PERSISTENT PULMONARY HYPERTENSION IN NEWBORN RECENT PROGRESS

Dr. Upendra Yadav\textsuperscript{1, 2}, Dr. Zhu Xiao Fang\textsuperscript{2} and Dr. Jeetendra Yadav\textsuperscript{1}

\textsuperscript{1}Yangtze University, 1 Nanhuan Road Jingzhou Hubei 434023, P.R. China
\textsuperscript{2}Department of Pediatrics, Clinical Medical College of Yangtze University, Jingzhou Central Hospital, Jingzhou, Hubei Province, PR China

ABSTRACT

Persistent pulmonary hypertension in newborn (PPHN) is a collection of symptoms showing failed circulatory adaptation at birth. This is characterized by increased pulmonary vascular pressure resistance which leads to extra-pulmonary shunting from right to left flow of blood across the ductus and/or foramen ovale. PPHN occurs mostly in term and near term infants but it is not uncommon in preterm infants who have respiratory distress syndrome. The treatment of PPHN include oxygen supplementation, mechanical ventilation, nitric oxide, phosphodiesterase inhibitors, prostaglandins analogs, endothelin receptor antagonists to maintain ideal vital signs and internal environment homeostasis required and also decrease pulmonary pressure, to decrease the need of ECMO, progression of disease and duration of hospital stay.

Key words: Persistent pulmonary hypertension in newborn, Dopamine, Surfactant, Milrinone, Inhaled nitric oxide,

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INTRODUCTION

Persistent pulmonary hypertension of the newborn (PPHN) can occur as a primary or secondary neonatal emergency and is a potentially life threatening condition with a high mortality rate. More often full term and near term infants are affected, however not uncommon to see PPHN in preterm infants who have respiratory distress syndrome. PPHN has high morbidity. A lot of Management strategies have been taken, but still there are some PPHN has no good response, so we review some references to know the new progress.

Morbidity and Mortality:

PPHN is a serious neonatal illness, which in the past was associated with high mortality and morbidity. About 10-50% of the victims die of the problem. Some researchers have reported that PPHN occur 1-2 per live born infants. Other article has mentioned PPHN is relatively common condition occurring in 7 per 1000 live births and results mortality up to 30%. Studies from developed countries have reported that PPHN incidence rate of 0.46–6.8/1,000 live births with a mortality rate of 10%–20%, the incidence is thought to be much higher in developing countries.

Pathogenesis:

When the normal cardiopulmonary transition fails to occur, the result is persistent pulmonary hypertension of the newborn (PPHN). PPHN is generally lies in one of these three: (1) Under-development, (2) Mal-development, (3) Mal-adaptation. (1) Under-development (decreased vascular growth) include congenital diaphragmatic hernia (CDH), pulmonary hypoplasia, oligohydramnios from premature rupture of membranes or renal agenesis, pleural effusion, vascular anomalies, asphyxiating thoracic dystrophy, phrenic nerve agenesis, and alveolar capillary dysplasia. (2) Mal-development (abnormal vascular structure) include idiopathic or Primary (10-20%) PPHN, chronic fetal hypoxia, fetal anemia, and premature closure of the ductus arteriosus. Some cause of idiopathic PPHN is due to maternal exposure to non-steroidal anti-inflammatory drugs (NSAIDs) during the third trimester, and SSRI. Some rare causes of severe and intractable PPHN include alveolar capillary dysplasia, mutations in surfactant protein B (SP-B) gene. Byers et al. has said genetic variants in corticotropin-releasing hormone (cRh) receptor1 (CRHR1) and cRh-binding protein (CRHBP). 3. Mal-adaptation (perinatal hypoxia-induced vascular spasm) include asphyxia, MAS, neonatal respiratory distress syndrome (RDS), and sepsis/pneumonia, transient tachypnea of the newborn (TTN). Other predisposing factors are congenital heart diseases such as total anomalous pulmonary venous return, left atrial or mitral obstruction, and hypoplastic left heart syndrome can be responsible for PPHN. Polycythemia, hypoglycemia, and hypocalcemia can also be responsible for PPHN. Pneumothorax change of fetal heart beat pattern and asphyxia are also risk factors for PPHN in MAS. MAS being the most common cause of PPHN results from airway obstruction, inactivation of surfactant, and chemical pneumonitis from the release of pro-inflammatory cytokines.
High Risk Factors:

