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Nebulized Furosemide for Pulmonary Inflammation in Intubated Patients With COVID-19: A Phase 2 Randomized Controlled Double-Blind Study

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OBJECTIVES: Respiratory failure secondary to COVID-19 is associated with morbidity and mortality. Current anti-inflammatory therapies are effective but are given systemically and have significant side effects. Furosemide has anti-inflammatory properties, can be administered by inhalation, and is inexpensive. We investigated the efficacy of nebulized furosemide as an adjunctive therapy for COVID-19 respiratory failure.

DESIGN: A double-blind, randomized, placebo-controlled trial.

SETTING: Multicenter ICU study.

PATIENTS: Adults requiring invasive mechanical ventilation secondary to COVID-19.

INTERVENTION: Patients were randomized within 48 hours of intubation to receive inhaled furosemide or placebo until day 28, death, or liberation from mechanical ventilation.

MEASUREMENTS AND MAIN RESULTS: The study was stopped early due to waning incidence of COVID-19; 39 patients were available for analysis with mean ± SD age of 70.5 (10.8) years, Acute Physiology and Chronic Health Evaluation II 26.1 (7.8) and F_{IO_2} 60.0% (21.9). Baseline characteristics were similar between the groups. For the primary outcome of change in P_{aO_2}/F_{IO_2} ratio between day 1 and day 6, it was +31.4 (83.5) in the furosemide arm versus +20.1 (92.8) in the control ($p = 0.58$). For secondary outcomes, furosemide versus control: 60-day mortality was 48% versus 71% ($p = 0.20$), hospital stay was 25.6 (21.9) versus 27.4 (25.0) days, $p = 0.94$ and VFD was 6.0 (9.1) versus 3.1 (7.1), p value of equals to 0.28. A post hoc analysis of the hierarchical composite outcome, alive and ventilator-free favored furosemide. There were no adverse events.

CONCLUSIONS: In this trial of inhaled furosemide for COVID-19 respiratory failure, differences in P_{aO_2}/F_{IO_2} ratio to day 6 and other clinical outcomes were not significantly different, although the trial was underpowered due to early termination. Given the favorable profile of inhaled furosemide, further study is warranted in disease states where acute pulmonary inflammation contributes to the underlying pathophysiology.

KEYWORDS: artificial; COVID-19; furosemide; humans; inflammation; pneumonia; respiration

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can cause severe disease (COVID-19) including respiratory failure requiring mechanical ventilation and ICU admission. Although there was a paucity of therapies at the onset of the COVID-19 pandemic, both anti-viral (1, 2) and anti-inflammatory therapies have since emerged as effective treatments (3, 4).

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KEY POINTS

Question: Does anti-inflammatory therapy with inhaled furosemide, in addition to usual care, improve pulmonary gas exchange in patients with respiratory failure secondary to COVID-19?

Findings: This randomized, double-blind controlled study was stopped early due to waning incidence of severe respiratory failure caused by COVID-19. The addition of inhaled furosemide was safe but did not improve the primary outcome of pulmonary gas exchange within the first 6 days of randomization.

Meaning: Further adequately powered studies are warranted to investigate the anti-inflammatory effects of inhaled furosemide in acute respiratory failure where inflammation is a component of its pathophysiology.

Corticosteroids, which have broad anti-inflammatory activity, reduce morbidity and mortality in severe COVID-19 pneumonia (5). More focused anti-inflammatory strategies also reduce mortality and improve outcomes, including those targeting the interleukin-6 (IL-6) pathway, and Janus kinase (JAK)-mediated inflammation (6–8) with tumor necrosis factor α (TNF) also emerging as a possible therapeutic target (9).

Although current anti-inflammatory therapies have been shown to be effective for COVID-19, there are therapeutic concerns. They may be "too specific" since COVID-19 and other pulmonary infections are associated with elevation of multiple pro-inflammatory cytokines (10, 11). They are administered systemically (rather than locally to the lungs) and thus may produce systemic side effects such as myopathy and immunosuppression. Finally, agents other than corticosteroids are difficult and expensive to produce, resulting in shortages or complete nonavailability in developing countries. The ideal therapeutic agent for COVID-19 respiratory failure (and broadly, for respiratory failure secondary to lung inflammation) would have broad anti-inflammatory activity, could be delivered directly to the lungs, be inexpensive, easy to manufacture, and have little toxicity. Furosemide is a promising candidate that has all of these attributes.

