ORIGINAL ARTICLE

Prostacyclin in Intubated Patients with COVID-19 and Severe Endotheliopathy

A Multicenter, Randomized Clinical Trial

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Abstract

Rationale: The mortality in patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) who require mechanical ventilation remains high, and endotheliopathy has been implicated.

Objectives: To determine the effect of prostacyclin infusion in mechanically ventilated patients infected with SARS-CoV-2 with severe endotheliopathy.

Methods: We conducted a multicenter, randomized clinical trial in adults infected with coronavirus disease (COVID-19) who required mechanical ventilation and had a plasma level of thrombomodulin >4 ng/ml; patients were randomized to 72-hour infusion of prostacyclin 1 ng/kg/min or placebo.

Measurements and Main Results: The main outcome was the number of days alive and without mechanical ventilation within 28 days. Key secondary outcomes were 28-day mortality and serious adverse events within 7 days. Eighty patients were randomized (41 prostacyclin and 39 placebo). The median number of days alive without mechanical ventilation at 28 days was 16.0 days (SD, 12) versus 5.0 days (SD, 10) (difference of the medians, 10.96 days; 95% confidence interval [CI], −5 to 21; $P = 0.07$) in the prostacyclin and the placebo groups, respectively. The 28-day mortality was 21.9% versus 43.6% in the prostacyclin and the placebo groups, respectively (risk ratio, 0.50; 95% CI, 0.24 to 0.96; $P = 0.06$). The incidence of serious adverse events within 7 days was 2.4% versus 12.8% (risk ratio, 0.19; 95% CI, 0.001 to 1.11; $P = 0.10$) in the prostacyclin and the placebo groups, respectively.

Conclusions: Prostacyclin was not associated with a significant reduction in the number of days alive and without mechanical ventilation within 28 days. The point estimates, however, favored the prostacyclin group in all analyses, including 28-day mortality, warranting further investigation in larger trials.

Clinical trial registered with www.clinicaltrials.gov (NCT 04420741); EudraCT Identifier: 2020-001296-33.

Keywords: COVID-19; endotheliopathy; thrombomodulin; prostacyclin

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Data sharing statement: Data collected for the study, including deidentified participant data and related documents, including the protocol, statistical analysis plan, and informed consent form, will be made available to qualified researchers after publication of the manuscript upon reasonable request via application to the corresponding author (P.I.J.).

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At a Glance Commentary

Scientific Knowledge on the Subject: The mortality in patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) who require mechanical ventilation remains high. Endotheliopathy, including cleavage of thrombomodulin from the endothelial cell membrane leading to a perturbed protein C system, has been implicated as a pivotal pathophysiological mechanism linked to the development of multiorgan failure and high mortality.

What This Study Adds to the Field: This randomized clinical trial found that low-dose prostacyclin infusion for 72 hours was not associated with a significant reduction in the number of days alive and without mechanical ventilation within 28 days. Furthermore, the point estimates favored the prostacyclin group in all analyses, including mortality. A significant reduction in the mean Sequential Organ Failure Assessment score in the ICU until Day 90, however, was observed in the prostacyclin group. No difference in serious adverse reactions or serious adverse events were observed, and collectively, these data merit further investigation in adequately powered randomized clinical trials.

As of October 11, 2021, more than 236 million people have been infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection globally, with more than 4.8 million deaths (1). To date, only glucocorticoids and IL-6 receptor antagonists are known to improve survival among those severely ill with coronavirus disease (COVID-19) (2–4). Mortality rates around 30–40% have been reported in patients with critical COVID-19 and are highest in those requiring invasive mechanical ventilation (5). In autopsy series, microvascular thrombosis of the pulmonary vasculature has frequently been observed (6–9). These findings are in alignment with the observation of endotheliopathy as a prominent feature of the COVID-19 acute respiratory distress syndrome pathophysiology (10–12). Similar to findings in patients with varying degrees of other severe infections (13), the level of circulating soluble thrombomodulin (sTM) was significantly associated with mortality in patients with COVID-19 (10). Thrombomodulin is a key member of the anticoagulant protein C system, and its cleavage from the endothelium may be involved in the pathophysiology of the prothrombotic phenotype observed in patients with COVID-19 (14).