Male infants, black or Asian maternal race, pre-conception elevated body mass index (BMI>27 vs. BMI<20), diabetes, asthma, cesarean section before 39 weeks of gestation, late preterm, and large for gestational age (LGA) are high risk factors\[^{13}\]. Athar Razzaq\[^{14}\] shows that positive pressure ventilation while resuscitation (44.2%), MAS and birth asphyxia (40.5%) were observed the major risk factors for developing PPHN. Other factors include RDS, pneumonia or sepsis, pulmonary vasoconstriction from asphyxia, and pulmonary hypoplasia secondary to congenital diaphragmatic hernia (CDH) or oligohydramnios\[^{15}\]. Compared to the term, post term and preterm, preterm male infants (88.8%), born by cesarean-section (77.7%), complicated by respiratory distress syndrome (44.4%) and sepsis (44.4%) were relatively more associated with PPHN\[^{16, 17}\]. Except that, maternal SSRI exposure is other high risk factors\[^{7}\], antenatal exposure of NSAID\[^{16, 18}\], intrauterine growth restriction\[^{19}\], genetic risk factor\[^{20}\], antenatal smoke exposure\[^{21, 22}\], infection\[^{23}\], include histological chorioamnionitis, GroupB Streptococcus(GBS) and funisitis. Perinatal nutrition has been well established that maternal obesity and diabetes are associated with increased risks of maladaptation at birth\[^{24}\]. The exact mechanisms are unclear, but include perinatal asphyxia, parenchymal disease and polycythemia. Studies have highlighted that infants with PPHN are deficient in the amino acid, L-arginine, which is required for nitric oxide (NO) synthesis\[^{25}\].

Diagnosis:

PPHN should be suspected clinically in infants who have cyanosis with or without history of fetal distress, intrauterine growth restriction, meconium stained amniotic fluid, hypoglycemia, polycythemia, diaphragmatic hernia, pleural effusion, pneumothorax, birth asphyxia. Hypoxemia is universal and is unresponsive to high oxygen (60-100%) given by face mask or ventilator, the diagnosis is PPHN or acyanotic heart disease are suspected.

Physical examination of neonates who has PPHN usually reveals tachypnea, retractions, grunting, and cyanosis. Abnormal cardiac sounds, such as systolic murmur of tricuspid regurgitation or prominent may be heard, however, these are not diagnostic for PPHN. Many of these clinical signs are found in neonates with cyanotic congenital heart disease (CHD)\[^{26}\]. Preductal and postductal oxygen saturation PaO2 measurements are used to differentiate PPHN from structural heart disease. Saturation differences of >5-10% or PaO2 differences of 10–20 mmHg between right upper limb and right lower limb are considered significant. Respiratory distress is mild unless the pulmonary hypertension is secondary to lung disease such as meconium aspiration syndrome (MAS), respiratory distress syndrome (RDS), pneumonia\[^{27}\]. So differentiating cyanotic congenital heart disease from PPHN is of paramount importance.

Accessory examination can help us to make a decision:

A blood works up is helpful to identify the etiological factors responsible for PPHN, a complete blood count can show abnormal white blood cell counts and help rule out infections and can show polycythemia. Blood glucose and calcium level are helpful to rule out metabolic causes. Recently, Brain natriuretic peptide (BNP) is a reliable and easily available marker which contributes to the diagnosis of PPHN especially if an
echocardiogram is not readily available. Reynolds et al. in a prospective cohort study shown that an initial BNP level of 550 pg/ml or greater was predictive of PPHN with a sensitivity of 85% and a specificity of 100%. Vijlbrief et al. performed another prospective cohort study, shown that BNP level significantly increases in patients with rebound pulmonary hypertension following the discontinuation of NO.

