ONLINE DATA SUPPLEMENT

Use of aerosolized prostacyclins in critically ill patients and association with clinical outcomes

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Study Design, Participants and Setting

We performed a retrospectively cohort analysis of patients admitted to all the intensive care units of the University of Oklahoma Health Sciences Center (OUHSC) between the years 2015-2018. Patients were included in the study if they were 18 years and above, had hypoxic respiratory failure and had received either aerosolized iloprost or aerosolized epoprostenol. Only those patients with hypoxic respiratory failure requiring mechanical ventilation were included. To be included in the study, patients must have received either aerosolized iloprost or aerosolized epoprostenol for at least four (4) hours.

Exclusion criteria included patients less than 18 years of age, patients with hypoxic respiratory failure not on mechanical ventilation and patients who received either agent for less than 4 hours. To avoid contamination and overlap, patients who had received more than one pulmonary vasodilator at any time during their hospitalization were also excluded.

Some patients had multiple ICU admissions during their hospital stay, for analysis only data from first ICU admission was included in the analysis.

Aerosolized Prostacyclin

The type of agent used and timing of initiation of aerosolized prostacyclin was based on the clinical judgement of the treating physician. As an institutional policy, iloprost was used as nebulized aerosol at a dose of 20 mcg every 2-4 hours. Iloprost preparation was dissolved in 0.9% sodium chloride (NaCl) to keep the ventilator circuit moist. Epoprostenol was administered through a syringe pump as a continuous nebulization at a dose of 50 ng/kg/min. Weaning of epoprostenol was performed per the institution policy. Patients were assessed for weaning parameters every four hours. Weaning criteria included i) oxygen saturation (SaO2) > 92%, ii) partial pressure of oxygen (PaO2) > 65%, iii) P/F ratio > 150. The dose could not be decreased more than 10 ng/kg/min at a time. Patients were monitored for rebound hypoxemia.

Collection of Demographic, Laboratory, Hemodynamic Variables

Baseline demographic and social variable were collected using chart review in electronic medical record (EMR). Demographic variables recorded include age, gender, height (in cm) and ideal body weight. The type of ICU team taking care of the patient (medical ICU, surgical ICU, trauma ICU, neuro ICU) was also recorded.

Pressor requirements, lactate levels and PO2/Fi02 ratios were noted at initiation of aerosolized agent (time 0), after 4 h, after 8 h, after 12 h, after 16 h, after 20 h, after 24 h and after 48hr. As patients are on different vasopressor medications at a time, a norepinephrine equivalent dose was calculated using standardized formula. (NE equivalent dose = NE dose (mcg/min) + epinephrine dose (mcg/min) + [phenylephrine dose (mcg/min) ÷10] + [dopamine dose (mcg/kg/min)÷ 2]; if on vasopressin, (0.1*actual weight in kg) was added to NE equivalent dose.) (1)

Documentation of right ventricular function was based on 2-D echocardiographic data and was only qualitative in nature. Presence of right ventricular dilation and systolic dysfunction was noted.

For collection of PO2/FiO2 ratio, only arterial blood gases were used. EMR was analyzed to assess if patients were on concomitant rescue therapy for refractory hypoxia such as prone positioning and neuromuscular blockage.

Statistical Analysis

We compared baseline demographic and clinical data between groups. Information such as severity of illness, type of ICU service and mode of mechanical ventilation was also compared. Continuous data was reported as medians [interquartile range]. Categorical variables were reported as counts and percentages.

The primary outcome of the study was to compare the change in PaO2/FiO2 ratio between patients treated with iloprost and epoprostenol. Changes over time in PaO2/FiO2 (measured at 0, 4, 8, and 14 hours) were recorded. Changes in vasopressor requirements (NE equivalent dose, measured at 0 to 24 hours, every 4 hours), were additional outcomes of interest. Linear mixed models were used to analyze repeated measures of both outcome variables. Model terms included hours as a categorical variable, agents (iloprost, epoprostenol), and hours by agent's interaction. The interaction term was dropped from the model if its p-value is less than 0.1. If the interaction is significant, then both outcomes will be compared across hours; otherwise, both outcomes will be compared separately at each time point. A p value of ≤ 0.05 was considered statistically significant. SAS version 9.4 (SAS®, North Carolina) was used for analysis.

