Inhaled epoprostenol utilization pattern after implementation of an administration policy

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ABSTRACT

Epoprostenol, a pulmonary vasodilator, is used to reduce pulmonary artery pressure. Its inhaled administration results in ventilation and perfusion matching with oxygenation improvement. Epoprostenol is used as treatment for various conditions, particularly acute respiratory distress syndrome (ARDS) and pulmonary arterial hypertension. In 2018, Baylor University Medical Center implemented a policy for inhaled epoprostenol utilization aimed at standardizing clinical practice. This study analyzed epoprostenol utilization patterns in patients with ARDS after implementation of this administration policy. Drug responders and nonresponders were compared for clinical outcomes and physiologic changes before and after use, and policy compliance was evaluated. Of 79 eligible patients, 30 fulfilled inclusion criteria: 14 (47%) had ARDS and 16 (53%) had non-ARDS. In all patients with ARDS, epoprostenol was a second rescue agent after neuromuscular blockade, prone positioning, corticosteroids, and extracorporeal membrane oxygenation. Epoprostenol was associated with statistically significant improvement of oxygenation before and after utilization in patients with ARDS (ratio of arterial oxygen partial pressure to fractional inspired oxygen 70 vs 140, respectively; $P = 0.04$). Overall, 10 (71%) ARDS patients were epoprostenol responders; 9 (56%) were deemed responders among subjects with non-ARDS. Comparison of outcomes between responders and nonresponders showed no statistically significant variations. Policy compliance was obtained in 24 (80%) patients.

KEYWORDS Acute respiratory distress syndrome; inhaled epoprostenol; oxygenation; pulmonary arterial hypertension; rescue therapy

Epoprostenol enhances cyclic adenosine monophosphate concentrations to decrease right ventricular afterload and increase pulmonary vascular circulation, resulting in the treatment of pulmonary arterial hypertension (PAH), cardiac surgery–related PAH, right ventricular failure, and acute respiratory distress syndrome (ARDS).^{1–4} Currently, lung-protective ventilation strategies, prone positioning, and neuromuscular blocking agents are the only treatments showing survival benefits in ARDS.^{2,5–8} Alternative strategies such as conservative fluid management, corticosteroids, and extracorporeal membrane oxygenation (ECMO) have resulted in improved oxygenation and lung compliance only.^{2,9–11} Inhaled epoprostenol and nitric oxide have been evaluated in refractory hypoxemia with comparable outcomes; significant cost savings have been associated with epoprostenol.^{12,13} To reduce practice variation and

improve outcomes, an inhaled epoprostenol utilization policy was implemented.⁴ This study aimed to analyze epoprostenol utilization and outcomes as well as provider compliance after policy implementation.

METHODS

This was a single-center, retrospective analysis of data gathered within a quality improvement project to standardize inhaled epoprostenol utilization among patients with ARDS and non-ARDS. Adult patients (18 years of age or older) admitted to Baylor University Medical Center intensive care units (ICUs) between March 1, 2018, and March 1, 2019 treated with inhaled epoprostenol were eligible. Pregnant patients and patients treated with epoprostenol for cardiac surgery–related PAH were excluded. Informed consent was

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Table 1. Patient demographics and severity of illness scores^a

Variable	ARDS (n = 14)	Non-ARDS (n = 16)
Age (years)	46 [32–63]	59 [42–67]
Male	7 (50%)	10 (62.5%)
Weight (kg)		
Ideal	68 [50–73]	63.8 [58.7–77.5]
Actual	94.3 [75.1–128]	85.5 [64.8–129.8]
APACHE IV hospital mortality score	47.7 [15.6–79.1]	24.1 [7.6–66.6]
APS score	99 [63–116]	50.5 [38.8–109.3]
Etiology, ARDS		
Pulmonary	13 (93%)	—
Nonpulmonary	1 (7%)	—
Etiology, non-ARDS		
Pulmonary arterial hypertension	—	6 (37%)
Right ventricular failure	—	8 (50%)
Bridge therapy	—	2 (13%)

^aData presented as number (%) or median (interquartile range).

APACHE indicates Acute Physiology and Chronic Health Evaluation; APS, acute physiology score.

waived due to the retrospective nature of the study. Patients were identified through the presence of a physician order for inhaled epoprostenol. Included patients were grouped based on the indication for use as patients with ARDS or non-ARDS. Based on the Berlin criteria, the presence of ARDS was identified during chart review.¹⁴ Patients with non-ARDS included those with PAH, right ventricular failure, lung transplantation reperfusion injury, or use of the drug as a bridge to ECMO. Within the ARDS group, rescue therapies utilized prior to implementation of inhaled epoprostenol and physiologic data were assessed. Blood gases were obtained immediately prior to initiation and after epoprostenol discontinuation.