Imaging studies can be valuable to make the diagnosis of PPHN, a chest X-ray can show oligemic lung fields in primary PPHN and be helpful in diagnosing lung disease. Echocardiography is the gold standard investigation to establish the diagnosis of PPHN and to rule out structural abnormalities. Right ventricular hypertrophy, deviation of inter-ventricular septum to the left, tricuspid regurgitation (TR) and right to left or bidirectional shunting at the patent foramen ovale (PFO) and patent ductus arteriosus (PDA) are cardinal findings in PPHN. In infants with hypoxemia and left to right shunt at both PDA and PFO, the hypoxemia is due to intrapulmonary shunting. Right to left shunt at both PDA and PFO is suggestive of increased PVR and extra-pulmonary shunting and is likely due to PPHN. Right to left shunt at the ductus arteriosus and left to right shunt at the PFO are suggestive of pulmonary hypertension with left ventricular dysfunction and are often seen in CHD, asphyxia and sepsis. Left to right shunt in the ductus arteriosus and right to left shunt at the foramen ovale are seen in infants with cyanotic congenital heart disease with ductal depended pulmonary blood flow such as tricuspid atresia, critical pulmonary stenosis and pulmonary atresia.

Invasive method obtain direct measurements of pulmonary hemodynamic parameters is through cardiac catheterization. The hemodynamic criteria for the diagnosis of pulmonary hypertension are: Mean pulmonary arterial pressure (PPA) greater than or equal to 25 mm Hg, PVR greater than 3 Wood units × m², Pulmonary capillary wedge pressure less than or equal to 15 mmHg. However, complications from cardiac catheterization may be more likely in small and sick children, particularly those with low birth weight (<2500 g). Thus, catheterization is not frequently undertaken early in the course of neonatal illness (such as in the first month of life) unless complex congenital heart disease (CHD) and done only in a few experienced centers.

Assessment of severity of hypoxic respiratory failure (HRF) with oxygenation index (OI) and A-aDO2:

\[ OI = \frac{MAP \times FiO2 \times 100}{PaO2}, \text{Mild } <15, \text{ Moderate } 15 \text{ to } 25, \text{ Severe } 25 \text{ to } 40 \text{ and, very severe } >40, \text{ Alveolar - arterial oxygen gradient: } A-aDO2 = (Patm - PH2O) \times FiO2 - PaO2 - PaCO2/RQ, \text{ (RQ is the respiratory quotient and equal to 1 if the energy source is purely carbohydrate or equal to 0.8). Severity assessment based on P/F ratio: Mild } >200 \text{ to } <300, \text{ Moderate } >100 \text{ to } <200 \text{ and Severe } <100 \text{ mm Hg. More recently, oxygen saturation index: } OSI = \frac{MAP \times FiO2 \times 100}{Preductal SpO2} \]

Management:

1. Management in delivery room: Infants with PPHN become ill in the delivery room or within the first 12 hour of life. Early recognition of PPHN and correction of factors that prevents decrease of PVR are important management. Resuscitative efforts may be required in the delivery room based on the Neonatal Resuscitation Program or the American Academy of Pediatrics/American Heart Association guidelines focusing on optimal lung recruitment and ventilation. Pulse oxymetry should be placed on right upper limb and saturation is maintained in the range recommended by the neonatal resuscitation program.
2. General supportive care: Covering eyes and ears to maintaining a low noise environment, Minimal stimulation, along with judicious use of sedation and analgesia with narcotic analgesics, like morphine and fentanyl or benzodiazepines such as midazolam. Paralysis should be avoided as it has been associated with increased mortality[32]. Correct metabolic abnormalities, such as hypoglycemia, hypocalcemia, acidosis, and polycythemia. Intravenous nutrition and amino acid supplementation with an optimal chloride:acetate ratio should be administered preferably through a central line. Normothermia helps to maintain normal metabolism of body and prevents PVR. Systemic blood pressure should be maintained at normal values for gestational age.

3. Respiratory support: Oxygenation is the mainstay of PPHN therapy to achieve normoxia possibly[33]. Oxygen is a specific and potent pulmonary vasodilator and increased oxygen tension is an important mediator of reduction in PVR at birth. Hypoxia increases PVR[34] and contributes one of the main cause of PPHN by decreasing the producing of vasodilator agents. Neonate with mild and transient respiratory distress may respond well to supplemental oxygen alone or the use of nasal CPAP. Neonate with moderate respiratory distress and severe hypoxemia may need mechanical ventilator and monitoring of blood gas. Mechanical ventilation setting are adjusted to facilitates alveolar recruitment and lung expansion, potentially improving the ventilation/perfusion (V/Q) match.