Prostacyclin (PGI_2) is an endogenous prostanoid formed and released by endothelial cells, with paracrine function including dose-dependent vasodilation and platelet inhibition being the rationale for its use as a pharmacological therapy for patients with primary pulmonary hypertension and critical limb ischemia (15, 16). In the new millennium, multiple beneficial effects of prostacyclin on the endothelium were reported (17–23). In clinical trials in critically ill patients in the ICU, including those with septic shock, the use of low-dose (0.5–2.0 ng/ml/kg) continuous infusion of prostacyclin as compared with placebo was safe (24–26).

The aim of the present randomized controlled trial was, therefore, to investigate the safety and the efficacy of prostacyclin as compared with placebo on days alive without mechanical ventilation within 28 days in mechanically ventilated patients with COVID-19 with documented endotheliopathy, as measured by a circulating sTM level of ⩾4 ng/ml (27).

Methods

Design and Patients

This is a Danish multicenter, randomized (1:1, active: placebo), blinded, parallel-grouped exploratory trial of low-dose continuous infusion of prostacyclin versus placebo for 72 hours in mechanically ventilated patients with COVID-19.

Inclusion criteria were adult (aged ⩾18 yr) patients with confirmed SARS-CoV-2 infection who were invasively mechanically ventilated and had a level of circulating sTM >4 ng/ml measured using a lateral flow immunoassay (BioPorto Diagnostics A/S) (Figure 1).

Exclusion criteria were invasive mechanical ventilation for more than 72 hours; withdrawal from active therapy; pregnancy (nonpregnancy was confirmed by the patient being postmenopausal [aged ⩾60 yr] or having a negative urine or plasma human choriongonadotropin); known hypersensitivity to prostacyclin (iloprost) or to any of the other ingredients in the infusion; previously included in this trial or a prostacyclin trial within 30 days; consent could not be obtained; life-threatening bleeding as defined by the treating doctor; known severe heart failure (New York Heart Association class IV); or suspected acute coronary syndrome. Additional details concerning randomization are provided in the online supplement.

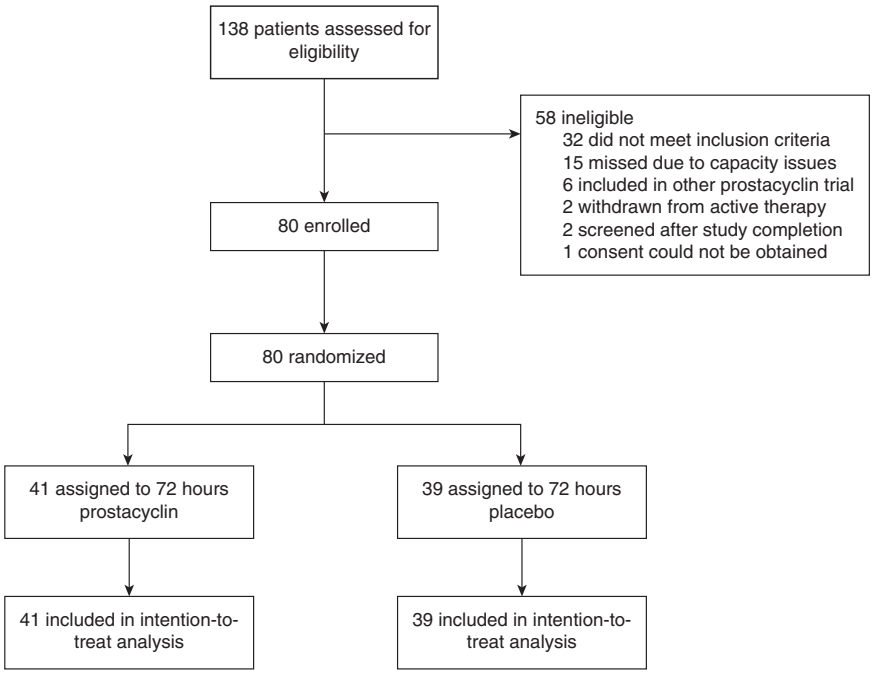

Figure 1. Trial profile.

