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Inhaled epoprostenol vs inhaled nitric oxide for refractory hypoxemia in critically ill patients☆

Heather Torbic PharmD, BCPS[a,*], Paul M. Szumita PharmD, BCPS[a], Kevin E. Anger PharmD, BCPS[a], Paul Nuccio MS, RRT, FAARC[b], Susan LaGambina RRT[b], Gerald Weinhouse MD[c]

[a]*Department of Pharmacy, Brigham and Women's Hospital, Boston, MA 02115*
[b]*Department of Respiratory Therapy, Brigham and Women's Hospital, Boston, MA 02115*
[c]*Department of Medicine, Brigham and Women's Hospital, Boston, MA 02115*

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Abstract

Purpose: The purpose of this is to compare efficacy, safety, and cost outcomes in patients who have received either inhaled epoprostenol (iEPO) or inhaled nitric oxide (iNO) for hypoxic respiratory failure.

Materials and methods: This is a retrospective, single-center analysis of adult, mechanically ventilated patients receiving iNO or iEPO for improvement in oxygenation.

Results: We evaluated 105 mechanically ventilated patients who received iEPO (52 patients) or iNO (53 patients) between January 2009 and October 2010. Most patients received therapy for acute respiratory distress syndrome (iNO 58.5% vs iEPO 61.5%; $P = .84$). There was no difference in the change in the partial pressure of arterial O_2/fraction of inspired O_2 ratio after 1 hour of therapy (20.58 ± 91.54 vs 33.04 ± 36.19 [$P = .36$]) in the iNO and iEPO groups, respectively. No difference was observed in duration of therapy ($P = .63$), mechanical ventilation ($P = .07$), intensive care unit ($P = .67$), and hospital lengths of stay ($P = .26$) comparing the iNO and iEPO groups. No adverse events were attributed to either therapy. Inhaled nitric oxide was 4.5 to 17 times more expensive than iEPO depending on contract pricing.

Conclusions: We found no difference in efficacy and safety outcomes when comparing iNO and iEPO in hypoxic, critically ill patients. Inhaled epoprostenol is associated with less drug expenditure than iNO.

1. Introduction

Pulmonary hypertension, right ventricular (RV) dysfunction, acute respiratory distress syndrome (ARDS), and refractory hypoxemia in heart and lung transplantation are clinical scenarios managed with supportive care and sometimes ventilatory support to optimize oxygenation and hemodynamics [1-3]. Pulmonary vasodilator agents have been used in some of these patients for hypoxemia refractory to conventional treatments. Inhaled nitric oxide (iNO) and inhaled epoprostenol (iEPO) are 2 pulmonary vasodilators that have been studied in these patients [1-3].

Inhaled nitric oxide is a colorless, odorless gas and a selective pulmonary vasodilator. It increases blood flow to

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* Corresponding author. Tel.: +1 617 732 7164.
E-mail address: htorbic@partners.org (H. Torbic).

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well-ventilated areas of the lung and reduces pulmonary shunting [4]. Inhaled epoprostenol is a naturally occurring prostaglandin and, similarly, is a potent pulmonary vasodilator, which only reaches well-ventilated areas of the lung [1]. These agents improve oxygenation, inhibit platelet aggregation, reduce inflammation, and decrease pulmonary vascular resistance [4,5]. Both agents are associated with a theoretical risk of bleeding and hypoxemia [1,4]. Inhaled nitric oxide may also cause methemoglobinemia and rebound pulmonary hypertension [1,4]. Inhaled epoprostenol can cause systemic hypotension and tachycardia [1].

Currently, there is a lack of data comparing the efficacy and safety of iNO and iEPO in patients requiring pulmonary vasodilator therapy. Although these medications continue to be administered for their putative benefits, there is little to guide which agent to use. At our institution, like many others, we transitioned from the use of iNO to the use of iEPO for cost-saving purposes. During that transition, we collected data on patient outcomes. The purpose of the current study is to determine if there was a difference in efficacy, safety, and cost outcomes in those patients who received either iNO or iEPO for improvement in oxygenation.