4. Target blood gas: There are 2 opinions about target blood gas. Jayasree Nair[35] recommend to maintaining pre-ductal oxygen saturation between 90% and 97% to achieve PaO$_2$ 55 to 80 mmHg and Paco$_2$ of 50 to 60 mmHg during management of infant with PPHN to ensures the optimal balance of pulmonary vasodilatation and minimizes adverse effects from oxidative stress. Nelson textbook[36] has mentioned hyperventilation to reduce pulmonary vasoconstriction by the PaCO$_2$ (=25mmHg) and increasing the pH (7.50 - 7.55). This strategy required high peak inspiratory pressure and rapid respiratory rate, often necessitating the use of muscle relaxants for control of ventilation. Ventilator settings are adjusted to achieve paO$_2$ between 90 and 100 mmHg. Alkalinization with sodium bicarbonate can also be used to elevate serum pH. But Ostrea EM et al.[4] has said Paco$_2$ level < 25 to 30 mmHg can increase incidence of cystic periventricular leukomalacia (PVL) and cebral palsy (CP) in preterm and near-term infants since CO$_2$ also controls cerebral perfusion, hypocapnia cause cerebral edema sensorial deafness[47, 48]. Therefore, mechanical ventilation should be targeting PaCO$_2$ level of 40-60 mmHg and paO$_2$ of 60-90 mmHg. However, hyperoxia (PaO$_2$ > 100 mmHg)[34, 39] does not decrease PVR instead results free radical injury[44]. Reactive oxygen species (ROS), such as superoxide interact with NO to form a potent oxidant peroxynitrite capable of vasoconstriction and surfactant inactivation[41].

HFO (high frequency oscillation) may help to optimize lung expansion in neonates who have PPHN secondary to lung disease and minimize lung injury. In those infants who can’t be adequately oxygenated with conventional ventilation, HFO ventilation should be considered early. Kinsella and colleagues[42] reported that HFO improves the oxygenation response to iNO when used in babies who have MAS and RDS.

5. Surfactant Replacement: In patients with PPHN secondary to parenchymal lung disease (such as RDS, pneumonia/sepsis, or MAS)[43], early administration of surfactant prior to iNO and lung recruitment is associated with better outcome with reduced risk of ECMO or death[45, 49]. Surfactant therapy leads to
improvement in oxygenation by improving V/Q matching and decreases intrapulmonary shunting\[^45\]. A multicenter trial demonstrated that this benefit was greatest for infants with relatively mild to moderate disease and with an oxygenation index (OI) of 15–25 Lotze\[^43\]. Lakshminrusimha and Vinay\[^46\] recommend that infants with PPHN secondary to parenchymal lung disease receive a dose of surfactant rich in surfactant protein – B (SP-B), such as calfactant or poractant alfa. In a multicentre study\[^43\] of 328 infants with MAS, sepsis or PPHN up to four doses of surfactant was associated with a reduction in the need for ECMO (p=0.038) especially seen in the lowest oxygen index(IO). It is not clear whether surfactant therapy is beneficial in infants with CDH. Animal studies reveal benefit, but a review of the CDH registry did not support the use of surfactant\[^47\]. Sharma Vinay et al,\[^46\] has mentioned that administration of surfactant only in the presence of clinical, radiologic, or biochemical evidence of surfactant deficiency in CDH and administer only 50% of the dose because of pulmonary hypoplasia.

6. Cardiac Support:

A. Limit fluid: Excessive administration of fluids in these circumstances results in further increase in right atrial pressure and exacerbation of right-to-left shunt at the foramen ovale and hypoxemia. Appropriate hydration and hematocrit (40-50%) should be maintained. Polycythemia (hematocrit > 55%) can increase blood viscosity and pulmonary vascular resistance 60~80ml/kg. Careful use of quick corrections with colloid or crystalloid solutions, unless there is evidence of intravascular depletion, is contraindicated, since the right atrial pressure is usually high (increased pulmonary vascular resistance and right ventricular dysfunction). Excessive administration of fluids in these circumstances results in further increase in right atrial pressure and exacerbation of right-to-left shunt at the foramen ovale and hypoxemia.