Outcomes

The primary outcome was the number of days alive without mechanical ventilation within 28 days from randomization. Secondary outcomes included 28- and 90-day mortality, mean daily Sequential Organ Failure Assessment (SOFA) score in the ICU up to Day 90, days alive without vasopressor in the ICU within 28 and 90 days, days alive without mechanical ventilation in the ICU within 90 days, days without renal replacement in the ICU within 28 and 90 days, number of serious adverse reactions within the first 7 days, and number of serious adverse events within the first 7 days.

Treatment

Prostacyclin (1 ng/kg/min) or placebo (equal volume of saline) was administered as a continuous intravenous infusion for 72 hours.

Procedures

All patients were assessed from randomization (Day 1) through Day 90. Adverse events were recorded from time of signature of informed consent and graded according to the Common Terminology Criteria for Adverse Events, version 5.0. Causality was assessed by the investigators for serious adverse events.

Statistical Analyses

Sample size estimation was based on a power calculation using the data from a randomized clinical trial in patients with acute respiratory distress syndrome (NTC 02622724) (28).

The mean number of days alive and free of mechanical ventilation was 10 days, with an SD of 3. If the true effect of the intervention is an increase in days alive and free of mechanical ventilation of 20% (relative), providing the trial with 80% power to detect this difference at a significance level of 0.05 will require a sample size of 70 patients. To allow for an ∼10% dropout, 80 patients were included (clinicaltrials.gov identifier: NCT04420741).

All analyses were performed in the intention-to-treat (ITT) population, defined as all randomized patients. The primary outcome was compared using the Wilcoxon test and differences expressed as changes in medians with non–parametric-based bootstrapped 95% confidence interval (CI) and the SD for the respective arms.

The secondary outcomes, 28- and 90-day mortality, were compared in the ITT population using Fisher exact test and effect size expressed as risk ratios with 95% CIs. The mean daily SOFA score was computed based on all postbaseline measurements of SOFA. The intervention groups were compared using a simple analysis of covariance adjusted for baseline SOFA score. Effects are described as adjusted change in mean postbaseline daily SOFA scores together with a 95% CI. Other secondary outcomes were compared using the Wilcoxon test and differences expressed as changes in medians with non–parametric-based bootstrapped 95% CI.

Ethics

The protocol was approved by the Danish regional ethics committee (H-20026049) and the Danish Medicines Agency (Eudract no. 2020-001296-33). The study was registered at clinicaltrials.gov, NCT 04420741.The study was conducted at five university hospital ICUs in the Capital Region of Denmark in accordance with Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. Written informed consent, in accordance with national legislation, was obtained from the patient's surrogate and confirmed by the patients who regained consciousness.

Results

Patients

Between June 15, 2020, and January 25, 2021, 138 patients were screened and 80 randomized, among whom 41 were allocated to prostacyclin and 39 to placebo; five patients discontinued the intervention (Figure 1). Baseline characteristics were generally well balanced between the intervention groups (Table 1).

Primary Outcome

In the ITT population, the number of days alive without mechanical ventilation at 28 days was a median of 16.0 days (SD, 12) versus 5.0 days (SD, 10) (difference of the medians, 10.96; 95% CI, −5 to 21; $P = 0.07$) in the prostacyclin group versus the placebo group, respectively (Table 2).