2. Materials and methods

This is a retrospective cohort analysis. This study was approved by the Institutional Review Board at Brigham and Women's Hospital. An internal respiratory therapy database was used to identify all patients who received either iNO or iEPO. Subjects were included in the study if they were admitted to an intensive care unit (ICU) at Brigham and Women's Hospital between January 1, 2009, and October 31, 2010, were 18 years or older, and received either iNO or iEPO for improvement in oxygenation. Patients were excluded if they received greater than 2 hours of concomitant iNO and iEPO therapy. Patients were consecutively enrolled if they met inclusion criteria.

Based on our institution's protocol, patients were typically started on pulmonary vasodilator therapy after failing maximal conventional therapy, including, but not limited to, prone positioning, chest weights, recruitment maneuvers, positive end-expiratory pressure of 15 or higher, oxygen, and calcium antagonists. The decision to initiate inhaled pulmonary vasodilator therapy was at the discretion of the attending physician. The acceptable dose range for iNO at our institution is 1 to 80 ppm and iEPO is 0.01 to 0.05 μg/kg per minute. Our protocol recommends starting iNO at 20 ppm and assessing patient for a favorable response (eg, >20% improvement in Pa_{O_2}, >20% reduction in mean pulmonary artery pressure [PAP]). Inhaled nitric oxide can be weaned by 50% every 1 to 2 hours as the patients tolerates until iNO has been titrated off. Per our protocol, it is recommended to start iEPO at 0.05 μg/kg per minute and decrease by 0.01 μg/kg per minute increments every 1 to 2 hours as tolerated until iEPO has been weaned off. Duration of therapy for both agents is determined on a per patient basis based on their clinical response to pulmonary vasodilator therapy and their ability to wean off therapy.

Baseline demographic information was collected to describe the study population including the following: age, sex, weight, ethnicity, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, comorbidities, concomitant medications, laboratory values, and indication for pulmonary vasodilator therapy. Per our institutional protocol, patients were started on pulmonary vasodilator therapy for ARDS if they were mechanically ventilated and had a partial pressure of arterial O_2 (Pa_{O_2})/fraction of inspired O_2 (Pa_{O_2}/F_{IO_2}) ratio less than 200, and pulmonary capillary wedge pressure less than 18, or no evidence of left atrial hypertension. Cardiac decompensation after heart or lung transplantation was defined as being within 14 days of surgery and having a mean PAP greater than 30 mm Hg, Pa_{O_2}/F_{IO_2} ratio less than 300, and central venous pressure greater than 15 mm Hg. Acute RV failure was defined as having a mean PAP greater than 30 mm Hg, Pa_{O_2}/F_{IO_2} ratio less than 300, central venous pressure greater than 15 mm Hg, and cardiac index less than 2.5 L/min per square meter. All patients in this analysis met 1 of these 3 indications for pulmonary vasodilator therapy, and no patients were excluded for inability to meet one of these criteria. At our institution, patients must meet one of the above criteria before initiation of pulmonary vasodilator therapy.

The primary outcome of the study was the change in the Pa_{O_2}/F_{IO_2} ratio after 1 hour of pulmonary vasodilator therapy. The secondary outcomes assessed in this study included ICU length of stay, hospital length of stay, duration of study therapy, duration of mechanical ventilation, incidence of adverse events, and cost. A subgroup analysis was performed to separately evaluate patients with ARDS, acute RV failure, and cardiac decompensation after heart or lung transplant to determine if there were any differences in end points when comparing more homogenous patient populations.

Adverse events were defined as (1) bleeding events during pulmonary vasodilator treatment, which were treated with transfusions of packed red blood cells and/or platelets or by (2) documentation in the medical record indicating that there was pulmonary vasodilator treatment–related bleeding. The cost of iNO was determined by using the lowest, highest, and mean contract prices per hour for iNO at institutions in the United States in 2010 based on a University Health System Consortium survey. The cost of iEPO was determined based on the noncontract average wholesale price from 2010.

Continuous variables were reported as mean (SD) or median (interquartile range [IQR]) and compared via the Student t test or Mann-Whitney U test, where applicable. Comparison of categorical data was made via the χ^2 test. Statistical significance was defined as $P \leq .05$. A sample size analysis was performed, which indicated that enrollment of 16 patients in each group would have 80% power at an α of .05 to detect a 15% difference in the primary end point, change in oxygenation after 1 hour of iNO or iEPO therapy [6].