B. Reduce right-to-left shunting: Dopamine, dobutamine and epinephrine have been widely used in the management of PPHN, primarily to optimize cardiac function, stabilize systemic blood pressure, and reduce right-to-left shunting by increasing systemic vascular tone\[^46\]. Recently, norepinephrine has been shown to increase systemic pressure and oxygenation in neonates who have PPHN\[^48\]. B-Adrenergic agonists can decrease pulmonary vascular resistance more than systemic vascular resistance and might have a more favorable effect in PPHN especially in cases with poor myocardial function such as in birth asphyxia associated with PPHN\[^49\]. Systemic hypotension due to low systemic vascular resistance or left ventricular dysfunction is common in infants with PPHN. Right ventricular dysfunction and failure occurs due to increased afterload in infants with severe PPHN. Optimizing cardiac output with adequate volume expansion and inotropic support is important for achieving optimal gas exchange and systemic oxygen delivery.

Drug to choose for optimal effect are:

a. In the presence of systemic hypotension without cardiac dysfunction, the agents of choice are dopamine, norepinephrine and vasopressin (pressor support).

b. When systemic hypotension is associated with cardiac dysfunction, epinephrine or a combination of dopamine/vasopressin and milrinone are the agents of choice.
c. In the presence of stable systemic blood pressure and cardiac dysfunction, milrinone is the agent of choice.

d. Some sickest newborns with PPHN demonstrate hypotension refractory to vasopressor administration. This results from desensitization of the cardiovascular system to catecholamine by overwhelming illness and relative adrenal insufficiency. Hydrocortisone (1mg/Kg) can be repeated 12 hourly for 2–3 days) rapidly up-regulates cardiovascular adrenergic receptor expression and serve as a hormone substitute in case adrenal insufficiency.

<table>
<thead>
<tr>
<th>Drug/dose</th>
<th>Action mechanism</th>
<th>Effects</th>
<th>Side effects</th>
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<tbody>
<tr>
<td>Dopamine 1.5 – 20</td>
<td>Endogenous precursor of Norepinephrine Dose-dependent action 2.5 – 5 mcg/kg/min: Stimulation of dopaminergic receptors 5 - 10 mcg/kg/min: Beta 1 receptors stimulation 10 - 20 mcg/kg/min: alfa receptors stimulation</td>
<td>Dopa: mesenteric, kidney, brain, and spleen vasodilation Beta: increase in myocardial contractility and coronary flow, with increase in blood pressure and cardiac output Alpha: peripheral vasoconstriction and increased systemic vascular resistance, systemic arterial pressure, and pulmonary pressure; decreased kidney and mesenteric flow</td>
<td>High doses increase pulmonary and systemic vascular resistance</td>
</tr>
<tr>
<td>mcg/kg/min</td>
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<tr>
<td>Dobutamine 5 - 20</td>
<td>Dopamine synthetic analogue. Stimulates beta receptors, mainly Beta 1, and has little action over Alfa 2</td>
<td>Improves cardiac output through beta 1 inotropic action Little peripheral vascular effect</td>
<td>Tachycardia at high doses</td>
</tr>
<tr>
<td>mcg/kg/min</td>
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<tr>
<td>Epinephrine 0.05 -</td>
<td>Endogenous catecholamine with alfa and beta adrenergic effect, depending on the dose 0.05 --- 0.5 mcg/kg/min: beta receptor</td>
<td>Improves cardiac output through potent inotropic action Increases systemic blood pressure</td>
<td>Pulmonary and systemic vasoconstriction at high doses</td>
</tr>
<tr>
<td>2 mcg/kg/min</td>
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stimulation (beta1> beta 2) 0.5 - 2 mcg/kg/min: stimulation of alfa receptors

<table>
<thead>
<tr>
<th>Norepinephrine 0.5 - 2 mcg/kg/min</th>
<th>Endogenous catecholamine, which stimulates _1 and 2 receptors, as well as _1 and 2 receptors</th>
<th>Improves cardiac output through the inotropic action of alfa receptors, and increases blood pressure by peripheral action of alfa receptors. Possible improvement in pulmonary blood flow secondary to the release of endothelial nitric oxide</th>
<th>Systemic and pulmonary vasoconstrictor</th>
</tr>
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<tbody>
<tr>
<td>Milrinone 0.3 - 0.8 mcg/kg/min</td>
<td>Inhibitor of phosphodiesterase enzyme type III, which degrades cAMP</td>
<td>Improves cardiac output by reducing Afterload. Pulmonary vasodilation by increasing intracellular cAMP</td>
<td>Possible systemic vasodilation at high doses</td>
</tr>
</tbody>
</table>

