

An overview on PPHN and management with Sildenafil and High frequency ventilator

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Introduction

Persistent pulmonary hypertension of the newborn (PPHN) was first described by Gersony et al, the persistence of the fetal circulation in 1969.¹ Persistent pulmonary hypertension of the newborn (PPHN) can occur as a primary or secondary neonatal emergency and remains a serious management challenge with a high mortality rate. The failure of a rapid fall in pulmonary vascular resistance in the early postnatal period that characterizes PPHN can progress into a vicious pulmonary vasoconstrictive cycle if not promptly managed. The condition occurs in near-term, term and post-term infants with an incidence of 0.43 - 6.8/1000 live births and carries a high risk of mortality of about 10 - 20%.²

The disruption in the normal perinatal fetal to neonatal circulatory transition that results in PPHN. It can be due to intrauterine

1. Pulmonary vascular under development / decreased vascular growth,
2. Mal-development (abnormal vascular structure) and / or
3. Mal-adaptation (perinatal hypoxia induced pulmonary vasospasm). Intrauterine or perinatal asphyxia and meconium aspiration syndrome remain the most common associated diagnoses.³

Chronic risk factors are chronic fetal hypoxia, Intra uterine growth retardation (IUGR), hypotension, pulmonary hypoplasia. Acute risk factors are hypoxia, hypercarbia, acidosis, hypothermia, meconium aspiration, severe pneumonia, septicemia, respiratory distress syndrome, polycythaemia, hypotension.

PPHN can also be caused by

- o Use of non-steroidal anti-inflammatory medications (such as aspirin, ibuprofen, naproxen) by mother during pregnancy

- o Late trimester maternal use of antidepressants (particularly a group called SSRI antidepressants).

- o Amniotic fluid leak

- o Oligohydramnios due to any reason

- o Abnormal lung development as a result of congenital diaphragmatic hernia or Potter syndrome

- Stress during pregnancy

- Isolated condition with an unknown cause

The main goals of treatment of PPHN are to decrease pulmonary vascular resistance and increase pulmonary blood flow. This is done by correcting the underlying disease, good supportive care and selective pulmonary vasodilators.

Clinical features

Clinical findings include tachypnea, grunting, retraction and cyanosis, especially with stimulation. The hypoxemia in PPHN is labile and disproportionate to the extent of the pulmonary parenchymal disease. Arterial blood gas shows severe hypoxemia with relatively normal pH and PCO₂. In infants with ductal level shunting, there is a gradient of >20mm Hg between right arm (pre-ductal) and lower extremity or umbilical artery (postductal) oxygen pressure. If the shunting is intrapulmonary or via patent foramen ovale (PFO), there is no difference in oxygenation of the right arm and the lower limb and umbilical artery blood.

The disease may present immediately after birth, such as, severe asphyxiated neonates or congenital diaphragmatic hernia with severe lung hypoplasia. It may present after 4-12 hours (subacute), for example, Meconium Aspiration Syndrome (MAS), or present after 12-24 hrs (late), such as infant with sepsis and those with progressive airway obstruction.

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Diagnosis and Investigation

Newborn with PPHN are typically term or post-term. A diagnosis of PPHN should be considered in a infant with extreme hypoxemia despite adequate ventilatory support. There are a number of clinical tests which can be used as screening procedures.

Hyperoxia test

An increase of the FiO_2 to 0.8~1.0 for 10 to 15 minutes allows diffusion of oxygen evenly into poorly ventilated areas of the lung and abolishes any ventilation-perfusion abnormalities. This results in an improvement in PaO_2 in most infants with parenchymal lung disease but no or slight response in those with PPHN and no response cyanotic congenital heart disease.

Preductal and postductal PaO_2 or oxygen saturation differences Right to left shunting of blood from the pulmonary artery to the thoracic aorta via the PDA results in a higher PaO_2 in preductal blood (obtained from a right radial or temporal artery) compared with postductal blood (obtained from the left radial, umbilical or tibial artery). A difference of PaO_2 more than 15~20 mmHg in the preductal artery indicates a significant right-to-left ductal shunt. However, PPHN can not be excluded if there is no preductal and postductal PaO_2 or oxygen saturation difference, as the right to left shunting may be predominantly at the atrial level, at the foramen ovale.

Hyperoxia-hyperventilation test

Hypoxia and acidosis augment pulmonary vasoconstriction. If the infant is manually ventilated at a rate of 100-150 breaths per minute for 10 minutes. This should result in a decrease in $PaCO_2$ to about 25 mmHg and a concomitant increase in the arterial Z^6 . In PPHN, an increase of PaO_2 by at least 30 mmHg is considered a positive response and little or no response is seen in infants with cyanotic congenital heart disease (CHD).

