Pulmonary Hypertension in Neonates: Inhaled Nitric Oxide vs Epoprostenol (Flolan)

Short Communication

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Introduction

Pulmonary hypertension is a complex disease with an assorted group of etiologies in the neonatal and pediatric populations [1]. The most common cause of acute pulmonary vascular crisis in neonates is persistent pulmonary hypertension of the newborn (PPHN), a condition where a neonates postpartum circulation physiologically changes back to fetal circulation, thus, causing high pulmonary vascular resistance, and directly affecting cardiopulmonary hemodynamics [1]. The condition of PPHN may be isolated, but is also associated with meconium aspiration syndrome, pneumonia, sepsis, congenital diaphragmatic hernia and/or other disease states [1]. In current practice, PPHN can be treated using either inhaled nitric oxide or epoprstenol (Flolan).

Inhaled nitric oxide is an endogenous free radical gas, which selectively targets pulmonary vessels, causing a potent and sustained vasodilatation, and therefore increasing pulmonary blood flow [2]. After diffusion across the alveolar capillary membrane, the iNO is absorbed by subjacent smooth muscles of the pulmonary vasculature to activate soluble guanylate cyclase, which is responsible for conversion of GTP to cGMP which activates relaxation of smooth muscles via several mechanisms [2]. Because iNO is scavenged and deactivated by the hemoglobin upon diffusion into the blood, its vasodilatory effects are limited largely to the lungs [2].

INO can be safely inhaled when inhaled through a mask, nasal cannula, or an endotracheal tube, and requires a specialized delivery device synchronized with respiration and minimal production of NO_2, which is toxic to the lung parenchyma, and can cause pulmonary edema [3]. Specifically speaking of administration during mechanical ventilation, the iNO is administered through the inspiratory limb of the ventilator, and the expiratory gas is scavenged from the expiratory wall block of the ventilator to the wall suction [3].

Staring dose of iNO is usually 20ppm, and doses >20ppm are rarely required, and must be consulted with the neonatologist [3]. Monitoring of the neonate during iNO administration is crucial to determine response to therapy and to prevent the adverse side effects related to iNO therapy [3]. All neonates receiving iNO should include monitoring of pre- and post-ductal SpO_2, blood pressure, transcutaneous CO_2, ABG's, NO and NO_2 levels, and met Hb levels [3]. Large clinical trials have demonstrated that iNO therapy is safe for use in the hypoxemic term neonates, and has not been associated with clinically evident bleeding in neonates with pulmonary disease [2]. In premature neonates, several studies have also helped to point out that iNO does not increase the incidence of intraventricular hemorrhages [2].

Although the cost of $2,7000 per day to use iNO may seem high, several studies have suggested that iNO is a cost effective therapy for neonates with hypoxic respiratory failure and pulmonary hypertension because it decreases the need for ECMO, which is far more invasive and costly [2,4].

Epoprostenol, also marketed under the brand name Flolan, is a synthetic analog of prostacyclin, which activates the prostaglandin receptor, causing an increase in the intracellular cAMP through activation of the adenylate cyclase within the smooth muscle cells, which leads to relaxation of the smooth muscles [5]. When administered in aerosolized form, it produces selective pulmonary vasodilation leading to improvements in V/Q mismatch, oxygenation, and hemodynamics, by reducing the pulmonary vasculature resistance, reducing right ventricular afterload, and increasing right ventricular stroke, and is indicated for patients with worsening hypoxemia and clinical deterioration despite the use of ventilator strategies recommended by the ARDS network [5].

Nebulization of Flolan during mechanical ventilation is done using a continuous aerogen nebulizer t-piece just proximal to the heating chamber of the ventilator circuit, while its administration is done using a syringe pump using desired dosage in mL/hr [5]. Using ideal body weight, initial dose of 50ng/kg/min is used and titrated down every 30 minutes as tolerated to 10ng/kg/min based on PaO_2 improvement [5]. Studies have shown that using doses higher than 50ng/kg/min have not been shown to improve patient outcomes [5]. During administration of Flolan, it is critical to monitor the patients PA pressures, SaO_2, PaO_2/FiO_2, PEEP, and vitals. Response to therapy should be seen within 10 minutes of initiation of treatment, with positive response showing >20% increase in PaO_2, and >20 reduction in pulmonary artery pressures [5]. A decline in >25% reflects negative response, and a critical care clinician must contacted immediately for further consultation [5].

The cost of using Flolan therapy is less than $200, which computes to a fraction of the cost to use iNO therapy, which over a

long period of time would mean huge savings, which could be re-invested towards treatment of more patients, and improvement in their care [4].

Early treatment of PPHN, regardless of etiology is crucial, because advanced disease may be less responsive to therapy [1]. Although many factors contribute towards the selection of therapy, it is ultimately dependent upon the clinicians and hospitals to choose between either iNO or Flolan, as both offer lifesaving therapies, with each having its advantages and disadvantages in treating pulmonary hypertension in critically ill neonates.

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