3. Results

One hundred thirty-one patients were evaluated for study enrollment. Twenty-six patients were excluded because they concomitantly received iNO and iEPO for greater than 2 hours. The remaining 105 patients were included in the analysis, 53 patients in the iNO group and 52 patients in the iEPO group.

Baseline characteristics are presented in Table 1. The 2 groups were similar at baseline in regard to age, sex, ethnicity, and APACHE II score. Patients who received iEPO weighed more at baseline compared with those patients who received iNO (84.2 ± 28.7 vs 102.9 ± 47.3 kg; $P = .04$). The 2 groups were also similar with regard to comorbidities at baseline, except more patients who received iNO also had a history of solid organ transplantation compared with those patients who received iEPO (15.1% vs 1.9%; $P = .04$). There was no difference in the number of patients requiring vasopressors and/or inotropes while receiving pulmonary vasodilator therapy ($P = 1.0$ and $P = 1.0$, respectively). There was also no difference in anticoagulation use for treatment or prophylaxis and steroid use between the 2 groups ($P = .36$, $P = .14$, and $P = .63$, respectively).

Table 1 Baseline characteristics

	iNO (n = 53)	iEPO (n = 52)	*P*
Age, y (mean ± SD)	51.8 ± 17.9	56.4 ± 15.3	.21
Sex, male, n (%)	22 (41.5)	21 (40.4)	.91
Weight, kg (mean ± SD)	84.2 ± 28.7	102.9 ± 47.3	.04
Ethnicity, n (%)			
White	44 (83.0)	47 (90.3)	.74
African American	4 (7.5)	2 (3.8)	.66
Hispanic	3 (5.7)	2 (3.8)	.98
Asian	2 (3.8)	1 (1.9)	.57
APACHE II, median (IQR)	18 (15.5-21)	18 (15-22)	.69
Comorbidities, n (%)			
Hypertension	20 (37.7)	21 (40.4)	.94
Coronary artery disease	26 (49.1)	16 (30.8)	.09
Diabetes	10 (18.9)	13 (25.0)	.60
PAH	8 (15.1)	12 (23.1)	.43
CHF	13 (24.5)	7 (13.5)	.23
COPD	11 (20.8)	7 (13.5)	.46
Asthma	6 (11.3)	6 (11.5)	.97
Active malignancy	6 (11.3)	4 (7.7)	.76
SOT	8 (15.1)	1 (1.9)	.04
Indication for pulmonary vasodilator therapy, n (%)			
ARDS	31 (58.5)	32 (61.5)	.84
Heart/lung transplant with cardiac decompensation	5 (9.4)	1 (1.9)	.22
Acute RV failure	17 (32.1)	19 (36.5)	.68
Vasopressors/inotropes, n (%)			
Vasopressors	47 (86.7)	46 (88.5)	1.00
Inotropes	24 (45.3)	23 (44.2)	1.00
Anticoagulation, n (%)			
Treatment	24 (45.3)	18 (34.6)	.36
Prophylaxis	22 (41.5)	30 (57.7)	.14
Steroids, n (%)	21 (39.6)	24 (46.2)	.63

PAH indicates pulmonary arterial hypertension; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; SOT, solid organ transplant.

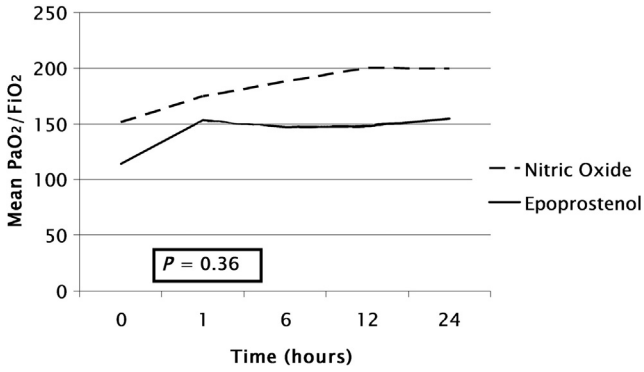

Fig. 1 Change in Pa_{O_2}/F_{IO_2} ratio after 1 hour of therapy.

