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Evaluation of aerosolized epoprostenol for hypoxemia in non-intubated patients with coronavirus disease 2019

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ABSTRACT

Objectives: Patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) frequently present with a febrile illness that may progress to pneumonia and hypoxic respiratory failure. Aerosolized epoprostenol (aEPO) has been evaluated in patients with acute respiratory distress syndrome and refractory hypoxemia. A paucity of literature has assessed the impact of aEPO in patients with SARS-CoV-2 receiving oxygen support with high flow nasal cannula (HFNC). The objective of this study was to evaluate whether aEPO added to HFNC prevents intubation and/or prolong time to intubation compared to controls only treated with HFNC, guided by oxygen saturation goals.

Methods: This was a single-center, retrospective study of adult patients infected with coronavirus 2019 (COVID-19) and admitted to the medical intensive care unit. A total of 60 patients were included. Thirty patients were included in the treatment, and 30 in the control group, respectively. Among patients included in the treatment group, response to therapy was assessed. The need for mechanical ventilation and hospital mortality between responders vs. non-responders was evaluated.

Results: The primary outcome of mechanical ventilation was not statistically different between groups. Time from HFNC initiation to intubation was significantly prolonged in the treatment group compared to the control group (5.7 days vs. 2.3 days, P = 0.001). There was no statistically significant difference between groups in mortality or length of stay. Patients deemed responders to aEPO had a lower rate of mechanical ventilation (50% vs 88%, P = 0.025) and mortality (21% vs 63%, P = 0.024), compared with non-responders.

Conclusion: The utilization of aEPO in COVID-19 patients treated with HFNC is not associated with a reduction in the rate of mechanical ventilation. Nevertheless, the application of this strategy may prolong the time to invasive mechanical ventilation, without affecting other clinical outcomes.

Introduction

Coronavirus disease 2019 (COVID-19) is an ongoing pandemic that has resulted in a tremendous strain on the healthcare system throughout the world. Patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) frequently present with a febrile illness that may progress to pneumonia and hypoxic respiratory failure. Patients may require hospitalization and management with supportive care consisting primarily of oxygen support. As the disease progresses, higher oxygen requirements may be needed to sustain peripheral oxygen saturation (SpO2) goals. Rates of mechanical ventilation among patients admitted to the hospital range from 15% to 33.1% [1]. However, availability of resources largely influences the threshold for mechanical ventilation[1]. Throughout the pandemic, hospital systems have reported shortages of essential equipment necessary to care for critically ill patients, including a limited number of ventilators[2]. As a result, several therapeutics have been established and are being evaluated to prevent disease progression and improve clinical outcomes. Current treatment strategies for patients with COVID-19 consist of supportive care, anti-

inflammatory agents, and antiviral medications [3,4]. Hypoxic respiratory failure is treated with conventional oxygen therapy, heated high-flow nasal cannula (HFNC), or invasive mechanical ventilation. The RECOVERY trial showed that the use of corticosteroids in COVID-19 patients requiring oxygen therapy improved mortality at 28 days and reduced the risk of progression to mechanical ventilation [5]. The antiviral medication remdesivir may be considered early in the treatment course (within 10 days of symptom onset), as its use showed shortened time to patient's recovery [3,4]. Lastly, use of interleukin-6 antagonists (tocilizumab or sarilumab) was associated with positive clinical outcomes, such as reduction of mortality at 28 days, or increase in organ failure free-days, when used early in the disease course [6,7]. Despite the aforementioned therapeutic strategies, many patients experience disease progression, particularly in the setting of an overwhelmed healthcare system.

Epoprostenol, a synthetic prostacyclin analog, enhances cyclic adenosine monophosphate concentrations with subsequent pulmonary artery vasodilation [8]. Aerosolized epoprostenol (aEPO) is not an FDA approved route of administration

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for this intravenous product and is considered experimental, particularly in patients with acute respiratory distress syndrome (ARDS) and refractory hypoxemia[9]. Physiologically, it aides in the recruitment of blood flow to ventilated lung segments with transient improvements in oxygenation. Despite these physiologic effects, no improvements in clinical outcomes, such as survival, ventilator-free days, or length of stay have been noted [10]. Current literature has predominately assessed the impact of aEPO via noninvasive routes among patients with right ventricular dysfunction and refractory hypoxemia; however, there is no evidence to date evaluating its role in patients with COVID-19 requiring high flow nasal cannula (HFNC) [11–13]. Thus, the objective of this study is to evaluate whether aEPO (1) prevents intubation and/or (2) prolong time to intubation compared to controls.

