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Literature Review

Articles That May Change Your Practice: Inhaled Epoprostenol

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Acute respiratory distress syndrome (ARDS) is a devastating syndrome that affects both adults and children. It is characterized by an inflammatory process that causes extensive alveolar damage, alveolar capillary leakage, and pulmonary edema, leading to disturbances in gas exchange and hypoxemia. ARDS is a complication of either direct or indirect lung injury, with a mortality rate between 40% and 50%. Survivors tend to be young or those without comorbid illness; many have long-term abnormalities in pulmonary function and an impaired quality of life.

Prostacyclin is a naturally occurring prostaglandin that has vascular smooth muscle relaxant and anti-inflammatory properties and also inhibits platelet aggregation and neutrophil adhesion. It is a potent vasodilator of the systemic and pulmonary vasculature resulting in a reduction of right and left heart afterload and can be administered intravenously or by the inhaled route. Inhaled prostacyclin appears to improve oxygenation, lower pulmonary vascular resistance and mean pulmonary arterial pressure, and reduce pulmonary shunt fraction. As a result, it may have potential benefits in resolving hypoxemia from ARDS and treatment of pulmonary hypertension and right heart failure, similar to inhaled nitric oxide (iNO). A Cochrane review of aerosolized prostacyclins for ARDS in 2017[1] found a paucity of quality evidence to guide the use of inhaled prostacyclins. There are limited studies examining inhaled prostacyclin in patients with ARDS, and there are no studies comparing inhaled prostacyclin with nitric oxide or the various possible ways to deliver inhaled prostacyclin to patients with ARDS.

There is growing interest in inhaled epoprostenol (iEPO) in the transport setting. Patients with severe ARDS are often considered for complex, invasive therapies, including extracorporeal membrane oxygenation (ECMO). However such therapies are only available in specialized centers. Transporting a patient after the initiation of ECMO is either not widely available or difficult, and iEPO is increasingly considered as a temporary "bridge" to more complex therapies. Articles published subsequent to the Cochrane review are presented here.

Ammar MA, Bauer SR, Bass SN, Sasidhar M, Mullin R, Lam SW. Noninferiority of inhaled epoprostenol to inhaled nitric oxide for the treatment of ARDS. *Ann Pharmacother*. 2015;49:1105-1112.

The authors of this study compared the efficacy and safety of iEPO in mechanically ventilated patients with iNO. They performed a retrospective, noninterventional, propensity-matched cohort study in adult patients admitted to an intensive care unit (ICU) with ARDS on mechanical ventilation who received either iEPO or iNO for at least 1 hour. Patients were followed for 28 days after the initiation of inhaled therapy or until death. The primary outcome was mechanical ventilator-free days, with secondary outcomes of ICU-free days, death at ICU discharge, and changes in partial pressure of arterial oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) at specified time points during therapy. Safety end points included hypotension, methemoglobinemia, renal dysfunction, rebound hypoxemia, bleeding, and thrombocytopenia. The study was designed to show the noninferiority of iEPO compared with iNO. In total, 102 patients met the inclusion criteria, and 47 patients were propensity matched to each of the iEPO and iNO groups. Their baseline characteristics were the same, as was their ARDS management before the initiation of inhaled therapy. The authors found there were no significant differences in the primary or secondary outcomes between the 2 groups and no significant differences in any of the safety outcomes.

This was the largest study evaluating iEPO and iNO strictly in patients with ARDS. The patients in this study had severe ARDS, with 70 of the 94 patients (74.5%) dying before discharge. The authors point out the optimal dose of either agent is not well-known, and it is unclear whether the findings could be extrapolated to treatment protocols that differ from what was noted in the study. However, what this study does suggest is that iEPO is noninferior to iNO in ARDS patients with severe disease from day 1 to day 28.

Kallet RH, Burns G, Zhuo H, et al. Severity of hypoxemia and other factors that influence the response to aerosolized prostacyclin in ARDS. *Respir Care*. 2017;62:1014-1022.

Lung injury in ARDS is nonhomogeneous, with portions of the lung remaining functionally normal. Inhaled vasodilators exploit these differences by inducing local pulmonary vasodilation, thereby increasing alveolar ventilation/perfusion matching. Prostacyclin may also lessen the impact of pulmonary vascular endothelial injury and abnormal procoagulation that take place with ARDS.

The authors of this study hypothesized the initial response to aerosolized prostacyclin in ARDS would be greater in those with less impaired oxygenation. They also evaluated whether the ARDS etiology modifies the response to aerosolized prostacyclin. The authors retrospectively reviewed the records of 208 patients with severe ARDS who received aerosolized prostacyclin and had arterial blood gases done before and after the initiation of therapy without any other ventilator manipulations. Prostacyclin was delivered via a volumetric pump and jet nebulizer connected to the ventilator circuit with a T-adapter, with therapy beginning at 50 ng/kg/min and titrated downward. Response to therapy was determined by

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changes in in PaO_2/FiO_2, and a stepwise logistic regression model was constructed to determine the impact of 18 variables such as age, sex, ethnicity, Acute Physiology and Chronic Health Evaluation II and Simplified Acute Physiology Score scores, duration of ARDS, and other clinically relevant variables.

