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Mini Review

Persistent Pulmonary Hypertension of the Newborn

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Abstract

PPHN is a complex medical condition associated with significant mortality and morbidity in neonatal population. It is due to the failure to transition from fetal to postnatal circulatory pattern resulting in persistent elevation of pulmonary vascular resistance and hypoxia. Since the introduction of inhaled nitric oxide, surfactant, and high frequency ventilation, mortality outcomes have improved tremendously. In this review we summarize the current knowledge on this condition including the management strategies, the remaining challenges, and the future directions for research.

Keywords: Persistent Pulmonary Hypertension of the Newborn; Inhaled Nitric Oxide; Pulmonary Vasodilator

Abbreviations

PPHN: Persistent Pulmonary Hypertension of the Newborn; PVR: Pulmonary Vascular Resistance; iNO: inhaled Nitric Oxide; HFV: High Frequency Ventilation; MAS: Meconium Aspiration Syndrome; RDS: Respiratory Distress Syndrome; PDA: Patent Ductus Arteriosus; PFO- Patent Foramen Ovale; PaO_2: Partial Pressure of Oxygen; FiO_2: Fraction of Inspired Oxygen Concentration; OI: Oxygen Index; ECMO: Extracorporeal Membrane Oxygenation; PDE: Phosphodiesterase; cGMP: cyclic Guanosine Monophosphate

Introduction

PPHN is a syndrome caused by failure of spontaneous decrease of the PVR at birth. This failure may be secondary to pulmonary vasoconstriction, structural thickening of pulmonary arterial wall, or dysmorphic angiogenesis in the lung. The prevalence rate of PPHN has been reported as 1.8 - 2.9 cases per 1000 live births with mortality ranging from 4% - 33% [1-4]. The incidence is higher, and the survival rate of affected newborns is poorer in resource limited countries where iNO and HFV are not readily available.

Etiology and Pathophysiology of PPHN

PPHN could be primary or secondary based on the etiology. Primary PPHN is seen with abnormally developed pulmonary vasculature with normal lungs. Secondary PPHN is seen in the background of MAS, transient tachypnea of newborn, RDS, pneumonia, sepsis, and congenital diaphragmatic hernia [1,5]. Hypothermia for hypoxic ischemic encephalopathy may also contribute to PPHN [6]. Risk factors independently associated with PPHN include gestational age under 37 weeks; African American race; large or small size for gestational age; maternal diabetes, obesity and advanced age; and exposure to selective serotonin reuptake inhibitors [1,3].

PVR is high in utero as the fetus does not need to use lungs to oxygenate blood. Normally PVR decreases precipitously with the first breath allowing lungs to assume the role of main respirators of the body. Interruption of this physiological transition due to any of the above-mentioned factors leads to persistence of fetal pulmonary hypertension. High PVR ex utero decreases the blood flow to lungs and diverts it to systemic circulation instead. Cyanosis develops due to ventilation-perfusion mismatch and extra pulmonary right-to-left shunting of deoxygenated blood across the PDA and PFO.

Clinical Manifestations & Diagnosis

Infants with PPHN usually show signs and symptoms of the underlying cause. The usual presentation is with signs of respiratory distress including tachypnea, retractions, and grunting along with cyanosis within the first 24 hours of life. The infants may also have low Apgar scores and most of them would have received delivery room resuscitation including positive pressure ventilation and endotracheal intubation [2].

Clinical evaluation should begin with a thorough history and physical examination followed by investigations including chest x-ray, arterial blood gas sampling, and echocardiography to estimate the severity of pulmonary vascular pressures.

In infants with hypoxia, it's important to differentiate cyanotic congenital heart condition from PPHN. If PDA is open in PPHN, a difference of greater than 5-10% in oxygen saturations or a gradient of 10-20 mmHg of PaO_2 in blood gas is seen between the pre and post ductal measurements. If PDA is closed, right to left shunting occurs at atrial level, both pre and post ductal saturations will be low. In congenital heart disease, hypoxemia is always fixed with PaO_2 <100 mmHg, but in PPHN, PaO_2 usually increases with increase of the FiO_2. Chest radiograph shows features of underlying pulmonary condition. Pulmonary vasculature might appear reduced or normal. The gold standard test to confirm the diagnosis of PPHN is echocardiography. Features of PPHN include flattening or left deviation of interventricular septum, elevated right sided pressures and right to left blood flow *via* PDA or PFO.

Management

Infants with PPHN require care with oxygen supplementation, noninvasive or invasive mechanical ventilation based on the severity. Administering surfactant early in the course is beneficial to these infants if the PPHN is secondary to RDS or MAS [7,8]. Fluid management is important for circulatory support and correction of acidosis. Inotropes play a vital role in increasing the systemic pressures

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above pulmonary pressures and preventing right to left shunt *via* PDA and PFO. As sepsis, especially sepsis by group b Streptococcus or the gram-negative bacilli could cause PPHN, most of the clinicians lean towards treating these infants with empiric antibiotics until the sepsis work up is negative. Other supportive measures include providing optimal thermal environment, nutritional support, avoidance of stress, and administration of sedation and analgesia as required to minimize oxygen consumption by the infant.