Materials and methods

This was a single-center retrospective analysis of data gathered within a quality improvement project to standardize aEPO utilization among patients with COVID-19. Adults who were admitted to the medical intensive care unit (MICU) between 1 June and 1 December 2020 with a diagnosis of COVID-19 were screened. Patients were included in the study if they were ≥18 years, required oxygen support with HFNC (Flow ≥50 L/min; FiO2 ≥ 80%), and were treated with corticosteroids (dexamethasone 6 mg daily for 10 days or equivalent). Patients were not eligible for inclusion if any of the following criteria were met: do not intubate (DNI) advanced directive, disruption of HFNC for bilevel-positive airway pressure (BiPAP), receipt of inhaled nitric oxide, or a past medical history of pulmonary hypertension. Our institutional policy for the management of COVID-19 limited the use of BiPAP as possible due to the risk of aerolization. Few patients were treated outside this consideration and were therefore excluded from the study. Patients were separated into two groups: (1) a treatment group, if they received aEPO for at least 1 h after reaching the aforementioned cutoffs for oxygen flow and concentration; and (2) a control group, if HFNC was maintained after reaching HFNC cutoffs. Patients were identified through the EPIC-based self-service cohort query tool (Slicer Dicer) in the presence of a positive COVID-19 PCR test. The study was approved by the institutional review board (#021-230). Informed consent was waived due to the retrospective nature of the study.

The primary outcome of this study was the rate of patients requiring invasive mechanical ventilation. Secondary outcomes were time to mechanical ventilation, 28-day mortality and ICU, and hospital lengths of stay. Time to mechanical ventilation was defined as the time from HFNC initiation to intubation. Furthermore, within the treatment group, we assessed whether patients were responders to treatment or not. Patients were deemed responders if there was a sustainable (> 4 hours) 10% reduction in FiO2 requirements from baseline, while maintaining SpO2 > 92% within the first 24 hours of treatment. Patients were non-responders if the aforementioned criteria for improvement were not fulfilled or worsened.

Administration of aEPO was initiated according to the institutional policy at a dose between 10 and 50 ng/kg/min based on ideal body weight and titrated by 10 ng/kg/min every 30 minutes to maintain a SpO2 ≥ 92%. Since a dose range for initiation was provided within the policy, initial dosing and subsequent titrations were selected at the discretion of the ordering provider. Due to the short onset of action of aEPO, response to therapy was assessed as early as 1 hour. Epoprostenol was prepared in the Department of Pharmacy in a 60 mL syringe to a final concentration of 30,000 ng/mL (1.5 mg/50 mL). Following medication preparation, the vibrating mesh nebulizer, placed at the humidifier, was connected to the breathing circuit. Next, the syringe was attached to the tubing, primed, and screwed into the nebulizer. Lastly, the syringe was inserted into the syringe pump and activated with continuous flow. Notably, delivery of aEPO via an open-circuit creates an aerosolized generating procedure. Due to COVID-19, the risk posed to health-care providers was mitigated by limiting entry into rooms, airborne precautions, and the use of personal protective equipment (PPE). HFNC settings were optimized according to the attending physician. Although there was no formal criteria established to titrate HFNC settings, the flow was titrated for work of breathing, and FiO2 was titrated to maintain a SpO2 ≥ 92%. All patients received standardized management, consisting of routine encouragement of self-proning as tolerated, venous thromboembolism prophylaxis, and glycemic control.

Patient demographics and study outcomes are presented as total numbers plus percentages for categorical variables and compared between groups using chi-square or Fisher's exact tests. Continuous variables are presented as medians plus interquartile range (IQR). A logistic regression model was performed to examine the association between the use of aEPO compared to control and the odds of intubation. This model was adjusted for diuretics. All data analysis was performed using SAS 9.4.

Results

A total of 147 patients were screened for inclusion in the study, and 60 patients met the criteria. The treatment group and control groups consisted of 30 patients each. The primary reason for exclusion was a maximum HFNC requirement below the threshold for inclusion, as shown in Figure 1.