The authors found that 62% of patients responded to the inhaled therapy. The patients with the highest initial PaO_2/FiO_2 ratio showed the greatest improvement. Those with sepsis had smaller improvements compared with those without sepsis. In the final model, the only factors that predicted a positive response to aerosolized prostacyclin were baseline PaO_2/FiO_2 and respiratory system compliance.

Based on their findings, the authors concluded the amount of aerated lung parenchyma determined the impact of the inhaled therapy. In other words, those with a greater proportion of unaffected lung were more likely to respond to aerosolized prostacyclin. They also proposed that therapeutic efficacy could be enhanced with lung recruitment strategies, such as higher positive end-expiratory pressure, prone positioning, and alveolar recruitment maneuvers.

Anderson AC, Dubosky MN, Fiorino KA, Quintana V, Kaplan CA, Vines DL. The effect of nebulizer position of aerosolized epoprostenol delivery in an adult lung model. *Respir Care*. 2017;62:1387-1395.

Aerosolized epoprostenol is an alternative to iNO in ARDS and pulmonary hypertension. However, clinical data regarding the effect of placement of the nebulizer in the mechanical ventilator circuit on drug deposition are not known. In addition, variations in dosing practices and nebulizer equipment used to deliver aerosolized epoprostenol make the comparison of various studies problematic. The authors of this study evaluated differences in drug deposition based on different nebulizer positions in the ventilator circuit at a variety of drug dosing regimens and ventilator settings.

The authors used a standard ventilator setup with humidifier and heated wire circuit connected to a test lung, vibrating mesh nebulizer, intravenous pump, and epoprostenol reconstituted in sterile water according to the manufacturer's instructions. The nebulizer was connected in 4 locations in the ventilator circuit: inspiratory limb, between the tracheal tube and Y-piece, the humidifier's dry side (inlet), and the humidifier's wet side (outlet). Epoprostenol was delivered at 30, 50, and 70 ng/kg/min with 3 permutations of tidal volume and frequency for each of the 4 nebulizer positions. A total of 180 trial runs were performed.

Epoprostenol delivery increased significantly as the dose increased. There were no differences found between variations in ventilator settings nor were there differences found between the humidifier inlet and outlet, but these nebulizer positions resulted in greater drug delivery compared with the nebulizer on the inspiratory limb of the ventilator circuit or between the tracheal tube and Y-piece. The authors concluded the humidifier inlet or outlet are the positions on which to place the nebulizer to achieve the greatest amount of epoprostenol delivery.

Ammar MA, Sasidhar M, Lam SW. Inhaled epoprostenol through noninvasive routes of ventilator support systems. *Ann Pharmacother.* 2018;52:1173-1181.

iEPO is used as a potential rescue therapy for patients with severe hypoxemia caused by ARDS who fail conventional therapies to improve gas exchange. iEPO is usually delivered into a ventilator circuit in mechanically ventilated patients. There are circumstances in which iEPO may be beneficial to patients who are not mechanically ventilated, but the use of iEPO by noninvasive ventilatory routes has not been well described.

The authors describe a retrospective case series of adult patients admitted to the ICU to whom iEPO was delivered via a noninvasive route for at least 1 hour, either by high-flow nasal cannula or noninvasive positive-pressure ventilation. A positive response was defined as a 20% increase in PaO_2, whereas an adverse response was defined as a drop greater than 20% in the mean arterial pressure, a drop in systolic blood pressure below 90 mm Hg, heart rate above 16 or below 60, change in heart rate greater than 20%, or any other sign of hemodynamic instability.

Of the 521 patients who received iEPO, 36 received it via a noninvasive route. All patients tolerated the maximum dose of 50 ng/kg/min. Overall, 16 patients experienced respiratory improvement, 8 experienced a decline, and 12 had no change in their respiratory status. Sixteen of 36 experienced hypotension at 6 hours postinitiation of iEPO, 2 had significant bleeding, and 6 experienced thrombocytopenia. In-hospital mortality was 58%. Noninvasive iEPO may be 1 of the last options to improve oxygenation in patients who failed conventional therapies and are not good candidates for mechanical ventilation.

The authors caution that the delivery of iEPO through an open circuit may pose a risk to caregivers. Patients should be managed in a private room with the door closed during therapy. Staff should wear appropriate personal protective equipment, including an N95 respirator. The authors note the study lacked a comparator group and the impact of iEPO by the noninvasive route beyond 12 hours was not studied and conclude that further evaluation of iEPO by this route is needed to determine its impact and efficacy in patients with severe ARDS.

Patients suffering from ARDS have a high mortality and are often refractory to multiple therapies. The available evidence suggests that iEPO may have a role in improving respiratory function and may have an impact on patient outcome. However, the evidence is far from conclusive given the lack of well-designed clinical trials. This information is relevant in the transport setting because patients with severe, refractory ARDS are often transferred to specialty centers to receive more invasive, complex therapies such as ECMO. Air and land critical care transport services are called on to transport these inherently unstable patients, and these patients pose a significant challenge to transport personnel. iEPO may be a possible option in transport to bridge patients to more complex therapies if other options have proven unsuccessful.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amj.2019.04.001.

Reference

1. Afshari A, Bastholm BA, Allingstrup M. Aerosolized prostacyclins for acute respiratory distress syndrome (ARDS). *Cochrane Database Syst Rev*. 2017;7:CD007733.

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