Table 1: Inotropic and vasopressor drugs commonly used in pulmonary hypertension

cAMP, cyclic adenosine monophosphate

7. Pulmonary Vasodilator Agents: The pulmonary circulation has similar behavior to that of systemic circulation. Thus, the great difficulty in the pharmacology treatment of PPHN is to dilate pulmonary vessels without effecting systemic vasculature. Inhaled nitric oxide is a potent and selective pulmonary vasodilator without a significant decrease in systemic blood pressure (selective effect of iNO) because iNO gets inactivated by hemoglobin in the circulation and hence has minimal systemic vasodilator effect. iNO distributed to the ventilated segments of the lungs, resulting in increased perfusion of the ventilated segments, optimizing ventilation-perfusion match (microselective effect of iNO). iNO therapy is the only therapy approved by the US Food and Administration for clinical use in term or near term newborn infants (>34-weeks'gestation) with PPHN. Large multi-center trials have demonstrated that iNO reduces the need for ECMO. A meta-analysis of seven randomized trials of iNO use in newborns with PPHN also revealed that 58% of hypoxic near-term and term infants responded to iNO within 30–60 min. Konduri et al. demonstrated that earlier initiation of iNO with an oxygenation index (OI) of 15–25 did not reduce the need for ECMO but may have a tendency to reduce the risk of progression to severe hypoxemic respiratory failure. Based on current available evidence, an
acceptable indication for treatment with iNO would be an OI >15–25 with echocardiographic evidence of PPHN or a higher OI with or without evidence of right to left shunt. On abrupt withdraw, rebound vasoconstriction and resultant pulmonary hypertension is seen, iNO needs to be weaned gradually\(^{53}\). Weaning in steps from 20 ppm gradually over a period of time before its discontinuation has been shown to prevent the rebound effect\(^{54}\). If there is oxygenation response, inspired oxygen concentration is first weaned below 60% and then iNO is weaned at the rate of 5 ppm every 4h. Once iNO dose is 5 ppm, gradual weaning at the rate of 1ppm q4h is performed. Almost 40% of infants with PPHN do not respond or sustain a response to iNO. Adequate lung expansion should be established by increasing PEEP, surfactant therapy, and use of HFV prior to administration of iNO. If oxygenation remains low in spite of ventilator and hemodynamic optimization on iNO, ECMO is considered as a therapeutic option. The Committee on the Fetus and Newborn, American Academy of Pediatrics, has suggested that iNO use be limited to tertiary care centers where ECMO is available\(^{55}\). However, many centers without ECMO capability have access to iNO. Care should be taken to continue iNO therapy during transport from non-ECMO to ECMO centers.

Inhaled NO has several potential side effects, including platelet dysfunction, pulmonary edema, methemoglobinemia, and production of toxic byproducts such as nitrates. In combination with superoxide, it further potentiates oxidative injury by forming peroxynitrites. So optimal dose is required to administered to minimize the potential side effects.