Furosemide is an analog of 3-hydroxyanthranilic acid which is found diffusely throughout the human body and is able to reduce circulating levels of both IL-6 and TNF (12). Preclinical data demonstrate that furosemide exhibits anti-inflammatory effects. It has been found in vitro to reduce lipopolysaccharide-induced production of pro-inflammatory cytokines including IL-6 and TNF release, promotes the release of anti-inflammatory cytokine products (IL-1RA, arginase), and promotes the phenotypic change of macrophages from the pro-inflammatory M1 state to the anti-inflammatory M2 state (13). Incubated peripheral blood mononuclear cells stimulated with lipopolysaccharide produce less TNF, IL-6, and IL-8 in supernatants with the reduction in IL-8 levels comparable to that found with equivalent molar concentrations of hydrocortisone (14–16).

Furosemide is commonly administered as a diuretic either orally or intravenously, but it has a long history of administration by inhalation as a bronchodilator or for dyspnea (17–19). Multiple clinical investigations have reported reduction in lung IL-6, IL-8, and TNF levels upon administering inhaled furosemide to patients with respiratory conditions (20, 21). Dosing of inhaled furosemide is variable across studies, ranging from 20 to 120 mg per dose across studies with 40 mg of furosemide being the most commonly used dose (18, 22). No side effects or Adverse Events have been reported, except increased urine output at higher doses. The inhaled route of administration for furosemide is promising for respiratory disease owing to the low volume of distribution of furosemide; it primarily stays in the vasculature when given by oral or IV route. The inhalational route may provide higher concentrations of furosemide in alveolar and lung interstitial spaces than when administered systemically. Finally, furosemide is readily available around the world and is inexpensive.

Given these promising attributes, we sought to investigate the effect of inhaled furosemide as an adjunctive therapy in patients with respiratory failure requiring invasive mechanical ventilation secondary to COVID-19 in phase 2 of 3 randomized double-blinded placebo-controlled study with a planned efficacy analysis at the conclusion of phase II phase before proceeding to phase III. Herein, we report the phase II results.

MATERIALS AND METHODS

Nebulized Furosemide for Pulmonary Inflammation in Intubated Patients with COVID-19 (FAST-1) was a phase 2, double-blind, placebo-controlled, multicenter

randomized trial assessing the efficacy of inhaled furosemide in patients with COVID-19-associated respiratory failure requiring invasive mechanical ventilation. The study was registered on clinicaltrials.gov (NCT04588792). The **Consolidated Standards of Reporting Trials (CONSORT) checklist** (http://links.lww.com/CCX/B298) was used for writing this report (23). Patients were eligible for inclusion if they were adults over the age of 18 with:

1 Respiratory failure requiring invasive mechanical ventilation secondary to COVID-19 (SARS-CoV-2 infection) as confirmed by polymerase chain reaction from any source.
2 Duration of invasive mechanical ventilation less than 48 hours.

Patients were excluded if the following were present:

1) Known history of severe chronic pulmonary disease (e.g., preinfection requirement for home oxygen therapy or presence of chronic hypercapnia defined as a baseline $PaCO_2$ > 50 mm Hg).
2) In the opinion of the principal investigator, the patient was unlikely to survive for greater than 48 hours from time of enrollment.
3) Enrollment in another investigational trial studying anti-inflammatory therapies for COVID-19.
4) Known allergy to furosemide or sulfonamides. If the patient was allergic to sulfonamides but had or was receiving furosemide without incident, they could be enrolled since cross-reactivity between furosemide and sulfonamides is rare (24).
5) Pregnancy at the time of enrollment as determined by a serum or urine pregnancy test.

Study Procedures

Following confirmation of eligibility criteria, absence of exclusion criteria and signed informed consent, patients were randomized by study coordinators to study allocation using web-based randomization (www.randomize.net). Randomization used computer-generated permuted blocks of random size stratified by sex and center. Study medications were started within 6 hours of randomization and delivered through the endotracheal tube circuit using an in-line nebulizer over 30 minutes as per the nebulization protocol (**Supplemental Digital Content—Page 2**, http://links.lww.com/CCX/B298) and every 6 hours thereafter. The study interventions continued until extubation, liberation from mechanical ventilation, death, or the completion of 28 days of therapy. If a patient was re-intubated or resumed mechanical ventilation within 48 hours, the allocated study arm was resumed.