Within each group (ARDS and non-ARDS), patients were analyzed as responders or nonresponders according to policy criteria. Clinical outcomes were compared between the groups. Noncompliance was defined as administration of epoprostenol that varied from explicitly stated policy recommendations in regard to dose initiation, rate of titration, and maximal dose. The study had four outcomes of interest: (1) epoprostenol utilization patterns in patients with ARDS; (2) physiologic changes before and after utilization in ARDS; (3) comparison of clinical outcomes between epoprostenol responders and nonresponders; and (4) policy compliance.

The inhaled epoprostenol administration policy was developed by a multidisciplinary workgroup to standardize practice associated with its utilization. This policy served as an educational tool to provide indications for use and

information on the management and monitoring of inhaled epoprostenol. Indications for epoprostenol use included ARDS not responding to lung-protective ventilation strategies, decompensated right heart failure, severe PAH, and decompensated right heart failure in the postoperative period.⁴ Contraindications included active pulmonary hemorrhage, PAH due to left ventricular systolic dysfunction, and thrombocytopenia defined as a platelet count <50,000 μ L at baseline. Administration was initiated at 20 to 50 ng/kg/min based on ideal body weight with a maximal dose of 50 ng/kg/min and minimal dose of 10 ng/kg/min. Titration of inhaled epoprostenol was recommended every 30 minutes by 10 ng/kg/min based on oxygenation improvement or a reduction in mean pulmonary artery pressure. Due to the short onset of action, responses were expected to be seen within 10 minutes.⁵ Patients were considered responders if there was a $\geq 20\%$ increase in arterial oxygen partial pressure (PaO_2) or $\geq 20\%$ reduction in mean pulmonary artery pressure measured by pulmonary artery catheter monitoring. Patients were nonresponders if the aforementioned criteria for improvement were not fulfilled or worsened. Inhaled epoprostenol was to be weaned off in nonresponders within 2 hours of that determination. Patients were to be monitored for adverse events including nausea, facial flushing, headaches, thrombocytopenia, systemic hypotension, and pulmonary edema. Following the approval of this policy, educational documents regarding standardized content were disseminated to various departments, including physicians, pharmacists, nurses, and respiratory care practitioners.

Patient characteristics and study outcomes are presented as percentages for categorical variables and were analyzed utilizing the Fisher's exact test. Continuous variables are presented as medians (25th–75th interquartile range) and were compared using the Wilcoxon rank sum test. All analyses were performed using STATA (Version 14.0, StataCorp, College Station, TX).

RESULTS

Review of the electronic health record revealed 79 ICU patients with an order for inhaled epoprostenol during the study period. Forty-nine patients (62%) were excluded due to post–cardiac surgery–related PAH, leaving 30 (38%) patients. Of these patients, 14 (47%) were included in the ARDS group and 16 (53%) in the non-ARDS group. All patients with ARDS were intubated/mechanically ventilated; 3 (19%) patients in the non-ARDS group received epoprostenol through noninvasive ventilation or high-flow nasal cannula. *Table 1* shows basic demographics, severity of illness scores, and etiologies for the ARDS and non-ARDS groups.

Among ARDS cases, 10 (71%) were severe based on the Berlin definition of ARDS severity, and epoprostenol was utilized as a second-choice rescue therapy. *Figure 1* shows the distribution of rescue therapies used in patients with ARDS prior to epoprostenol administration. Continuous renal replacement therapy was used in 4 (29%) patients with

ARDS for fluid management. *Table 2* displays physiologic changes assessed within the ARDS group. A statistically significant improvement in the ratio of arterial oxygen partial pressure to fractional inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) was seen after treatment compared to before treatment. Other gasometrical and ventilator parameters were not affected.

Patient response to epoprostenol and the associated clinical outcomes were assessed within the groups independently (*Table 3*). Though there were no statistically significant differences in outcomes, ARDS responders required a median lower maximum dose of inhaled epoprostenol compared to nonresponders (30 ng/kg/min vs 50 ng/kg/min, respectively). Similarly, responders for non-ARDS indications required a

median lower maximum dose of inhaled epoprostenol and received inhaled epoprostenol for a shorter period of time.