In preterm neonate’s surfactant therapy has proven to be successful in reducing the risk of pneumothorax and mortality. However, many preterm neonates may have respiratory failure despite of surfactant treatment and pulmonary hypertension may complicate the course of these neonates. iNO reduces the lung inflammation and oxidant stress, preserves surfactant function, and promotes the growth and development of lungs pulmonary vasculature in animal models\(^{56-58}\). Unfortunately, the theoretical benefits of iNO have not transformed into a significant clinical advantage in preterm neonates. Cochrane review has evaluated the effect of iNO in preterm (<35 weeks of gestation) neonates with respiratory disease\(^{59}\). Based on the analysis of data from 11 RCTs(n=2536), the viewers concluded that:(a) iNO as rescue therapy for the very ill, ventilated preterm neonates did not appear to be effective and may increase the risk of severe intra-ventricular hemorrhage. (b) Late use of iNO to prevent chronic lung disease did not appear to be effective. (c) Early routine use of iNO in mildly sick preterm neonates may decrease serious brain injury and may improve survival without chronic lung disease. The results of two new RCTs\(^{60}\) and the follow-up data from three of the trials included in the Cochrane review have also not shown significant benefits of iNO\(^{61}\). In fact, the European Nitric Oxide (EUNO) trial has reported slightly more deaths, and a trend towards an increased number of deaths with an intra-cerebral bleed in extremely preterm (<26 weeks’ gestation) neonates treated with iNO. The role of iNO in preterm neonates with respiratory failure is not yet well established, despite extensive research. However preterm infants born with oligohydramnios, frequently following premature prolong rupture of membrane, and without significant acute RDS, may have pulmonary vascular physiology similar to that of term
and near-term infants who are treated with iNO. There are several reports describing acute improvements in oxygenation following initiation of iNO in this clinical situation[62, 63].

Milrinone is a PDE3A inhibitor and enhances cAMP levels in the arterial smooth muscle cells and cardiac myocytes resulting in vasodilation and inotropy. Milrinone administered as a loading dose of 50 mcg/kg/min over 30 min followed by 0.33 mcg/kg/min as continuous infusion. The dose may be titrated up to 1 mcg/kg/min with close monitoring of systemic blood pressure. Infants with PPHN refractory to iNO therapy have responded to IV milrinone in 3 case series[64, 65]. Milrinone may be the pulmonary vasodilator of choice in the presence of PPHN with left ventricular dysfunction.

Sildenafil is a PDE5 inhibitor presently available both in oral and intravenous form in the United States and is FDA approved only for adults with pulmonary hypertension. Studies have shown that oral sildenafil (dose range: 1–3 mg/kg every 6 h) improves oxygenation and reduces mortality in centers limited by non-availability of iNO[66, 67]. Intravenous sildenafil was shown to be effective in improving oxygenation in patients with PPHN with and without prior exposure to iNO. Being systemically administered, the risk of side effects like hypotension due to systemic vasodilatation is high. This risk may be diminished by slowly administering a loading dose (0.4-mg load over 3 h), followed by a maintenance dose (0.07 mg/kg/h). Sildenafil may reduce the rebound pulmonary hypertension noted during iNO weaning. A randomized control pilot trial of IV sildenafil prior to the use of iNO was stopped due to poor enrollment.

Magnesium promotes vasodilatation by antagonizing the entry of calcium ions into the smooth muscle cells[68]. The loading dose is 200 mg/kg. If response is adequate, then an infusion at 20–100 mg/Kg/hour can be started[69]. However, pre-term neonates are at high risk for respiratory depression due to magnesium sulphate. Magnesium sulphate is limited because it causes systemic hypotension. Few observational studies have indicated the benefits of MgSO\(_4\) in term and preterm neonates with PPHN[70, 71], however, no RCTs has been conducted. Oral sildenafil use may therefore be preferable in pre-term neonates.