The allocation arms consisted of 40 mg furosemide in 4 mL of 0.9% saline in the experimental arm or 4 mL of 0.9% saline alone in the control group. We used commercially available supplies of furosemide (SteriMax Inc.) for the preparation of the nebulized solution at a concentration of 10 mg/mL based on previous clinical trials of inhaled furosemide. Both the furosemide solution and control solutions were prepared in sterile conditions and packaged into vials labeled with the trial number, study participant number, vial number, and any other required information as mandated by regulatory authorities. A no-objection letter was obtained from Health Canada for the administration of nebulized furosemide.

Study Blinding

Investigators, members of the clinical team, and patients were blinded to allocation. Furosemide and saline solutions were identical in appearance and solution characteristics. The investigational product was prepared by an unblinded study pharmacist, put in identical vials, and delivered to the clinical area. The unblinded study pharmacist did not have any contact with the clinical team, did not participate in clinical care, or had any other study role. Since the materials and study medications were readily available at each site, preparation of study materials was done locally to avoid the costs of preparing these solutions centrally and shipping them to their respective centers.

Outcomes

The primary outcome was improvement in oxygenation as determined by change in a standardized Pao_2/Fio_2 ratio determination between randomization and study day 6. In all patients, the Pao_2/Fio_2 ratio was determined after randomization before the first study treatment and on day 6. Standardization for the measurement of the Pao_2/Fio_2 ratio included stable ventilator settings defined as lack of change in ventilator settings for 30 minutes or longer, determination on a minimum of 10 cm H_2O positive end-expiratory pressure (PEEP) or higher if clinically indicated and a Fio_2 required to keep peripheral oxygen saturation 92–96%.

Secondary outcomes included all-cause mortality (ICU, hospital, and day 60), duration of mechanical ventilation, ventilator-free days (VFDs) (25), oxygen-free days (26, 27), and length of stay (ICU and hospital).

Exploratory post hoc analyses included Pao_2/Fio_2 ratio over time in the 28 days postrandomization in those alive and still in the ICU and alive ventilator free as defined by Novack et al (28). Safety was measured as the occurrence of serious adverse events in accordance with guidelines for academic ICU drug trials (29) and the occurrence of allergic reactions.

Statistical Analysis

Sample size was calculated to detect a clinically significant change in Pao_2/Fio_2 at 6 days which we defined as at least 40 mm Hg. To achieve 80% power at a one-sided alpha equal to 0.025 to detect an increase of 40 in the Pao_2/Fio_2 ratio using analysis of covariance (ANCOVA) adjusting for baseline Pao_2/Fio_2, conservatively assuming no correlation between the baseline and 6-day Pao_2/Fio_2 and allowing for 10% missing data required a sample size of 72 patients per arm or 144 patients total. This sample size would have 90% power if the within-patient correlation between the baseline and 6-day Pao_2/Fio_2 is $r = 0.5$ (i.e., 25% of the variance in 6-day Pao_2/Fio_2 explained by baseline Pao_2/Fio_2). The 144 phase II patients were to have been enrolled into a phase III trial if the phase II null hypothesis that inhaled furosemide does not increase the 6-day Pao_2/Fio_2 compared with usual care was rejected. The primary outcome of the phase III trial was to have been 28-day VFDs (25).

The primary analysis followed intention-to-treat principles. The change in Pao_2/Fio_2 (primary outcome) was calculated by subtracting the baseline Pao_2/Fio_2 ratio from the day 6 Pao_2/Fio_2 among survivors. The difference in the change in Pao_2/Fio_2 between treatment arms was estimated by ANCOVA with treatment group and sex as fixed factors and baseline Pao_2/Fio_2 as a covariate. The conclusions were confirmed by a rank-based analysis in which decedents before day 6 were ranked lowest, and any participants who were discharged from the ICU alive before day 6 were ranked highest. All numeric variables were compared between groups by the van Elteren test stratified by sex; the one exception was the post hoc alive and VFD which followed the approach of Novak (28) by applying the Wilcoxon Rank-Sum test to the total scores calculated by comparing the outcome of the current patient to each other patient and adding a 1, 0, and –1 to the current patient's total score if the outcome of the current patient was better, tied, or worse respectively compared with the other patient; this scoring considers death within 28 days as worse than any number of alive-free days." All binary variables were compared between groups by the Mantel-Haenszel test stratified by sex, except variables with less than five events in either group were tested by the Fisher Exact test. Due to the smaller than expected sample size (with multiple sites enrolling a single patient), we did not stratify the analysis by site as initially planned. The analysis was performed using SAS Version 9.4 (SAS Institute Inc., Cary, NC).