Baseline demographics of the included patients are shown in Table 1. Baseline demographics were fairly distributed between both groups. The study population was evenly split between males and females, had a median age of 62.5 years, and a BMI of 34.3 kg/m^2. Both groups had a comparable severity of illness based on predicted mortality, expected length of stay, and admission comorbidities. Baseline inflammatory markers were collected at the onset of HFNC. Despite the lack of significant differences between groups in levels of C-reactive protein, ferritin, and D-dimer, a significant difference was detected in lactate dehydrogenase. Management strategies were also assessed. There were no differences between management strategies with the exception of more
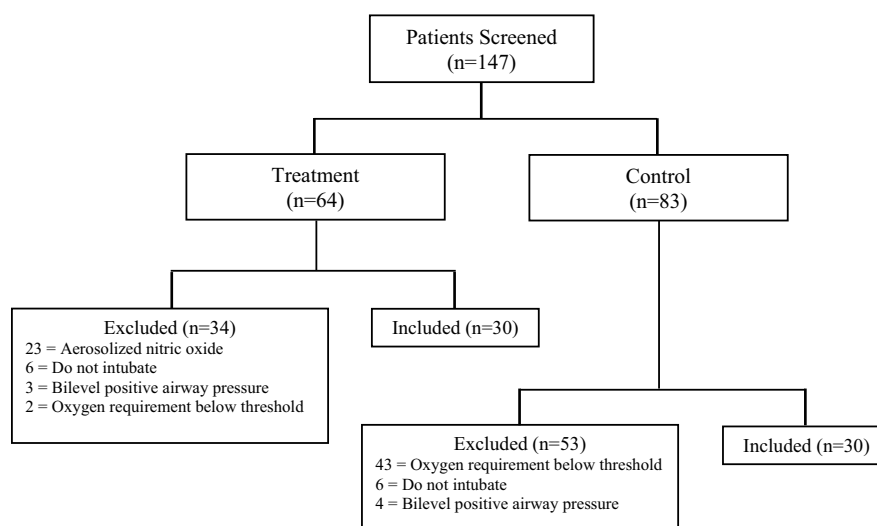
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                    Patients Screened
                        (n=147)
                           |
            +--------------+--------------+
            |                             |
        Treatment                      Control
         (n=64)                        (n=83)
            |                             |
      +-----+-----+                       |
      |           |                       |
 Excluded    Included (n=30)              |
  (n=34)                           +------+------+
                                   |             |
                               Excluded     Included (n=30)
                                (n=53)
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Excluded (n=34)
23 = Aerosolized nitric oxide
6 = Do not intubate
3 = Bilevel positive airway pressure
2 = Oxygen requirement below threshold

Excluded (n=53)
43 = Oxygen requirement below threshold
6 = Do not intubate
4 = Bilevel positive airway pressure

Figure 1. Flow diagram of study selection.

patients in the treatment group receiving diuretics (63% vs 33%, $p = 0.02$).

The primary outcome of mechanical ventilation was not statistically significant between groups (Table 2). Despite not achieving significance, 70% of patients in the treatment group required mechanical ventilation compared with 90% in the control group. Furthermore, the likelihood of intubation was not statistically significant in both the unadjusted (odds ratio: 3.86 (0.93–16.05), $p = 0.064$) and adjusted (odds ratio: 3.23 (0.74–14.18),

Table 1. Baseline Demographics.

