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Review Article

Evidence Based Practice towards Pharmacological Management of Persistent Pulmonary Hypertension of Newborn in Neonatal Intensive Care Unit

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Abstract

Persistent pulmonary hypertension of newborn (PPHN) is a common problem encountered in neonatal intensive care units. The problem arise because of failure of smooth transition from fetal circulation to post-natal circulation after birth. This causes hypoxemia due to high resistance in pulmonary vasculature causing impediment into normal pulmonary blood flow apparently causing right – to – left shunt.

The problem is more commonly associated with fullterm neonates and there are a number of therapies available to manage the problem. This article discusses the evidence based approach towards the pharmacological management of persistent pulmonary hypertension of newborn.

Keywords: Persistent Pulmonary Hypertension of Newborn; PPHN; Pharmacological Management; Neonate; NICU; Newborn; Hypoxia; Neonatal Ventilator Dependency; iNO; Inhaled Nitric Oxide; Pulmonary Hypertension

Abbreviation

BP: Blood Pressure; BPD: Bronchopulmonary Dysplesia; CDH: Congenital Diaphregmatic HERNIA; CHDs: Congenital Heart Diseases; ECMO: Extra Cororeal Mebrane Oxygenation; HFV: High Frequency Ventilation; I.V: Intravenous; iNO: Inhaled Nitric Oxide; MAS: Meconium Aspiration Syndrome; OI: Oxygenation Index; PA: Pulmonary Artery; PDE: Phospho-Di-Estrase; PEEP: Peak End Expiratory Pressure; PGE1: Prostaglandin E1; PIP: Peak Inspiratory Pressure; PPHN: Persistent Pulmonary Hypertension of Newborn; RDS: Respiratory Distress Syndrome; SPO2: Saturation of Arterial Oxygen; SVR: Systemic Vascular Resistance.

Introduction

Persistent pulmonary hypertension of the newborn (PPHN) is characterized by the faulty or failed circulatory transition of fetal circulation to post-natal circulation. This non-transition results into altered homeostasis culminating into myriads of symptoms marked by pulmonary arterial hypertension causing right shunting of blood (extra-pulmonary) and hypoxemia. Mostly it is a disease of near-term or full term newborns but it does affect the premature babies.

This disease is largely diagnosed by 2D echocardiogram and Doppler studies. There are a number of treatment options, an overview of which has been presented in this article with specific focus on pharmacological management.

Definition

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Incidence

PPHN is seen more in term newborns [2] with a frequency of 1900/million live-births (0.4-6.8/1000 live births) with a mortality of 4-33% [3].

Pharmacological interventions

Oxygen

- Supplementary oxygen is first therapy, being potent vasodilator for pulmonary vasculature [4].
- In lamb studies, 100% oxygen for small period resulted in enhanced contractility of pulmonary artery (PA) [5].
- It is recommend to maintain preductal-SpO_2 in low-to-mid 90s and PaO_2 55- 80 mmHg [6].

Assisted ventilation

- It helps by providing lung expansion, necessary for optimal oxygenation and adequate iNO delivery [7].
- Conventional as-well-as high-frequency ventilation (HFV) may be used [8].
- HFV in combination with iNO provided better oxygenation in few neonates with complicated PPHN viz. MAS and RDS [9].
- Ventilation strategies: low-PIP, optimal-PEEP, and permissive hypercapnia to ensure adequate lung expansion while preventing barotrauma.
- Degree of severity is calculated by oxygenation index (OI)
    - OI = (MAP in cm H_2O * FiO_2 * 100) /(PaO_2 in mmHg).

Surfactants

- Exogenous surfactant is shown to boost oxygenation and decrease the need for ECMO in newborns with PPHN secondary to parenchymal lung disease
- Improvement was more in newborns with OI between 15-25.
- Surfactant rich in surfactant protein-B (SP-B) is recommended [10].
- Congenital diaphragmatic hernia (CDH) causes hypoplasia sometimes surfactant is used, if clinical, radiological or biochemical evidences of deficiency are present.
- In CDH, half the normal dose is recommended because of pulmonary hypoplasia [11].

Catecholamine in PPHN [12]

- Low cardiac output and hypotension are common in PPHN.
- Hemodynamic evaluation and repeat echocardiography are recommended to find primary cause of hypotension.
- First management is to give bolus (@10ml/kg isotonic-saline).

Dopamine is first line inotropic drug, it act by

- Increasing myocardial contractility, cardiac output, SVR and blood pressure
- **Dose:** 1-20µg/kg/min
- At higher doses (typically > 10mcg/kg/min) it is associated with increase in systemic and pulmonary pressure. It is non-selective vasoconstrictor.

Noradrenalin is second line inotrope

- Augments cardiac output through inotropic effect
- Action on alpha-receptors increases SVR (Increased BP)
- May Improve pulmonary blood flow by release of endothelial NO
- **Dose:** 0.05-1µg/kg/min.

Vasopressin used sometimes as third line drug

- Effective and selective for systemic vasoconstriction.

Steroids [13]

- There are no strong recommendations about use of corticosteroids in PPHN.
- Corticosteroid may help stabilizing the patients with catecholamine resistant hypotension.