Ethics and Informed Consent

The study was approved by the Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board (file no. 6030813, approved on November 4, 2020 under the name: CCM-027-20; FAST-1—Nebulized Furosemide for Pulmonary Inflammation in Intubated Patients with COVID-19—a Phase 2 of 3 Study) and each of the local research ethics boards of participating hospitals. Informed consent was obtained from each study participant or their substitute decision-maker before any study procedures were conducted. All study procedures followed were in accordance with the ethical standards of responsible committees on human experimentation and with the Helsinki Declaration of 1975.

RESULTS

Health Canada approval for the study was received on October 13, 2020. The study was operationalized in four tertiary ICUs in Canada and three tertiary ICUs in the Republic of Georgia. Owing to a dearth of COVID-associated respiratory failure in participating ICUs, the study was stopped early due to lack of recruitment in February 2023. The CONSORT diagram is outlined in **Figure 1** with a total of 40 patients randomized and 39 patients available for analysis. Baseline characteristics are in **Table 1**. The study cohort had a mean age ± SD of 70.5 ± 10.8 years old with an Acute Physiology and Chronic Health Evaluation II of 26.1 ± 7.8. Almost all subjects 38 of 39 (97%) were treated with corticosteroids, and 23 of 39 (59%) received additional anti-inflammatory therapies. At enrollment, average Fio_2 requirement was 60.0 ± 21.9% with a PEEP of 12.0 ± 3.6 cm H_2O.