Characteristic	aEPO (N = 30)	Control (N = 30)	P Value
Age, years (IQR)	61.5 (30.0–80.0)	65 (36.0–82.0)	0.594
Gender, n (%)			
Male	17 (56.7)	15 (50.0)	0.796
Total body weight, kg (IQR)	96.6 (54.0–181.4)	91.0 (54.0–144.4)	0.695
Ideal body weight, kg (IQR)	62.7 (45.5–79.9)	59.0 (45.0–84.5)	0.175
BMI, kg/m^2 (IQR)	32.6 (25.1–73.1)	35.2 (22.3–56.0)	0.455
Admission comorbidities, n (%)			
Congestive heart failure	1 (3.3)	3 (10.0)	0.301
Coronary artery disease	3 (10.0)	5 (16.7)	0.448
Hypertension	19 (63.3)	21 (70.0)	0.584
Pulmonary hypertension	0 (0.0)	0 (0.0)	1.000
COPD	2 (6.7)	1 (3.3)	0.554
Asthma	1 (3.3)	1 (3.3)	1.000
Chronic kidney disease	1 (3.3)	4 (13.3)	0.161
End stage renal disease	2 (6.7)	2 (6.7)	1.000
Cirrhosis	0 (0.0)	0 (0.0)	1.000
Diabetes	14 (46.7)	18 (60.0)	0.301
Severity of illness*			
Predicted mortality, % (IQR)	9.8 (5.1–13.9)	8.8 (5.5–17.5)	0.544
Predicted length of stay, days (IQR)	5.1 (3.6–7.5)	5.3 (3.2–8.9)	0.277
Symptom onset to hospital presentation, days, (IQR)	7 (1–14)	5 (1–14)	0.053
Management strategies, n (%)			
Corticosteroids	30 (100.0)	30 (100.0)	1.00
Remdesevir	27 (90.0)	23 (76.7)	0.166
Diuretics	19 (63.3)	10 (33.3)	0.020
Renal replacement therapy	3 (10.0)	3 (10.0)	1.000
Therapeutic anticoagulation	11 (36.7)	9 (30.0)	0.584
Tocilizumab	0 (0.0)	0 (0.0)	1.000
Baseline inflammatory markers			
C-reactive protein, mg/dL (IQR)	14.2 (0.6–33.1)	13.3 (1.7–34.1)	0.717
Ferritin, ng/mL (IQR)	502 (135–7632)	784 (205–12,773)	0.150
Lactate dehydrogenase, U/L (IQR)	399 (239–1219)	543 (244–1398)	0.001
D-dimer, ug/mL (IQR)	1.1 (0.3–23.7)	1.0 (0.5–116.4)	0.824
Platelets, n (%)			
Baseline	295 (83–509)	229 (100–576)	0.056
Nadir	273 (83–509)	205 (100–448)	0.049

Aerosolized Epoprostenol = aEPO; Interquartile range = IQR; Body Mass Index = BMI; Kilogram = kg; Chronic Obstructive Pulmonary Disease = COPD;
*Severity of illness indicators (predicted mortality and length of stay) were calculated utilizing a proprietary prediction model integrated within EPIC

Table 2. Clinical Outcomes.

Characteristic	aEPO (N = 30)	Control (N = 30)	P-Value
Intubation, n (%)	21 (70.0)	27 (90.0)	0.053
Time to intubation from HFNC, days (IQR)	5.7 (0.8–18.3)	2.3 (0.1–17.1)	0.001
28-day mortality, n (%)	13 (43.3)	14 (46.7)	0.795
Length of stay, days (IQR)			
Intensive care unit	19.8 (3.5–81.0)	24.5 (6.7–80.0)	0.139
Hospital	23.8 (6.8–81.0)	27.1 (6.7–92.0)	0.211

Aerosolized Epoprostenol = aEPO; Interquartile range = IQR; High flow nasal cannula = HFNC

Discussion

The present study evaluated the impact of aEPO in patients with COVID-19 who received oxygen support with HFNC. While aEPO did not significantly reduce the rate of mechanical ventilation, the time from HFNC initiation to intubation was prolonged by 3.4 days, without affecting other clinical outcomes, such as 28-day mortality or length of stay.

The COVID-19 pandemic has caused an abrupt increase in patients requiring hospitalization that has resulted in limited resource availability. In an effort to mitigate ventilator shortages, unconventional strategies have been used, such as applying

Table 3. HFNC Setting Trends in Patients Receiving aEPO.

Characteristic	Responders			Non-responders	
	Flow	FiO2	Responders	Flow	FiO2
(n = 30)	L/min (IQR)	% (IQR)	n (%)	L/min (IQR)	% (IQR)
Pre-aEPO	60 [60–60]	90 [90–95]	N/a	60 [60–65]	95 [90–100]
1-hour post aEPO	60 [60–60]	90 [80–90]	7 (23.3)	60 [60–60]	100 [98–100]
6-hour post aEPO	60 [60–60]	80 [70–85]	14 (43.3)	60 [60–70]	100 [100–100]
12-hour post aEPO	60 [55–60]	80 [65–90]	10 (33.3)	60 [60–70]	100 [90–100]
24-hour post aEPO	60 [50–60]	75 [50–85])	10 (33.3)	60 [60–70]	100 [98–100]