Table 1. Characteristics of the Patients at Baseline according to Treatment Assignment

	Prostacyclin Group (*n* = 41)	Placebo Group (*n* = 39)
Age, yr	68 (60–73)	66 (57–75)
Sex		
M	30 (73)	23 (59)
F	11 (27)	16 (41)
Ethnicity		
White	38 (93)	37 (95)
Asian	0 (0)	2 (5)
Black	2 (5)	0 (0)
Hispanic	1 (2)	0 (0)
Other	0 (0)	0 (0)
Admitted from		
Emergency room	9 (22)	11 (28)
Ward	28 (68)	27 (69)
Operating room/postoperative care	1 (2)	0 (0)
Other ICU	3 (7)	1 (3)
Comorbidity		
Chronic cardiovascular disease	26 (63)	23 (59)
Chronic respiratory disease	6 (15)	4 (10)
Metastatic cancer	1 (2)	0 (0)
Hematological cancer	1 (2)	3 (8)
End-stage renal disease	1 (2)	1 (3)
Clinical observations at inclusion		
SOFA score at day of randomization	7 (6–9)	7 (6–9)
Lowest SBP 24 h before randomization, mm Hg	85 (77–93)	82 (74–89)
Vasopressor 24 h before randomization	37 (90)	34 (87)
RRT 24 h before randomization	1 (2)	2 (5)
Acute surgery 24 h before randomization	1 (2)	0 (0)
Mechanical ventilation before screening, h	12 (1–21)	15 (9–20)
ICU admission before screening, h	28 (11–62)	21 (12–44)

Definition of abbreviations: RRT = renal replacement therapy; SBP = systolic blood pressure; SOFA = Sequential Organ Failure Assessment.
Data are shown as *n* (%) or median (interquartile range).

Table 2. Outcome Measures according to Treatment Assignment

	Prostacyclin Group (*n* = 41)	Placebo Group (*n* = 39)	Difference of the Medians, Adjusted Difference of the Means, or Risk Ratio (CI)	*P* Value
Primary endpoint				
Median days alive without mechanical ventilation in the ICU at 28 d (intention-to-treat)	16	5.04	10.96 (−5 to 21)	0.07
Median days alive without mechanical ventilation in the ICU at 28 d (per protocol)	15	3.02	11.98 (−6 to 21)	0.08
Secondary endpoints				
Mortality at 28 d	9 (21.9)	17 (43.6)	0.50 (0.24 to 0.96)	0.06
Mortality at 90 d	13 (31.7)	19 (48.7)	0.65 (0.36 to 1.12)	0.17
Mean daily SOFA score adjusted for baseline values	5.75	6.67	1.1 (0.28 to 1.92)	0.009
Median days alive without vasopressor in the ICU at 28 d	22	13	9 (−1.5 to 18)	0.14
Median days alive without vasopressor in the ICU at 90 d	84	59	25 (−3 to 75.5)	0.16
Median days alive without RRT in the ICU at 28 d	28	21	7 (0 to 12)	0.06
Median days alive without RRT in the ICU at 90 d	90	79	11 (−2.5 to 74)	0.08
Median days alive without mechanical ventilation in the ICU at 90 d	77	13	64 (−6 to 80)	0.10
Serious adverse event(s) within 7 d	1 (2.4)	5 (12.8)	0.19 (0.01 to 1.11)	0.10
Serious adverse reaction(s) within 7 d	0 (0)	0 (0)	—	—

Definition of abbreviations: CI = confidence interval; RRT = renal replacement therapy; SOFA = Sequential Organ Failure Assessment.
Data are shown as *n* (%) unless otherwise stated.
For secondary endpoints, only the intention-to-treat population is analyzed.