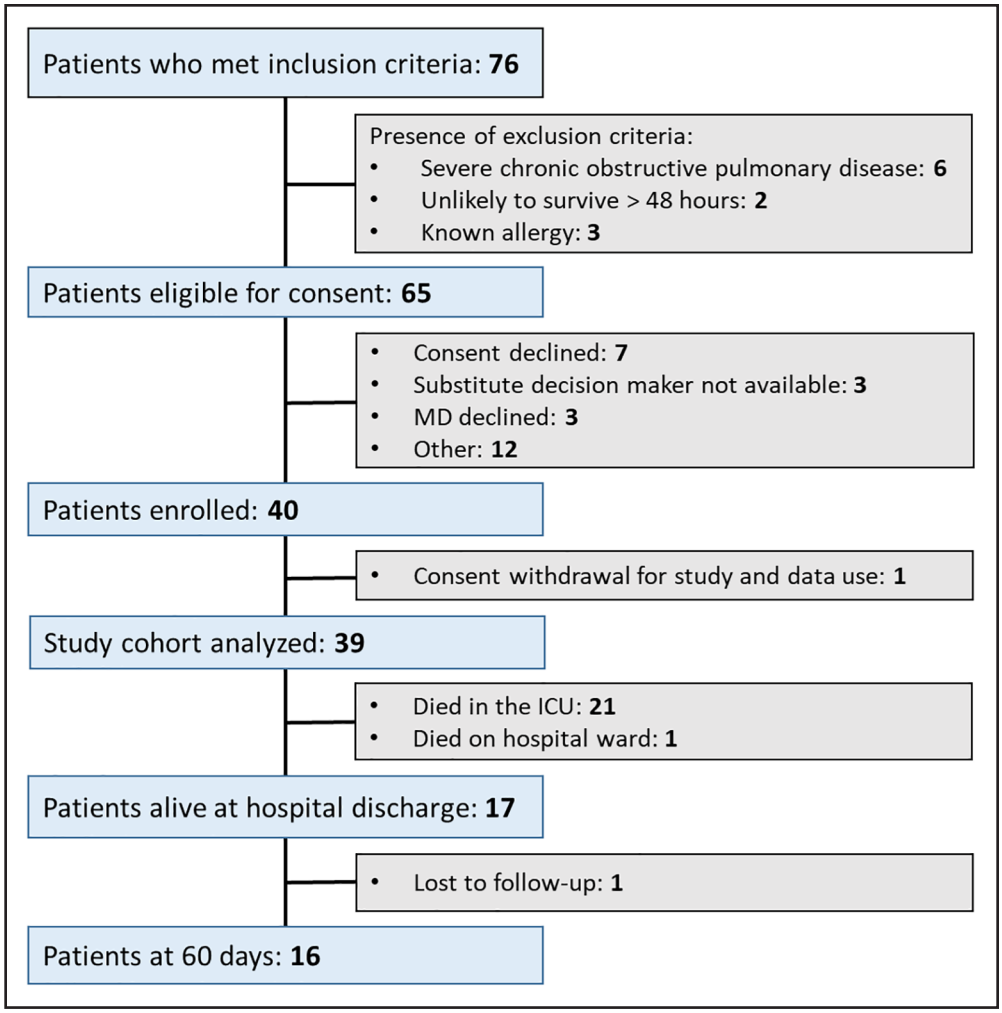

Figure 1. Consolidated Standards of Reporting Trials diagram.

Data from the course of enrolled patients are outlined in **Table 2**. Patients in both arms received approximately 15 days of study treatments with approximately 54 doses of either inhaled furosemide or placebo (14.6 ± 9.29 vs. 14.7 ± 10.8, $p = 1.0$, 54.0 ± 37.6 vs. 54.9 ± 41.6, $p = 1.0$ respectively). Maximum Sequential Organ Failure Score (SOFA) (30) was similar in the inhaled furosemide group versus placebo group (12.2 ± 2.9 vs. 13.7 ± 3.0, $p = 0.1$). Mean daily fluid balance was not significantly different between inhaled furosemide and placebo (median [interquartile range, IQR]: 202.0 [–188.6, 1553.0] vs. 513.9 [234.3, 1573.9]), respectively. No adverse events or allergic reactions were noted.

For the primary outcome of the difference in Pao_2/Fio_2 ratio between day 1 and day 6, the change in Pao_2/Fio_2 ratio was +31.4 ± 83.5 in the furosemide arm versus +20.1 ± 92.8 in the control. The difference in change in Pao_2/Fio_2 ratio between the arms after controlling for baseline Pao_2/Fio_2 ratio and sex via ANCOVA was found to be 14.7 (95% CI, –36.8, 66.2, $p = 0.56$). A rank-based analysis of Pao_2/Fio_2 ratio in which those who died before day 6 were assigned the lowest rank, and any participants who exited ICU alive before day 6 were assigned the highest rank, showed no significant difference between furosemide and placebo, respectively, in change in Pao_2/Fio_2 ratio (*n*, median [IQR]: 19, 30.0 [–67.0, 85.4] vs. 18, –26.7 [–98.5, 81.4], $p = 0.42$). **Table 3** and **Supplemental Figure 1** (http://links.lww.com/CCX/B298) outline primary outcome. **Table 4** reports the secondary outcomes; ICU, hospital, and 60-day mortality, duration of mechanical ventilation, VFDs, oxygen-free days, and length of stay were not significantly different between the groups. The average value across the 28 days in Pao_2/Fio_2 ratio was not significantly different between arms ($p = 0.58$). **Figure 2** charts the Pao_2/Fio_2 ratio curves over time in those who were alive, remained ventilated, and continued to receive study therapy. When comparing treatment arms on the basis of the alive and ventilator-free score, the probability of a randomly selected patient from the furosemide arm faring better than one randomly selected from the placebo arm was 76% (95% CI, 58–87%) with a corresponding Wilcoxon rank-sum test *p* value of 0.04.

DISCUSSION

The COVID-19 pandemic necessitated urgent efforts to develop therapies leading to the identification of the pivotal role that anti-inflammatory therapies, including corticosteroids, have in its treatment. Targeting