The indication for pulmonary vasodilator use was similar between the 2 groups (Table 1). The most common indication for iNO or iEPO use was ARDS (58.5% vs 61.5%; $P = .84$).

There was no difference in baseline laboratory values between the groups, except the serum urea nitrogen was initially higher in patients who received iEPO (30.25 ± 19.82 vs 41.42 ± 33.57 mg/dL; $P = .03$) and international normalized ratio was initially higher in patients who received iNO (1.90 ± 1.09 vs 1.53 ± 0.42; $P = .01$).

There was no difference in the primary outcome, the change in the Pa_{O_2}/F_{IO_2} ratio after 1 hour of pulmonary vasodilator therapy (Fig. 1). The change in the Pa_{O_2}/F_{IO_2} ratio at 1 hour was 20.58 ± 91.54 and 33.04 ± 36.19 ($P = .36$) for iNO and iEPO, respectively.

The duration of mechanical ventilation and duration of ICU and hospital length of stay were similar between the 2 groups receiving pulmonary vasodilator therapy (Table 2) as was the duration of pulmonary vasodilator therapy. More patients were started on iNO than iEPO in the operating room (OR) (24.5% vs 3.8%; $P = .006$). There was no difference in incidence of tracheostomy and in-hospital mortality between groups and no difference in bleeding events and changes in blood pressure.

There was a significant cost difference between the 2 pulmonary vasodilator therapies (Table 2). When comparing iNO and iEPO using a low contract price for iNO, iEPO is 4.5 times less costly than iNO ($3930 ± $4210 vs $838 ± $997; $P < .0001$). When comparing iNO and iEPO using a high contract price for iNO, iEPO is 17 times less costly than iNO ($14 240 ± $15 255 vs $838 ± $997; $P < .0001$).

We performed a subgroup analysis of each of the end points evaluating patients with each indication separately. When only comparing the change in the Pa_{O_2}/F_{IO_2} ratio at 1 hour in patients with ARDS, there was still no difference (45.73 ± 67.30 and 33.04 ± 36.19 [$P = .35$] for iNO and iEPO,

Table 2 Secondary end points

End point	iNO (n = 53)	iEPO (n = 52)	*P*
Duration of study therapy, d [a]	3.5 ± 2.7 2.3 (0.6-4.8)	3.2 ± 2.6 2.0 (0.9-4.3)	.66 .63
Duration of MV, d [b]	7 (3-17)	9.5 (6-19)	.07
ICU LOS, d [b]	15 (6-31)	15.5 (8-23)	.67
Hospital LOS, d [b]	33 (12-53)	20.5 (14-33)	.26
Therapy started in OR, n (%)	13 (24.5)	2 (3.8)	.01
Hospital mortality, n (%)	18 (34.0)	26 (49.1)	.14
Tracheostomy, n (%)	12 (22.6)	14 (26.4)	.78
Adverse events, n (%)			
PRBC	33 (62.2)	25 (47.2)	.21
Platelets	13 (24.5)	10 (18.9)	.67
Total cost, USD	206 945 486 775 749 190	43 995	<.0001
Cost of therapy per patient, USD [a]	3930 ± 4210 9250 ± 9910 14 240 ± 15 255	838 ± 997	<.0001

MV indicates mechanical ventilation; LOS, length of stay; PRBC, packed red blood cells; USD, US dollars.
[a] Denotes mean ± SD.
[b] Denotes median (IQR).

respectively). There were also no statistically significant differences in any of the other end points, including duration of pulmonary vasodilator therapy, duration of mechanical ventilation, ICU and hospital lengths of stay, adverse events, and in-hospital mortality within any of the subgroups. After evaluating patients with each of the 3 indications separately; there still remained a significant difference in cost, with iEPO being significantly less costly than iNO for each group ($P < .0001$, $P < .0001$, and $P < .0001$, respectively).