Echocardiography

With the use of real time echocardiography combined with colored Doppler flow studies, right to left shunting of blood through the foramen ovale and ductus arteriosus can be directly visualized^{4,5}. Deviation of intra atrial septum into the left atrium is seen in severe PPHN. The degree of tricuspid regurgitation can be used to estimate pulmonary artery pressure.

The clinical severity can be assessed by Alveolar-arterial oxygen gradient

1. Alveolar/ arterial oxygen gradient

$$(AaDO_2) = (760 - 47) - PaCO_2 - PaO_2,$$

when $FiO_2 = 1.00$,

where 760 = barometric pressure,

47 = water vapor pressure,

Normal $AaDO_2 < 20$ mmHg.

The higher the $AaDO_2$. 600 to 620 mm of Hg for 4 to 12 hours is a bad prognostic criteria.

2. Oxygen Index (O.I.)

$$= 100 \times MAP(P_{\text{aw}}) \times FiO_2 (\%) / PaO_2 \text{ post ductal.}$$

where MAP = mean airway pressure, if $OI > 25$ is an indication of inhaled Nitric Oxide (iNO) therapy. $OI \geq 40$ unresponsive to iNO are bad prognostic criteria or $OI \geq 40$ on 3 blood gas gases 30 minutes apart is predictive of high mortality.

Other investigations should include hematological and biochemical examinations, chest X-ray and bacteriology study. In PPHN chest x-ray may reveal clear and hypovascular lung fields and no anatomical cardiac lesions.

Management

The aims of treatment are to reduce the pulmonary vascular resistance and to maintain a systemic blood pressure higher than the pulmonary arterial pressure (estimated by echo).

Aim for $SpO_2 > 95\%$, arterial $PaO_2 > 7kPa$ (around 50 to 70 mm of hg) and $PaCO_2$ in the normal range.

- Wean oxygen according to blood gases rather than SpO_2 .
- Correct any underlying abnormalities such as hypothermia, acidosis, hypoglycemia, hypocalcaemia or hypomagnesaemia.
- First line treatment includes ventilation, oxygenation and maintenance of systemic blood pressure.
- Second line treatments such as high frequency ventilation and nitric oxide can be tried if the patient is not improving and
- ECMO is the last resort for PPHN.
- But ECMO is not available in our country and high frequency ventilation is available only in few centers.

Sildenafil

Sildenafil citrate (Viagra; Pfizer), a relatively new drug, is a phosphodiesterase type 5 (PDE5) inhibitor that selectively reduces pulmonary vascular resistance.⁶

Till to date about 10 case reports,^{7,8} 2 uncontrolled^{9,10} and 2 randomised controlled studies^{11,12} reported its efficacy in PPHN as an oral preparation in neonates. Generally used dosage range was 0.5-2mg/kg/ dose at 6-hourly intervals with dose titration based on response¹³ with document improved oxygenation as well as echocardiographic evidence of reduced pulmonary arterial pressures.

A Cochrane review on sildenafil for pulmonary hypertension in neonates¹⁴ included 2 randomised controlled trials conducted in resource-limited settings where iNO and HFOV are not available. Both included neonates in need of mechanical ventilation (with oxygenation index (OI) > 25) and echocardiographically confirmed PPHN. Baquero et al.¹¹ compared oral sildenafil with placebo and evaluated its effect on oxygenation in PPHN in 13 neonates > 35.5 weeks' gestation with severe hypoxaemia. Neonates in the treatment group were found to have improved OI and SpO_2 and a markedly lower mortality rate. Most published studies have evaluated sildenafil use in patients with

severe PPHN who were already receiving mechanical ventilation.

Adverse effects of sildenafil include gastro-intestinal, cardiovascular, visual, auditory, central nervous system and possibly haemostatic disturbances. Portal hypertension in a patient with cirrhosis was possibly exacerbated by sildenafil.¹⁵ Because it is eliminated primarily by the hepatic route, caution is needed when it is used concomitantly with P450 inhibitors such as erythromycin, clarithromycin, cimetidine and ketoconazole.¹⁶ Dose reduction is also necessary in patients with liver dysfunction or renal failure

A potential risk of irreversible retinal damage linked to PDE6 inhibition has been documented with the use of sildenafil, and a case of severe retinopathy was reported in a 31-week premature baby treated with sildenafil acetate for pulmonary hypertension.¹⁷ Sudden decreases in or loss of hearing following PDE5 inhibitor therapy have also been reported.¹⁸

Clinical indicators of a successful response would be improved oxygenation indices, namely a >10% increase in SaO₂ with a reduced differential between pre- and postductal PaO₂ values, ability to wean FiO₂, a decrease in OI. Response time can vary from 20 minutes to 3 hours after oral administration.