TABLE 1.
Baseline Characteristics

Characteristics	Furosemide, Mean ± SD or *n* (%), *n* = 21	Control, Mean ± SD or *n* (%), *n* = 18
Age (yr)	71.0 ± 10.0	70.1 ± 12.0
Sex, female	9 (43%)	6 (33%)
Charlson Comorbidity Index	1.5 ± 1.4	1.9 ± 2.2
Acute Physiology and Chronic Health Evaluation II Score	26.2 ± 7.1	25.8 ± 8.8
Primary diagnosis		
Respiratory	19 (90%)	18 (100%)
Gastrointestinal	1 (5%)	0 (0%)
Neurologic	1 (5%)	0 (0%)
Clinical Frailty Scale	3.9 ± 1.4	4.0 ± 1.5
On vasopressors	12 (57%)	15 (83%)
Dialysis in first 24 hr	1 (5%)	1 (6%)
Remdesivir use	4 (19%)	2 (11%)
COVID-19 adjunctive therapies		
Corticosteroids	20 (95%)	18 (100%)
Tocilizumab	11 (52%)	10 (56%)
Sarilumab	0 (0%)	0 (0%)
Baricitinib	1 (5%)	1 (6%)
Arterial blood gases		
FIO_2	59.1 ± 22.9	61.1 ± 21.4
PaO_2 (mm Hg)	90.7 ± 28.1	80.4 ± 28.5
$PaCO_2$ (mm Hg)	45.5 ± 12.2	45.5 ± 18.6
PaO_2/FIO_2 ratio	165.1 ± 76.0	157.1 ± 55.8
Ventilator settings		
Positive end-expiratory pressure (cm H_2O)	12.1 ± 4.0	11.8 ± 3.2
Tidal volume (mL)	459.0 ± 119.8	427.4 ± 70.5
Tidal volume (mL/ideal body weight)	7.2 ± 1.7	6.6 ± 1.1
Peak airway pressure (cm H_2O)	28.1 ± 6.2	25.83 ± 5.5
Respiratory rate-beats/min	23.4 ± 4.7	24.00 ± 4.4

the lung directly with an anti-inflammatory therapy has the potential benefit of avoiding systemic side effects. The anti-inflammatory activity of furosemide, its prior history of administration by inhalation, its long history of safety, and its low cost led to our efforts to study inhaled furosemide for COVID-19-associated respiratory failure. Unfortunately, operationalization and recruitment into the study were delayed and with time, COVID-19 respiratory failure requiring invasive mechanical ventilation virtually disappeared, leading to the premature termination of this study. However, there is still an unmet need of novel treatments for acute inflammatory respiratory conditions, including those due to common and emerging infections.

In the patients enrolled, the allocation groups were well balanced at baseline with patients meeting criteria for severe acute respiratory distress syndrome (ARDS) based on an average PaO_2/FIO_2 ratio of approximately 160. The vast majority received systemic nonprotocolized anti-inflammatory therapies for COVID-19. For the study primary outcome, there was an absence of a significant difference in the change of PaO_2/FIO_2 ratio

TABLE 2.
Characterization of Course in ICU

Variable	Furosemide	Control
Max SOFA	11.4 ± 3.2	13.7 ± 3.0
Mean SOFA	8.7 ± 3.6	10.0 ± 3.4
Mean positive end-expiratory pressure	10.8 ± 3.7	10.5 ± 3.0
Mean F_{IO_2}	54.1 ± 21.0	58.7 ± 19.3
Required prone ventilation	12 (57%)	9 (50%)
Days of prone ventilation	4.3 ± 3.8	6.1 ± 5.4
Required extracorporeal membrane oxygenation	2 (10%)	0 (0%)
New dialysis	1 (5%)	3 (17%)
Ever delirious	18 (86%)	16 (89%)
Ever positive culture	14 (67%)	9 (50%)
Number of positive cultures	2.1 ± 2.8	1.8 ± 2.8
Ever on anticoagulants	21 (100%)	18 (100%)
Ever adverse event	0 (0%)	0 (0%)
Days on corticosteroids	12.0 ± 8.0	11.0 ± 8.4
Days on diuretics	10.5 ± 7.9	9.1 ± 8.0
Days on pulmonary vasodilators	1.2 ± 3.1	2.2 ± 4.4
Days on vasopressors	8.7 ± 6.6	10.3 ± 7.9
Days on antibiotics	11.8 ± 8.9	10.1 ± 8.8
Mean fluid balance (median, interquartile range)	202.0 [−188.6, 1553.0]	513.9 [234.3, 1573.9]
Days on study drug	14.6 ± 9.3	14.7 ± 10.8
Study drug doses received	54.0 ± 37.6	54.9 ± 41.6

SOFA = Sequential Organ Failure Score.
Reported as mean ± SD or *n* (%) unless noted otherwise. No variables differed significantly between groups with all $p \geq 0.09$.