Compliance with the epoprostenol administration policy was assessed within the two groups. Based on the criteria of dose initiation, rate of titration, and maximal dose, three patients within each group were treated outside policy recommendations, resulting in an observed compliance of 80%. Specifically, two patients had epoprostenol titrated by 6 ng/kg/min, one patient had a 22 ng/kg/min titration, and one patient received a maximum dose of 70 ng/kg/min. *Table 4* shows the epoprostenol initiation dose, maximal dose, and rate of titration within each group. Inhaled epoprostenol was administered to three patients (one with ARDS and two with non-ARDS) with pulmonary arterial hypertension due to left ventricular systolic dysfunction, which is a contraindication to its use. Despite the contraindication, two out of the three patients were classified as positive responders to inhaled epoprostenol. Safety endpoints such as hypotension (a mean arterial blood pressure <65 mm Hg in two consecutive readings or vasopressor requirement) were seen in 12 (86%) patients with ARDS and in 10 (62%) patients with non-ARDS. Thrombocytopenia was seen in 4 (29%) patients with ARDS and 6 (38%) patients with non-ARDS.

DISCUSSION

The present study evaluated practice after the implementation of an inhaled epoprostenol administration policy. Four findings are notable. First, clinicians used epoprostenol as a second-choice treatment for refractory hypoxemia in ARDS. Corticosteroid treatment within 72 hours of ARDS diagnosis has been demonstrated to reduce mechanical

Figure 1. Rescue therapies utilized prior to epoprostenol in 14 patients with acute respiratory distress syndrome. ECMO indicates extracorporeal membrane oxygenation; RRT, renal replacement therapy.

Table 2. Physiologic changes and ventilator outcomes in 14 patients with acute respiratory distress syndrome^a

Variable	Baseline	Discontinuation	P value
pH	7.26 [7.22–7.37]	7.4 [7.32–7.46]	0.058
PaCO ₂ (mg/dL)	57.3 [51.9–69.5]	56.4 [49.6–62.5]	0.214
PaO ₂ (mg/dL)	69.5 [62.8–78]	79 [68–96]	0.678
MAP (mm Hg)	71 [69–79.5]	71 [64–82]	0.657
PaO ₂ /FiO ₂ ratio	70.5 [62.8–98.3]	140 [99–202]	0.038
FiO ₂ (%)	100 [90–100]	52.5 [50–60]	0.058
PEEP	13 [10–19.5]	10 [6.5–17.5]	0.152
V _t (mL)	350 [301.5–457.5]	400 [380.3–443.5]	0.221
V _t (mL/kg IBW)	6.1 [5.5–6.8]	6.4 [5.6–7.3]	0.185
Plateau pressure (mm Hg)	28 [23.5–34]	29 [26.3–32.8]	0.073

^aData presented as median (interquartile range). Bold indicates statistical significance. FiO₂ indicates fractional inspired oxygen; IBW, ideal body weight; MAP, mean arterial pressure; PaCO₂, partial pressure of carbon dioxide; PaO₂, arterial oxygen partial pressure; PaO₂/FiO₂ ratio, ratio of arterial oxygen partial pressure to fractional inspired oxygen; PEEP, positive end-expiratory pressure; V_t, tidal volume.

Table 3. Clinical outcomes associated with epoprostenol responsiveness or nonresponsiveness in patients with ARDS and non-ARDS^a

Variable*	ARDS			Non-ARDS		
	Responders	Nonresponders	P value	Responders	Nonresponders	P value
Total	10 (71%)	4 (29%)		9 (56%)	7 (44%)	
Mortality	6 (60%)	2 (50%)	0.552	5 (56%)	5 (71%)	0.780
Need for additional rescue therapy	3 (30%)	0 (0%)	0.505	2 (29%)	2 (22%)	0.585
ICU LOS (days)	18.5 [5–26]	8.5 [7.5–10.5]	0.288	10 [5–12]	5 [2–11]	0.491
Hospital LOS (days)	24.5 [5–27]	10.5 [8–13]	0.257	12 [10–15]	6 [4–17]	0.266
Max dose (ng/kg/min)	30 [20–50]	50 [40–60]	0.101	40 [20–50]	50 [30–50]	0.608
Duration of use (h)	58.8 [30–92]	38.8 [20–108.3]	0.480	38.5 [12.5–89]	51 [25–103.5]	0.560
Weaned off after 2 hours	—	1 (25%)		—	1 (14%)	

*Data presented as number (%) or median (interquartile range).

ARDS indicates acute respiratory distress syndrome; ICU, intensive care unit; LOS, length of stay.

Table 4. Inhaled epoprostenol administration^a

Variable	ARDS (n = 14)	Non-ARDS (n = 16)
Time from diagnosis until initiation (h)	15 [3.6–50.3]	6.3 [1.8–21.3]
Initial dose (ng/kg/min)	25 [20–37.5]	25 [20–42.5]
Maximal dose (ng/kg/min)	45 [20–50]	45 [30–50]
Dose titration amount (ng/kg/min)		
10	9 (75%)	7 (70%)
<10	1 (8%)	1 (10%)
>10	2 (17%)	2 (20%)
Duration of administration (h)	43 [31.5–91.3]	48 [14.1–92.6]

*Data presented as number (%) or median (interquartile range).