High flow nasal cannula = HFNC; Aerosolized Epoprostenol = aEPO; Liters/minute = L/min; Interquartile range = IQR

p = 0.318) logistic regression analysis. Time from HFNC initiation to intubation was significantly different between groups, with an observed prolonged time to intubation in the treatment group (Table 2). There was no statistically significant difference between groups in mortality or length of stay. Table 3 depicts HFNC changes in the first 24 h among patients who received aEPO. Furthermore, peak response rate occurred at 6 hours following administration, which consisted of all 14 patients. Patient response to aEPO and the associated clinical outcomes were also assessed (Table 4). Responder patients had a lower rate of mechanical ventilation (50% vs 88%, p = 0.025) and mortality 21% vs 63%, p = 0.024), compared with non-responders.

a single ventilator for multiple patients, liberalizing SpO2 goals, and combining high-flow oxygen with inhaled vasodilators [14]. In our study population, although the rate of mechanical ventilation was not statistically significant, there was a trend toward a reduced use in the treatment group. Furthermore, in the setting of a ventilator shortage, the median observed difference in time from HFNC initiation to mechanical ventilation may provide a buffer of time for ventilators to become available, providing pragmatic clinical relevance to this secondary outcome.

COVID-19 related respiratory failure has demonstrated distinct characteristics that may guide treatment, most notably steroid responsiveness. In addition to SARS-CoV-2 directed treatment, multiple society guidelines recommend to incorporate principles of ARDS management

Table 4. Responders versus non-responders to aEPO.

Variable	aEPO		P-value
	Responder N = 14	Non-responder N = 16	
Intubation, n (%)	7 (50)	14 (87.5)	0.025
Time to intubation from HFNC, days (IQR)	5.6 (2.62–8.9)	5.7 (2.5–9.6)	0.456
Time to aEPO start from HFNC, days (IQR)	1.7 [1.0–3.9]	3.9 [1.7–7.3]	0.059
28-day mortality, n (%)	3 (21.4)	10 (62.5)	0.024
Length of stay, days (IQR)			
Intensive care unit	11.6 (9.5–24.5)	21.4 (16.6–36.2)	0.170
Hospital	18.8 (11.0–27.0)	28.5 (19.0–36.6)	0.58
Initial dose, ng/kg/min (IQR)	30 (10–50)	40 (30–50)	0.099
Maximal dose, ng/kg/min (IQR)	35 (20–50)	40 (30–50)	0.088
Dose titration amount, n (%)			
10	9 (64.2)	3 (18.6)	0.011
<10	1 (7.1)	0 (0.0)	0.277
>10	0 (0.0)	1 (6.3)	0.341
None	4 (28.6)	12 (75.0)	0.011
Duration of administration, days (IQR)	2.0 (0.6–5.5)	1.4 (0.1–8.2)	0.124

Aerosolized Epoprostenol = aEPO; Interquartile range = IQR; High flow nasal cannula = HFNC; nanograms = ng; kilograms = kg; minute = min;

[3,4]. The surviving sepsis campaign guidelines on the management of adult patients with COVID-19 recommend lung protective ventilation, prone positioning, neuromuscular blockade, and conservative fluid management [4]. While these recommendations pertain primarily to mechanically ventilated patients, prone positioning, and conservative fluid management are tangible interventions in non-intubated patients. Awake prone positioning, in particular, has been shown to reduce the need for intubation in patients with hypoxemic respiratory failure due to COVID-19[15]. Although these findings were published following the inclusion timeframe of our cohorts, all patients were encouraged to self-prone daily as tolerated. Loop diuretics were used more frequently in the treatment group. The reasons for this finding remain unclear. It is possible that patients treated with aEPO were more closely monitored from a hemodynamic standpoint. Nevertheless, this explanation is hypothesis generating, rather than a proven one. Importantly, the evidence supporting conservative fluid management is based on the results of the Fluid and Catheter Treatment trial (FACTT), which exclusively included mechanically ventilated patients[16]. To further assess the statistical difference in diuretic use observed between groups, a logistic regression model was performed, resulting in no statistical difference in the likelihood of intubation.