Acidosis and alkalosis should be avoided and goal arterial PH should be between 7.30 and 7.40 [2,9,10]. Oxygen is the most potent pulmonary vasodilator and clinicians should have low threshold to use it albeit keeping in mind the danger of Retinopathy of Prematurity in premature infants. However, caution is required in administering oxygen as some recent studies have shown that higher oxygen concentrations (≥50%) can cause lung injury by generating free radicals, increase the contractility of pulmonary vasculature, and reduce the response to iNO [11,12]. The goal is to maintain PaO_2 levels 60-80 mmHg and preductal saturations 90-95% range. Also, maintain hemoglobin concentration in 15-16 g/dL range to maximize the oxygen carrying capacity.

Inhaled NO is a potent and selective pulmonary vasodilator without effect on systemic blood pressure. It improves oxygenation and decreases the need for ECMO in term and late preterm infants with severe PPHN, defined as the OI of ≥25 [13-15]. It made a dramatic impact on the outcome of infants with PPHN [16]. The mortality from PPHN decreased from 30% to under 10% since the introduction of iNO [17,18]. Early initiation of iNO at OI of 15-20 had 2.5 fold reduction in the need for ECMO compared to initiation of iNO at OI of 20-25 [7]. Cost of hospital care and time to discharge from hospital were also lower when iNO was initiated at OI of 15-20 [19]. The starting dose for iNO is 20 parts per million. A response to iNO is defined as increase in PaO_2 of 20 mmHg or more. Higher doses are not recommended due to risk for elevated nitrogen dioxide and methemoglobin levels. Monitor methemoglobin levels frequently during the iNO therapy. Using higher PEEP on conventional mechanical ventilation or HFV may boost the response to iNO. Start weaning iNO only when FiO_2 is below 60% and PaO_2 can be maintained >60mmHg. Wean iNO gradually to minimize the risk of rebound vasoconstriction [20].

Sildenafil is a PDE -5 inhibitor that reduces pulmonary vascular resistance by increasing the cGMP concentrations. Vasodilation mainly occurs in the pulmonary vascular bed and to a lesser degree in the systemic circulation. It can be used in cases not responding to iNO or in settings where iNO is not available [21]. Administer oral dose at 0.5-2 mg/kg/dose every 6 hours. For intravenous route, give initial bolus of 0.42 mg/kg sildenafil over 3 hours, followed by 0.07 mg/kg/hr as continuous infusion [22]. Monitor blood pressure closely for hypotension. Oral sildenafil therapy is recommended and IV sildenafil should be used only when oral administration is not feasible.

Milrinone is a selective PDE-3 inhibitor and has both positive inotrope and vasodilator effect, but it decreases both pulmonary and systemic pressures. Hence, it has to be used judiciously only when systemic blood pressures are normal with evidence of ventricular dysfunction [23,24]. The usual loading dose is 50 μg/kg given over 60 minutes followed by maintenance dose of continuous infusion at 0.25-0.75 μg/kg/minute [24]. It is not advised to use sildenafil and milrinone simultaneously due to risk for severe hypotension.

Around 40% of infants with severe PPHN remain hypoxemic even with iNO [13]. Other treatment options for severe PPHN resistant to iNO include endothelin receptor antagonists (Bosentan), prostaglandins like Epoprostenol (PGI_2), Iloprost(PGI_2), Alprostadil(PGE_1) and Treprostinil (prostacyclin) but these are not approved for routine use due to lack of data on efficacy and safety [25-28]. Future multicenter randomized trials are required before using these medications routinely. Steroids are commonly used for hypotension. Animal studies showed that steroids decrease pulmonary pressures and oxygen dependency in PPHN [29-31]. A small randomized controlled trial by Tripathi et al showed that steroids decrease the number of days of oxygen dependency in infants with MAS [32]. ECMO is the last treatment resort for neonates with severe PPHN (OI≥40) not responding to iNO. American Academy of Pediatrics recommends using iNO only in centers with ECMO or an established mechanism for timely transfer to an ECMO center [33].

Outcomes

The mortality rate for PPHN ranges between 6.5 to 10% in developed countries [2,34,35]. The survivors are at risk for neurodevelopmental and hearing impairments due to hypoxemia [34,36,37]. These infants need long term neurodevelopmental follow-up and hearing test at 18-24 months of age.

Conclusion

PPHN management has improved significantly in the last two decades, decreasing the mortality to under 10%. Surfactant, iNO and gentle ventilation strategies focusing on optimizing lung recruitment and minimizing oxygen toxicity have decreased the need for ECMO. Unfortunately, the incidence of PPHN remains high and survival rates remain low in resource limited countries where iNO, surfactant, and HFV are not readily available. Future studies are need in these settings where iNO is unavailable focusing on other treatment options.

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