ARDS indicates acute respiratory distress syndrome.

ventilation and ICU days.^{2,11} Controversy surrounds the utilization of neuromuscular blocking agents in patients with ARDS with severe gas-exchange deficiencies for ventilator synchrony.^{2,7} Previously, a large randomized controlled trial revealed survival improvement,⁷ but a recent study showed no benefits.⁸ Notably, prone positioning was used in only 21% of patients in this study. However, these patients with ARDS may have presented a contraindication or were deemed inappropriate candidates for its use. At present, inhaled epoprostenol is reserved for patients with refractory hypoxemia as salvage therapy.^{2,3,15,16}

Second, inhaled epoprostenol was associated with oxygenation improvement. Fuller and colleagues analyzed inhaled epoprostenol in ARDS and found improvement in oxygenation.¹⁰ Domenighetti and colleagues also analyzed inhaled epoprostenol in pulmonary/nonpulmonary ARDS and identified oxygenation enhancement manifested as PaO₂/FiO₂ ratio improvement.^{3,12,15} Siddiqui and colleagues evaluated 67 patients with

ARDS or elevated pulmonary arterial pressures.¹⁷ They concluded that inhaled epoprostenol improved diastolic left ventricular function and improved oxygenation.¹⁷ Pacheco and colleagues evaluated ARDS survivors and nonsurvivors to identify predictors of mortality with inhaled epoprostenol use.^{3,12,18} Notably, a higher body mass index, trauma-associated ARDS, and PaO₂/FiO₂ ratio improvement after 24 hours of inhaled therapy were all associated with a lower mortality.^{3,12,18}

Third, inhaled epoprostenol was not associated with improvement in clinical outcomes such as mortality or ICU length of stay when comparing responders vs nonresponders. Similarly, a previous study revealed that patients with ARDS improved from an acidotic pH at baseline to a normalized pH with inhaled epoprostenol administration. FiO₂ and positive end-expiratory pressure improved from baseline, resulting in only three patients requiring treatment escalation. Improvements in metabolic and oxygenation status were also seen in those with a non-ARDS indication. Specifically, 56.3% of patients with non-ARDS improved in baseline pH, FiO₂, and positive end-expiratory pressure. No benefits in clinical outcomes such as reduction of mechanical ventilation, ICU or hospital lengths of stay, or hospital mortality were seen.^{2,3,17}

Last, this study showed that implementation of an inhaled epoprostenol policy brought about similar clinician compliance in both groups. Specifically, 80% of patients were treated according to policy recommendations. The reason for policy deviation, specifically utilization of inhaled epoprostenol in patients with contraindications, was not explicitly understood in this retrospective review. Therefore, there are future opportunities for provider education and policy review. In addition, adverse effects such as hypotension and thrombocytopenia bring undesirable outcomes. Thus, a protocolized approach may optimize benefits while avoiding complications.

Despite the aforementioned four notable findings reported in the study, there are significant limitations that preclude further conclusions. First, due to the retrospective design, selection and/or information bias may have occurred. Specifically, selection and information bias may have resulted during group classification. Due to lack of or inaccurate data, patients may have been classified incorrectly, and physiologic information or clinical outcomes may have been incomplete. Second, the study was designed to assess utilization as a rescue therapy and physiologic changes among patients with ARDS treated with inhaled epoprostenol. Because no control group was included, it is unknown whether patients not treated with inhaled epoprostenol would have required similar rescue therapies or whether physiologic changes would have improved despite epoprostenol use. However, because epoprostenol was utilized as a second-choice agent for refractory hypoxemia, it is likely that the distribution of rescue therapies would not have changed. Third, there was a small sample size, which may have limited the ability to adequately identify statistical significance. Last, there is no information regarding patterns of utilization of inhaled epoprostenol prior to policy implementation. Whether clinicians were using inhaled epoprostenol in a comparable fashion before policy implementation is unknown.

In conclusion, the present study demonstrates outcomes associated with a policy outlining the use of inhaled epoprostenol in both patients with ARDS and patients with non-ARDS. With patients with ARDS, epoprostenol was most commonly utilized as a second-choice agent in refractory hypoxemia. Physiologic effects were associated with oxygenation improvement. However, there were no statistically significant differences in clinical outcomes between responders and nonresponders. Finally, implementation of an administration policy was associated with high clinician compliance in both patients with ARDS and patients with non-ARDS. The results of this study and current policy have been reviewed with various providers and disciplines to improve utilization patterns.

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