences in other outcomes (ie, ventilator-free days, ICU LOS, etc). Therefore, we believe this result is likely not clinically significant. Lastly, although the mortality rate was relatively high for both groups, this was not unexpected considering the overall patient population enrolled had a high severity of illness and mortality risk at baseline.

Conclusion

Inhaled epoprostenol, based on the results of this study have limited to no benefit in the treatment of severe COVID-19 complicated by ARDS. Larger, comprehensive, prospective randomized controlled trials are needed to determine the clinical impact of inhaled epoprostenol in COVID-19 ARDS.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Dr Nguyen is an employee of Southern Hills Hospital and Medical Center, a hospital affiliated with the journal's publisher.

Drs Chromi is an employee of MountainView Hospital, a hospital affiliated with the journal's publisher.

Drs McCoy and Murawsky are employees of HCA Healthcare Far West Division, an organization affiliated with the journal's publisher.

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