Secondary Outcomes

The 28-day mortality was 21.9% in the prostacyclin group versus 43.6% in the placebo group (risk ratio, 0.50; 95% CI, 0.24 to 0.96; $P = 0.06$). The 90-day mortality was 31.7% versus 48.7% (risk ratio, 0.65; 95% CI, 0.36 to 1.12; $P = 0.17$) in the prostacyclin group versus the placebo group, respectively (Figure 2). The SOFA score was 5.7 versus 6.7 (adjusted difference, 1.1; 95% CI, 0.28 to 1.92; $P = 0.009$) in the prostacyclin group versus the placebo group, respectively. The median days alive and free of renal replacement therapy in the ICU within 28 days was 28 days versus 21 days (difference of the medians, 7 days; 95% CI, 0 to 12; $P = 0.06$) and at 90 days was 90 versus 79 days (difference of the medians, 11 days; 95% CI, −2.5 to 74; $P = 0.08$) in the prostacyclin group versus the placebo group, respectively. The median days alive and free of vasopressors in the ICU within 28 days was 22 days versus 13 days (difference of the medians, 9; 95% CI, −18 to 1.5; $P = 0.14$) and within 90 days was 84 days versus 59 days (difference of the medians, 25 days; 95% CI, −3 to 75.5; $P = 0.16$) in the prostacyclin group versus the placebo group, respectively. The number of days alive and free of mechanical ventilation within 90 days was 77 days versus 13 days (difference of the medians, 64 days; 95% CI, −6 to 80; $P = 0.10$) in the prostacyclin group versus the placebo group, respectively.

Safety Outcomes

No significant difference between groups was found regarding serious adverse events and reactions within 7 days. The incidence was 2.4% versus 12.8% (risk ratio, 0.19; 95% CI, 0.001–1.11; $P = 0.10$) in the prostacyclin group versus the placebo group, respectively (Table 2).

Discussion

In this multicenter randomized trial, we did not find a statistically significantly difference in the number of days alive without mechanical ventilation within 28 days among patients with COVID-19 allocated to prostacyclin or placebo for 72 hours. The point estimate, however, did favor the prostacyclin group; the same was found for all the secondary outcomes, among which the mean daily SOFA scores were statistically significantly lower in the prostacyclin group than in the placebo group.

Prostacyclin has been reported to have several beneficial effects on the endothelium, including synthesizing endothelial glycocalyx constituents (17, 18), inducing reendothelization of damaged vessels (20), improving tight-junction integrity (19), and attenuating the inflammatory hit on the endothelium (21, 22). In alignment with this, the patients with COVID-19 included in this study were characterized by severe pulmonary failure requiring mechanical ventilation and severe endotheliopathy, as evidenced by circulating sTM levels at ⩾4 ng/ml (10), and we speculate that prostacyclin may be responsible for the results observed. Improvement in clinical condition of patients with severe COVID-19 secondary to infusion of prostacyclin was also recently reported by Moezinia and colleagues, who, in a case series of three patients, found that 5-day continuous infusion of low-dose prostacyclin was associated with decreasing oxygen requirements, increasing Pa_{O_2}: Fi_{O_2} ratio, and normalization of heart rate up to 48 hours, suggesting an improvement in vital organ function (29).

We found no difference in serious adverse events or reactions between the groups, indicating that prostacyclin at a dose of 1 ng/kg/min may be safe in critically ill patients with COVID-19 and severe endotheliopathy. These findings are corroborated by results from randomized clinical trials in patients receiving liver transplantation (24) and patients with septic shock (26).