Prostacycline is one of the most potent vasodilator. Most studies in infants have shown a similar or greater effect when compared iNO in decreasing pulmonary artery pressure and improving oxygenation[72, 73]. As it is non-selective pulmonary vasodilator, its administration via inhaled allows for selective pulmonary vasodilator, but its short half-life makes administration difficult. Iloprost is a longer acting prostacyclin analog with specific effect in pulmonary circulation and low risk of systemic hypotension and minimizing the effect on ventilation perfusion mismatch[12, 24]. Due to a short biologic half-life, low risk of toxic metabolites, and ease of delivery in the acute care setting, inhaled iloprost has been considered as an alternative to inhaled NO for postoperative care and vasodilator reactivity testing[75, 76]. A study suggested that the initial dose of iloprost 2.5 mcg inhaled five to nine times daily, could be increased to 5 mcg per inhalation, and could be maintained at that dose for chronic therapy[77]. Side effects, such as bronchospasm and poor compliance with frequent administrations (six to nine times daily), have discouraged its integration into the outpatient management of PAH in children.
Bosentan is a non-selective endothelin 1 receptor blocker that may be beneficial in the management of PPHN\cite{78}. Sitaxentan and ambrisentan are selective ETA receptor inhibitors. Theoretically, selective blockers of the ETA receptors should be superior to nonselective blockers. However, after an extensive review of the current evidence by Opitz et al. concluded that clinical superiority of selective versus nonselective blockers could not be demonstrated\cite{79}. Nakwan et al. have reported the benefits of bosentan in neonates with PPHN\cite{80}. A recent randomized controlled trial has shown its efficacy over placebo in a setting where NO was not available\cite{78}. Roberta L et al.\cite{81} has mentioned the dose he has used in his center is 1 mg/kg twice daily, and advanced to 2mg/kg twice daily under liver enzyme monitoring. A recent systematic review has identified a large number of observational studies (n = 21 studies) but no RCTs assessing the effects of bosentan in pediatric patients with pulmonary hypertension\cite{82}. These children had various underlying conditions including congenital heart disease, CDH, bronchopulmonary dysplasia, primary pulmonary arterial hypertension and collagen vascular diseases. Bosentan appeared to improve long-term functional status and hemodynamics in children with pulmonary arterial hypertension. Some side effects are Side effects such as abnormal liver functions, pulmonary hemorrhage or flushing. Clinical experience in the neonatal population has limited, RCTs in the neonatal population are warranted for more evidence to support bosentan use in PPHN.

**Newer Therapy:**

Several newer therapies for PPHN are under investigation. These include free-radical scavengers like recombinant human superoxide dismutase (SOD), which has improved oxygenation in lambs with PPHN\cite{83}. Use of antenatal betamethasone in animal studies has been shown to improve pulmonary arterial relaxation to ATP and NO donor in PPHN lambs\cite{3}. Increased endothelial NOS and reduced markers of oxidative stress were also revealed in the steroid-exposed group. Activators of sGC\cite{84} may be more effective than iNO in inducing pulmonary vasodilatation especially in the presence of oxidative stress.

**Long-Term outcomes:**

The infant with PPHN who survive and are discharged from NICU have long-term consequences, such as neurodevelopment, cognitive, and hearing abnormalities\cite{85}, depend on their underlying conditions and therapeutic interventions that they received at hospital stay. The rate of neurodevelopmental disabilities including cognitive delays and hearing deficit can be seen in 6.4% of PPHN survivors\cite{86}. Feeding problems and short term respiratory morbidities can be seen also in 24% of PPHN survivors. Rosenberg et al.\cite{86} found no differences in medical, neurodevelopmental, and social/emotional/behavioral outcomes at school age, between children with PPHN who were treated with iNO, with or without ECMO, and infants who were treated without exposure to iNO. Eriksen et al.\cite{87} found that infants, who were treated for PPHN at birth, had a higher prevalence of sensorineural hearing loss, chronic health problems, need for bronchodilator therapy, and remedial education at the age of 5–10 years in comparison to their controls\cite{87}. In their long-term follow-up of infants randomized to early iNO in PPHN, Konduri et al noted neurodevelopmental impairment in approximately 25% of infants and hearing impairment in approximately 23%\cite{85}(164). Long-term medical and neurodevelopmental multidisciplinary follow up of infants with PPHN after discharge is warranted.
CONCLUSION

PPHN can occur as a primary or secondary neonatal emergency and is a potentially life threatening condition with a high morbidity and mortality rate. PPHN requires early intervention and treatment to prevent severe hypoxia and various short term and long-term morbidities such as neurodevelopment, cognitive, hearing impairment. Survival of infants with PPHN has improved with advancement of PPHN therapy such as oxygen supplementation, mechanical ventilator, surfactant, iNO, prostaglandin analog, phosphodiesterase inhibitor, endothelin receptor antagonist. Supportive managements are blood pressure support and sedation and minimal handling. Oral/IV sildenafil, IV milrinone, and inhaled PGI2 may have a synergistic effect with iNO and are being used more frequently. Further research is requiring to bring new therapy such as Free radical scavengers like SOD, sGC activators, and antenatal steroids in clinical use to reduce morbidity and mortality associated with PPHN. After discharge from the NICU, infants with PPHN warrant long term follow up since they are at risk for neurodevelopmental disabilities and chronic health conditions.

REFERENCES