4. Discussion

In this study, there was no detectable difference in our primary end point of the change in the Pao_2/Fio_2 ratio after 1 hour of pulmonary vasodilator therapy nor the secondary end points of efficacy and safety outcomes when comparing iNO and iEPO for improvement in oxygenation in critically ill, hypoxemic patients. There was, however, a statistically significant difference in cost between the 2 agents. The results of this study are similar to those of other smaller studies evaluating the use of these agents for pulmonary vasodilation in more homogeneous populations and, we believe, justify the decision to transition from the use of iNO to iEPO as a cost-saving measure [1-3,7-9].

Current literature does not directly compare iNO and iEPO in a diverse patient population, and cost has not been considered in available literature. The direct comparison studies to this point have been small studies with less than 20 patients who were prescribed iNO and iEPO in a cross-over fashion for either ARDS or heart or lung transplantation [1-3,7-9]. Cost has only been evaluated in a small study of 9 children requiring either iNO or intravenous epoprostenol for pulmonary hypertension, with cost results favoring the use of epoprostenol [10].

Unlike other studies, this study evaluates the use of iNO and iEPO in a diverse patient population. Because of the diverse nature of the population, we performed a subgroup analysis of each of the end points to ensure there were no differences between the 3 indications for pulmonary vasodilator therapy. After evaluating each indication separately, we found no difference between patients treated with iNO or iEPO for any of the end points. The results of the subgroup analysis, we believe, further justifies the switch from iNO to iEPO use at our institution as a cost-saving measure.

One significant difference noted in our analysis was the more frequent initiation of iNO in the OR vs iEPO. This difference is due to limitations of iEPO preparation and delivery at our institution. Because of these limitations, if an inhaled pulmonary vasodilator needs to be urgently initiated in the OR, it is often faster to initiate iNO, rather than wait for the preparation and delivery of iEPO.

A recent meta-analysis evaluated 1303 patients receiving iNO for ARDS. The investigators found that most studies evaluated were of poor quality, but what they could conclude from the data is iNO has no effect on mortality, transient effects on oxygenation, and may actually be harmful to patients by causing higher rates of renal impairment [11]. These results were similar to other studies evaluating iNO for pulmonary vasodilation in transplantation [2,3,8]. Limitations with the available studies evaluating the efficacy of iNO in this context includes small sample sizes, cross-over design, homogeneous patient populations, and short study durations.

Inhaled epoprostenol has most commonly been studied in patients with pulmonary hypertension. In a study by De Wet et al [12], 26 cardiac surgery patients with pulmonary hypertension experienced improved oxygenation and few adverse events. Other studies evaluating iEPO in patients with pulmonary hypertension, after heart and lung transplantation, and in the setting of ARDS have produced similar results [5,13-16]. Limitations with the available studies evaluating iEPO include small sample sizes, cross-over design, homogeneous patient populations, short study durations, and lack of survival data.

There were several limitations to our study. First, this was a retrospective study of a cohort of patients at a single, academic medical center. As previously mentioned, the groups had different indications for use, which may have impacted the results, although based on our subgroup analyses, unlikely. Although a diverse patient population was studied, the results of this study may not be applicable to patients requiring pulmonary vasodilation for indications not evaluated in this study.

Another limitation of this study was the change in practice that occurred at Brigham and Women's Hospital. The hospital

had previously only been using iNO for pulmonary vasodilation. When iEPO was introduced, new training for our respiratory therapists, nurses, physicians, and pharmacists had to occur. Therefore, there could have been differences in patients based on the need for adjustment to a new agent and procedure. In addition, although our institution has a suggested titration and weaning protocol in place for both iNO and iEPO, the protocol may be deviated from based on individual patient response and attending physician preference. Therefore, not all patients may have followed the exact protocol, which may have affected the results.

Finally, because of the retrospective nature of this study, we were unable to control for other pulmonary vasodilation strategies and concomitant therapies. It is unknown if any concomitant therapies or any nonpharmacologic strategies affected the results of the study.

5. Conclusion

We found no detectable differences between iNO and iEPO in terms of Pa_{O_2}/F_{IO_2} ratio, duration of mechanical ventilation, ICU and hospital length of stay, and safety profile in a diverse cohort of hypoxic, critically ill patients. Inhaled nitric oxide is associated with a greater drug expenditure per patient than iEPO. Larger, prospective studies are needed to validate these results.

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