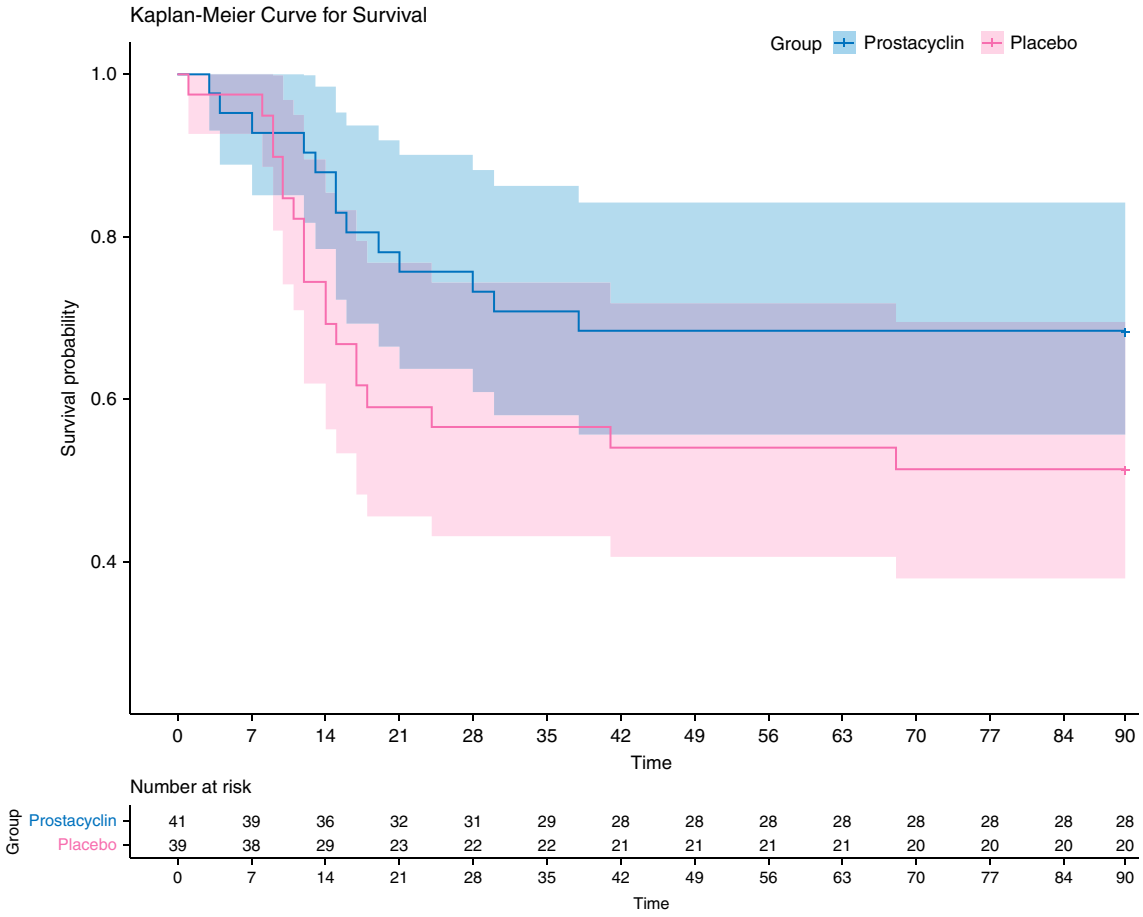

Figure 2. Kaplan-Meier curve of 28- and 90-day survival probability according to allocation (prostacyclin vs. placebo group).

The limited sample size, rendering the study underpowered, precludes firm conclusions about prostacyclin's effects on the primary and secondary outcome measures. Also, all patients were enrolled in ICUs in the Capital Region of Denmark only, which may reduce the generalizability of the results. Furthermore, a potential effect of coenrollment of the patients in other interventional clinical trials cannot be excluded. Lastly, the preplanned statistical methods used to investigate the mortality, CI (generalized linear model) and *P* value (Fisher exact test), may lead to different results in borderline cases, such as here, and this is a limitation for the interpretation of the results. The observed risk ratio of 0.5 and the trend observed for lower mortality suggest that a larger study or a meta-analysis of studies will be required to demonstrate a beneficial effect of the intervention.

In conclusion, we did not observe a statistically significant difference in the number of days alive without mechanical ventilation within 28 days among mechanically ventilated patients with COVID-19 and severe endotheliopathy allocated to infusion of prostacyclin or placebo for 72 hours. The point estimates favored the prostacyclin group in all analyses, including mortality. Collectively, the data warrant a large randomized clinical trial of prostacyclin in mechanically ventilated patients with COVID-19 with severe endotheliopathy owing to the continued considerable unmet medical need. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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