TABLE 3.
Primary Outcome

Pa_{O_2}/F_{IO_2} Ratio	Furosemide, *n* = 21	Control, *n* = 18
Among survivors remaining in ICU on day 6: [*n*] mean ± SD		
Day 1 Pa_{O_2}/F_{IO_2} ratio	[21] 165.1 ± 76.0	[18] 157.1 ± 55.8
Day 6 Pa_{O_2}/F_{IO_2} ratio	[17] 198.0 ± 59.8	[13] 183.9 ± 72.7
Change in Pa_{O_2}/F_{IO_2} ratio from day 1 to day 6	[17] 31.4 ± 83.5	[13] 20.1 ± 92.8
Ranked analysis counting death before day 6 Pa_{O_2}/F_{IO_2} ratio as worst value and discharge before day 6 Pa_{O_2}/F_{IO_2} ratio as best value: median [Q1, Q3]		
Day 1 Pa_{O_2}/F_{IO_2} ratio	161.0 [120.0, 215.0]	148.0 [111.0, 220.0]
Day 6 Pa_{O_2}/F_{IO_2} ratio	191.4 [137.0, 236.7][a]	148.4 [90.5, 207.0]
Change in Pa_{O_2}/F_{IO_2} ratio from day 1 to day 6	30.0 [−67.0, 85.4][a]	−26.7 [−98.5, 81.4]

[a]Two patients were excluded because they remained alive in ICU but did not have a day 6 Pa_{O_2}/F_{IO_2} ratio.

TABLE 4.
Secondary Outcomes

Outcome	Furosemide, *n* (%) or (*n*), Mean ± SD	Control, *n* (%) or (*n*), Mean ± SD	*p*
ICU mortality	10/21 (48%)	11/18 (61%)	0.45
Hospital mortality	10/21 (48%)	12/18 (67%)	0.28
60-d mortality	10/21 (48%)	12/17 (71%)	0.19
Duration of mechanical ventilation	[21] 14.8 ± 9.2	[18] 15.4 ± 10.9	0.93
Ventilator-free days	[21] 6.0 ± 9.1	[18] 3.1 ± 7.1	0.42
Oxygen-free days	[21] 4.3 ± 6.8	[18] 2.0 ± 5.8	0.16
Average daily Pao_2/Fio_2 ratio	[21] 184.7 ± 72.1	[18] 168.4 ± 63.1	0.58
ICU LOS	[21] 20.7 ± 17.2	[18] 25.6 ± 23.5	0.89
Hospital LOS	[21] 25.6 ± 21.9	[18] 27.4 ± 25.0	0.99

LOS = length of stay.