Other outcomes of interest included in-hospital mortality truncated to 90 days. Mortality was assessed as all-cause mortality. Mortality was recorded with the date of patient's death (or date of transition to palliative measures).

Survival was evaluated using Kaplan-Meier analysis and log-rank test. A Cox proportional hazard model was used for multivariate analysis. Covariates were included in the model if the p-value was ≤ 0.10 in the univariate analysis. Covariates were evaluated for collinearity. Proportional hazard model assumptions were assessed with Grambsch & Therneau 'ZPH' test and the supremum test for proportional hazard. Imputation analysis was planned for missing data in the survival model.

Supplemental Figures

Supplemental Table 1: Comparison of covariates distribution among groups

	Iloprost (n = 95)	**Epoprostenol (n = 31)**	**p value[a]**
Age, years	57 [41 – 64]	52 [37 – 63]	0.3288
Age			0.2825
18 – 40 years	23 (24.2)	9 (29)	
41 – 55 years	20 (21)	10 (32.3)	
56 – 63 years	26 (27.4)	5 (16.1)	
64 – 89 years	26 (27.4)	7 (22.6)	
Presence of shock	40 (42.1)	15 (48.4)	0.6771[b]
SOFA score (on admission)	7 [6 – 9]	8 [7 – 10]	0.0659
ICU service			0.6926
Medical ICU	22 (23.2)	5 (16.1)	
Trauma ICU	46 (48.4)	17 (54.9)	
Other ICU	27 (28.4)	9 (29)	
BMI, kg/m^2	29.8 [25 – 35.5]	31 [26.9 – 34.1]	0.5493
BMI			0.2070
BMI < 25 kg/m^2	23 (24.2)	5 (16.1)	
BMI 25 – 30 kg/m^2	26 (27.4)	7 (22.6)	
BMI ≥ 30 kg/m^2	46 (48.4)	19 (61.3)	

Continues variables are expressed as median [interquartile range], categorical variables are expressed as number (%). Total number of observations is 126 unless otherwise noted.

[a]p values calculated using Wilcoxon signed-rank test for continuous variables or chi-square test for categorical variables, unless otherwise noted.

[b]Fisher's exact test used

Definition of abbreviations: BMI = body mass index; SOFA = sequential organ failure assessment; ICU = intensive care unit.

Supplementary Table 2. Multivariate Cox proportional hazards model for mortality (model 2)

Type of Analysis	**Univariate analysis**		**Multivariable analysis**[ab]	
Variable	**Hazard ratio [95% CI]**	**p value**	**Hazard ratio [95% CI]**	**p value**
Epoprostenol use (Compared to Iloprost)	1.96 [1.103 – 3.485]	0.0219	3.045 [1.554 – 5.966]	0.0012

[a]Model adjusted for age, PaO2/FiO2 ratio, presence of shock, SOFA score, ICU service and BMI.

[b]N = 123 for model number 2 (due to missing data)

Definition of abbreviations: BMI = body mass index; SOFA = sequential organ failure assessment; ICU = intensive care unit.

Figure S1. Change in Vasopressor Dosage Over Time

Shown is change in vasopressor dosage from baseline. The bars indicate the standard error. Norepinephrine equivalent dose was numerically higher for the iloprost group for the first 12 hours, and then it was numerically lower after hour 12, although this difference was not statistically significant. There was a significant interaction between hour and agents (p=0.018).