The threshold for response to therapy in our cohort was chosen in consideration of the disease process of SARS-CoV-2. Notably, previous studies utilizing aEPO via noninvasive routes defined the response to therapy as an improvement in the partial pressure of arterial oxygen (PaO2) or SpO2 to FiO2 by 20% [11–13]. Since the PaO2-to-FiO2 ratio is not validated in HFNC, routine arterial blood gases were not obtained. Moreover, SpO2-to-FiO2 ratio was not selected to demonstrate the impact on oxygenation in consideration of the oxygen-hemoglobin dissociation curve. Due to the sigmoidal curve, at saturations above 90–92%, further increases in PaO2 have a limited impact on further oxygen saturation[17]. Thus, the maintenance of SpO2 > 92% with a sustained reduction in FiO2 was selected to reflect the response to therapy and its impact on oxygenation.

aEPO has a very quick onset of action due to its short plasma half-life. Duration of therapy is dependent on clinical response. In our cohort, 23% of patients responded at 1 h, with a peak response rate (43%) at 6 hours. Similarly, Sonti and colleagues found a response rate of 50% in their cohort of mechanically ventilated COVID-19 patients with a median onset of response of 3 hours[18]. Interestingly, in our cohort, response to therapy was associated with a statistically significant reduction in mechanical ventilation and mortality. Given these findings, several factors that may have impacted the response to therapy must be discussed. First, the delay in response observed in our cohort may have been due to aEPO's use as a rescue therapy. Gradual reductions in FiO2 were utilized to prevent desaturation episodes from overly aggressive FiO2 down titration, as further decompensation on maximum HFNC settings may have prompted endotracheal

intubation. As a result, evaluation of FiO2 requirements and associated response at 6 hours may be more reflective of real-world practice. Second, aEPO was initiated at a lower median dose (30–40 ng/kg/min) compared to historical studies (50 ng/kg/min) [11–13,18]. Significant variation in dosing aEPO has led to controversies on the optimal dose and corresponding response. Fuller and colleagues conducted a systematic review on the use of inhaled prostacyclins and demonstrated a linear dose response relationship between oxygenation and increasing dose[10]. As a result, it remains unclear if a more robust response rate would have been observed if dosing was initiated at 50 ng/kg/min. Moreover, in our cohort, responders had significantly more dose titrations compared to non-responders. Despite this, the median initial dose of non-responders was 40 ng/kg/min. Frequency of dose titration was therefore not likely to impact the response to aEPO. Lastly, the clinical impact of HFNC gas flow on aEPO responsiveness should be considered. Li and colleagues evaluated that varying gas and patient inspiratory flows effect on aerosol delivery [19]. During non-distressed breathing, the degree of aerosol delivery was inversely related to gas flow. Furthermore, in distressed breathing, a plateau effect was seen when the gas flow was approximately 50% of inspiratory flow [20]. These findings confirm the investigator hypothesis of increasing medication wasting with gas flows that exceed inspiratory flow. Due to the limited ability to measure patient's inspiratory flow on HFNC, clinical decisions are often made on the degree of respiratory distress that a patient exhibits. In our cohort, HFNC gas flow was titrated at the discretion of the attending physician. Moreover, work of breathing and corresponding gas flows were not captured when assessing the response to therapy. Based on the previously described findings, patients treated with aEPO should be evaluated between 3 and 6 hours following initiation for a response, with a subsequent down titration plan if no benefit is observed after that time period.

Our study presents several strengths. First, it evaluates the utilization of a novel combination of therapies in non-mechanically ventilated COVID-19 patients. Second, the applicability of the results during times of equipment shortage becomes useful in clinical practice. Third, it provides guidance on the implementation of aEPO in non-intubated patients, by describing expectations on how to deem patients as responsive vs. non-responsive. Despite the aforementioned strengths, our study also presents several limitations. First, due to the retrospective design, selection and/or information bias may have occurred. Lack of or inaccurate data, physiologic information, or clinical outcomes may have therefore been incomplete. In particular, self-prone rates and fluid balance were not captured. Additionally, safety outcomes such as bleeding rates, hypotension, and rebound hypoxemia were not assessed. Second, although we attempted to control for confounders through strict inclusion criteria, confounding factors may have impacted the evaluated outcomes. Third, the small sample size may have limited the ability to

adequately identify statistical significance. Therefore, we are unable to draw definitive conclusions from this data set, but rather view them as hypothesis generating. Large, randomized, and prospective studies are needed to confirm these findings.

Conclusion

The present study demonstrates that the utilization of aEPO in COVID-19 patients treated with HFNC is not associated with a reduction in the rate of mechanical ventilation. Nevertheless, the application of this strategy may prolong the time from HFNC initiation to the need for invasive mechanical ventilation, without affecting other clinical outcomes. The aforementioned strategy may provide an alternative tool during times of ventilator shortages.

Declaration of funding

Disclosure of any financial/other conflict of interest

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