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

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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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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].