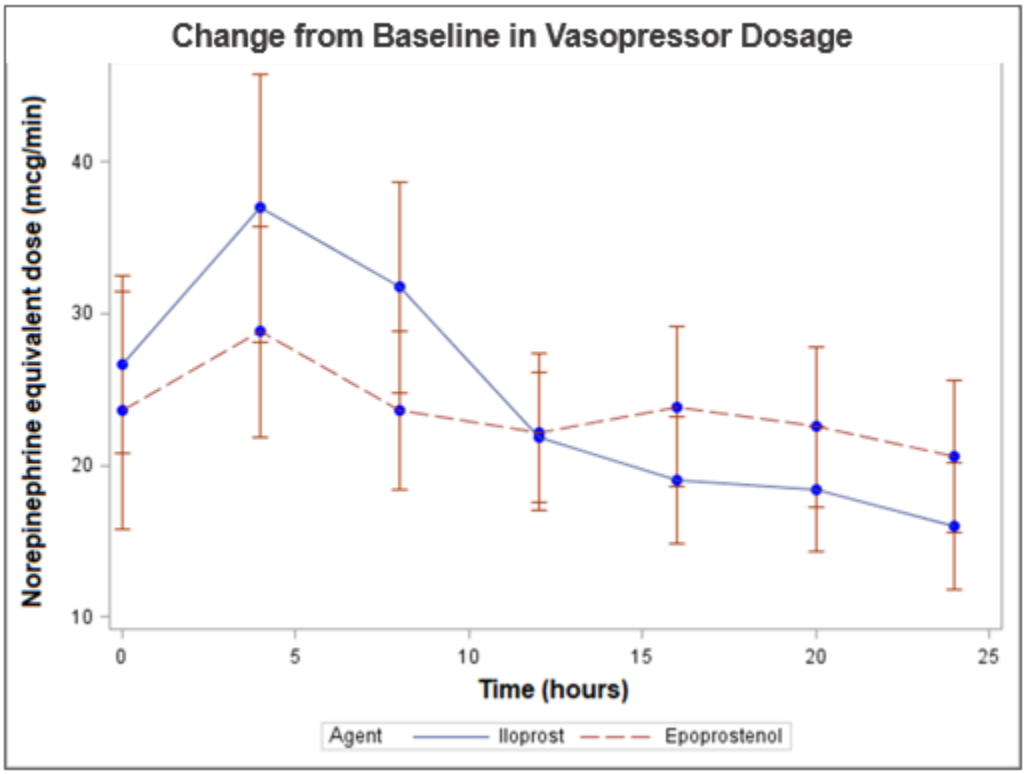
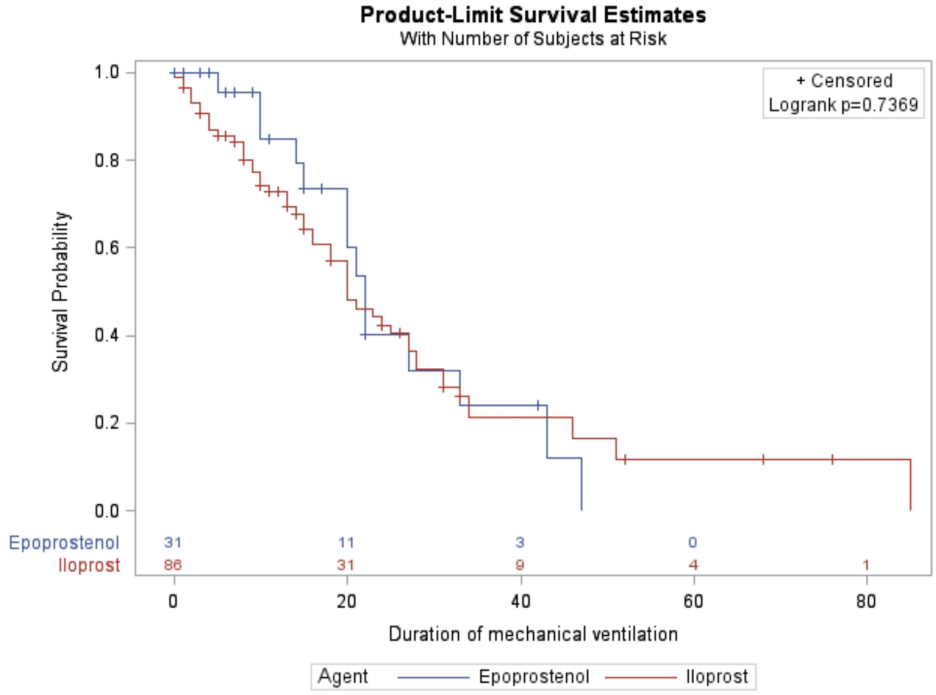


Figure S2: Time to liberation from mechanical ventilation

The figure displays comparison of time to liberation from mechanical ventilation. Duration of mechanical ventilation in hours. No differences were observed in time to liberation from mechanical ventilation (log rank test p = 0.7369)



REFERENCES

1. Khanna A, English SW, Wang XS, Ham K, Tumlin J et al; ATHOS-3 Investigators: Angiotensin II for the Treatment of Vasodilatory Shock. *N Engl J Med*. 2017; 377(5):419- 430.