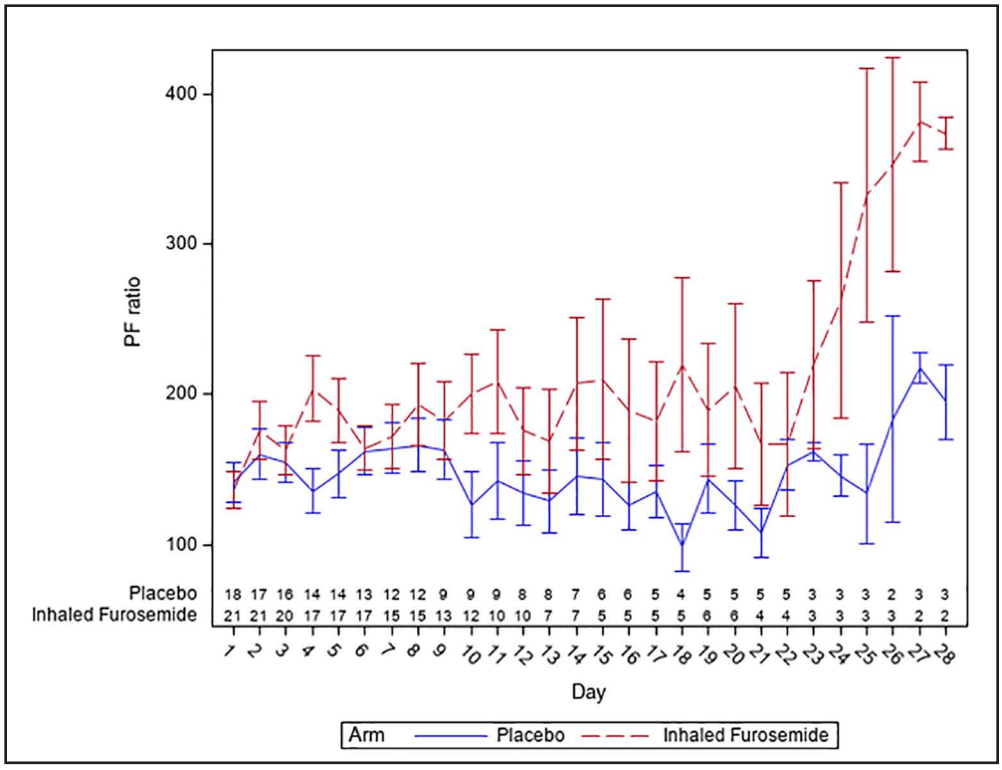

Figure 2. Pao_2/Fio_2 (PF) ratio over the ICU stay. *Error bars* depict 1 SE above and below the mean. Number of patients on each day contributing data is indicated at the bottom of the graph.

over the first 5 days of treatment between the groups. In addition, there were no significant differences between the groups in our a priori-defined secondary outcomes. In the exploratory analysis of the hierarchal composite outcome alive and ventilator free (28), which overcomes some of the limitations of VFDs, patients in the furosemide group were statistically more likely to have a superior outcome although this finding may be spurious due to the small number of patients. There were no adverse events reported supporting prior evidence of the safety of inhaled furosemide.

Due to the small number of patients enrolled in this study, it was underpowered and the findings from this study, especially the post hoc exploratory analyses should be considered hypothesis-generating and tested in future studies. The possible separation of Pao_2/Fio_2 ratio curves over time in those remaining in the ICU and mechanically ventilated starting after 9–10 days in contrast to no difference between day 1 and day 6, may indicate that the inhaled furosemide may require time to have effect or only have impact when the effects of anti-inflammatory therapy delivered on ICU admission started to wane. VFDs were not significantly different between groups but when analyzed using the alive and ventilator-free hierarchical outcome, patients in the furosemide arm fared significantly better than the placebo group, may be accounted for by the increased number of deaths in the placebo group. Although our data need to be considered

in the design of future larger adequately powered studies of inhaled furosemide, these findings are in a small number of patients and should be considered fragile (31).

Daily fluid balance was similar between the groups. The lack of a significant difference in fluid balance between the two groups may make it more likely that any effects seen are from furosemide's anti-inflammatory activity rather than a diuretic effect. Future studies should continue to report on fluid balance to look at the diuretic effects of nebulized furosemide and study the inflammatory milieu in the lungs using bronchoalveolar lavage, as well as changes in systematic inflammation in response to inhaled furosemide.

Although the incidence of COVID-19-associated respiratory failure has diminished, there is still an unmet need for novel treatments for acute inflammatory respiratory conditions, including common and emerging infections, causing respiratory failure. Modifying the pulmonary inflammatory cascade for respiratory infections in general is emerging as key therapeutic aim (32, 33). Recent data suggest that corticosteroids are effective adjunctive therapies for community-acquired pneumonia although the evidence has been conflicting in the past (34, 35). However, corticosteroids may have systemic effects including muscle weakness, impaired glucose tolerance, etc. that may decrease their therapeutic index. A therapy with limited systemic activity such as inhaled furosemide could overcome these limitations. The pivot of COVID-19 studies to non-COVID-19 conditions is being increasingly done and may be particularly applicable to respiratory failure due to similarities between COVID-19 and non-COVID-19 ARDS (36).

Strengths of this study include that it was placebo-controlled, double-blind, and randomized. Limitations include the small sample size including the possibility that any observed differences were due to chance, the premature stopping of the study due to lack of recruitment, and inability to stratify by site due to low patient numbers.

CONCLUSIONS

In this phase II randomized placebo-controlled trial of inhaled furosemide for severe COVID-19 pneumonia, enrollment was stopped early due to slow recruitment. Inhaled furosemide was well tolerated with no adverse events reported. Although outcomes tended to be in the direction favoring furosemide, there were no significant differences in the primary outcome of improvement in Pao_2/Fio_2 ratio at day 6 or in any prespecified secondary outcomes. These findings should be considered hypothesis-generating, with further study required to determine the effect of inhaled furosemide on acute inflammatory lung disease from various etiologies.

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