Duration of treatment is not yet well defined, and one approach is to observe the individual response and stop the medication after a clear response and improvement. The treatment should also be discontinued after 6-8 doses if there is no improvement, and reduction in dose or cessation of treatment is necessary if hypotension develops despite inotropic support.

High frequency ventilation (HFOV)

It is a mode of ventilation that executes supra-physiological breath rates and tidal volumes frequently less than dead space. The use of high frequency ventilation at low tidal volume allows the primary goals of ventilation, oxygenation and CO₂ removal, to be achieved without the costs of pressure-induced lung injury.

At present HFOV is only indicated as a rescue therapy. Failure of conventional ventilation in the term infant in Persistent Pulmonary Hypertension of the Newborn [PPHN], MAS.^{19, 20}

Both high frequency jet ventilation and high-frequency oscillator ventilation are very effective in controlling PaCO₂. So, it was postulated that these ventilatory modalities may be effective in improving oxygenation in PPHN patients. However, most studies showed no effect on ultimate outcome and even had increased incidence of severeIVH.²¹

For inhomogeneous lung diseases

Low volume strategy aim to minimize lung trauma i.e. Meconium aspiration or even where there is no lung disease i.e. PPHN. In these instances over distension of the alveoli must be prevented. Other inhomogeneous lung diseases are focal pneumonia, pulmonary haemorrhage, unilateral lung hypoplasia and BPD. The aim is to oxygenate and ventilate at minimum mean airway pressure. Due to regionally different compliances and / or resistances, there is always the danger of overinflating the more

compliant lung units.

- Set MAP equal to the MAP on conventional ventilation
- Set frequency to 7 to 8 Hz.
- Adjust amplitude (ä) to get an adequate chest wall vibration

The oscillatory frequency should be low. If necessary, turn up MAP in small increments until PO₂ slightly increases. Then keep MAP constant. Mostly the situation will continue to improve. If not, return to conventional ventilation.

Other general measures at NICU set up

In addition to Sildenafil citrate and HFOV the following measures could be required for the management of PPHN.

A. Treat and prevent hypoxia

Aim PO₂ ≥ 10KPa(75mmHg) / saturations ≥ 95%, (preductal)

Ventilation, (may need HFOV)

Consider surfactant

Use OI to guide management:

OI = 100xMAP(cm) x FiO₂(%)/

Post ductal PaO₂(mmHg) (1kPA = 7.5mmHg)

B. Circulatory support

- Aim to maintain systemic BP above pulmonary pressures (estimated by echo). Often repeated fluid boluses are required to maintain adequate filling volume.
- Consider early inotropic support, Inotropes to reduce right to left shunt,
 - Dopamine - increases RV ejection fraction
 - increases systemic vascular resistance
 - Dobutamine - limited value in PPHN
 - increases contractility and causes mild vasodilation
- Milrinone (a phosphodiesterase III inhibitor) may be a useful adjunctive inotrope as it potentiates the effects of NO, causes pulmonary vasodilatation and improves diastolic function.

Aim to maintain systemic BP 95% upper confidence limit of average mean

Birth weight	Average mean arterial BP	95% upper confidence limit
2000-2999g	41mmHg	50mmHg
3000-3999g	47mmHg	55mmHg
4000g	52mmHg	62mmHg

Sedation

- Ensure minimal handling as these patients are very labile and can deteriorate following minor stimulation.
- Sedate with morphine (some patients will require >20mcg/kg/hr).
- Paralysis remains controversial as it may be associated with increased mortality and deafness. However if patients are "fighting the ventilator" or have asynchronous ventilation it may be useful. In our unit we use fentanyl or midazolam for the sedation.

Alternate therapies

These are experimental and would usually be considered after discussion with ECMO centers.

1. Inhaled Prostacyclin (two small studies have shown improvement in oxygenation a doses of 20-50ng/kg/min).
2. Adenosine infusions have been demonstrated to improve oxygenation in small trials.
3. Magnesium sulphate can be used but the vasodilation effect is short lived.

Natural history, complications and prognosis

This varies with the underlying etiologies, PPHN may expected to have a short natural history (3-5 days), However, severe cases do not response within 3-4 days to conventional mechanical ventilation, high frequency ventilation, vasodilators (include iNO) and eventually have to put on ECMO.

Complications include pulmonary interstitial emphysema, pneumothorax, chronic lung disease; cerebral infarction in severe asphyxiated babies; cerebral hemorrhage in those attached to ECMO.

Conclusion

Significant progress has been made in the understanding of pathophysiology of PPHN, and its new therapies, such as high frequency ventilation, iNO, ECMO. However, management of these infants remains very difficult and present one of the major challenges in NICU. Sildenafil has shown successful outcome in different study and could be a good option for us. Combination of HFO with Sildenafil is excellent if available.

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