Vasodilators

Nitric Oxide [12]

- iNO is main treatment, iNO is selective and potent pulmonary vasodilator and does not decrease PVR.
- iNO decreases V/Q-mismatch because it enters only ventilated alveoli, thus channelizes pulmonary blood flow by dilating neighboring pulmonary arterioles.
- A meta-analysis iNO treatment in neonates found 58% neonates were benefitted by iNO within 1 hour and requirement of ECMO was decreased.
- Dose: An initial dose of 20ppm. In case dose exceeds 20 ppm there was minimal increase in response but side-effects (viz methmoglobinemia) increased.
- An OI more than 15-25 with echocardiographic features of PPHN or higher OI with/without right-to-left shunt is indication for starting iNO generally.
- iNO should be weaned gradually; sudden withdrawal can precipitate vasoconstriction. FiO_2 is weaned below 60% first, followed by iNO in steps of 5ppm every 4th hour. At 5ppm the weaning takes place as 1ppm every 4^{th} hour.
- Forty percent neonates are not able to respond and/or sustain response to iNO. Hence, adequate PEEP to achieve optimal lung expansion, surfactant therapy (if needed), and HFV should be considered prior to iNO.
- If HFV, iNO and supportive measures are not able to sustain, ECMO is final measure. If a child needs transport to ECMO facility, he should be transported on continuous iNO therapy.

- Inhaled NO is not indicated in neonates with CHDs which are dependent on Right-to-left shunts (viz. HLHS, interrupted aortic arch, etc.).
- There is a risk of pulmonary edema in infants with pre-existing left ventricular dysfunction with iNO therapy. Therefore, echocardiogram must be performed before starting iNO.
- Inhaled NO is not effective in PPHN in neonates with congenital diaphragmatic hernia and these neonates should be delivered or transported to ECMO facility.

Inhaled-NO resistant PPHN [14]

- It is found in about 30% neonates affected with PPHN
- Alveolar recruitment is essential part of its management by optimal use of surfactant, PEEP as-well-as HFV.
- Repeated echocardiography to assess cardiac functions, cardiac anomalies (multiple echocardiograms increases sensitivity many folds) and se- verity of PPHN.

Vasodilators for PPHN beyond neonatal period

Prostacyclin

- It has vasodilatory effect. Epoprostenol (Inhaled prostacyclin) can synergistically act along iNO.
- Epoprostenol has short half-life (~5min); interrupted delivery (e.g. catheter block, dislodgment) can result into potentially fetal rebound pulmonary hypertension. Tachyphylaxis is known.
- Other side-effects: dizziness, headache, facial flush, jaw-pain etc.

Phosphodiesterase inhibitors

Sildenafil [15]

- PDE5 inhibitor, which selectively decreases pulmonary artery resistance and found useful in management of infants suffering from PPHN.
- One Cochrane meta-analysis concluded substantial betterment in oxygenation in infants receiving sildenafil, without use of iNO and/or HFV [15].
- Presently, more studies are recommended to use sildenafil without iNO as first-line drug.
- FDA warns about, increased deaths, attributed to high doses of sildenafil used for long-term treatment. Although, the warning is dependent upon very limited data, yet warrants bigger studies to establish safety of sildenafil especially for long-term treatment in infants [16].
- Systematic analysis about off-label use of drug in preterm neonates with risk of bronchopulmonary dysplasia/ BPD-associated pulmonary hyper- tension, found insufficient evidence to use sildenafil in term-neonates with PPHN at places where iNO is available [17].
- Sildenafil is used in case of severe PPHN not responding to optimal ventilation and iNO/unsuccessful attempts to wean iNO.
- Intravenous sildenafil loading dose is 0.42mg/kg over 3-hours (0.14mg/kg/h) followed by continuous infusion of maintenance dose 1.6mg/kg/day (0.07mg/kg/h).

Milrinone

- An inhibitor of PDE3 and found to be effective in relaxing pulmonary arteries.
- It has vasodilatory and inotropic properties. It reduces the afterload. It dilates pulmonary arteries, hence recommend as first choice vasodilator in left ventricular dysfunctions in presence of PPHN
- Loading dose of 50 mcg/kg (infused over 30-60min) and maintenance dose of 0.33mcg/kg/min is used. Escalation in steps to a dose of 0.66 and 1mcg/kg/min may be considered.
- Loading dose is skipped in systemic hypotension or premature newborns.
- Hypotension is common: BP monitoring recommended [18].

Endotheli-1 (ET-1) receptor antagonists (Bosantan)

- Bosentan is orally active drug, which improved outcomes in PAH. It was found to be effective in improving oxygenation, and was well tolerated in term as-well-as late-preterm infants [19].
- **Dose:** 2mg/kg/dose BID
- It can cause serious hepatic injuries and has potential to cause fetal harm [20].

Other drugs

- Magnesium sulfate seems potent vasodilator. It checks calcium ions from entering into smooth muscle cells.
- However, pulmonary vasodilator properties of magnesium sulfate are not investigated.
- It can be used in non-responding patients [21].

Prostaglandins

- Prostaglandin E1 (aerosolized): safe for treating PPHN.
- Intravenous PGE1 are used to treat duct depended cyanotic CHDs [22].

Sedation

- Optimal sedation (Morphine I.V) and minimal handling strategies.
- Midazolam if adequate sedation is not obtainable with Morphine [8].

Muscle relaxants and paralysis

- Paralysis is avoided: association with increased mortality [23].

Metabolic

- Alkali infusions and Hyperventilation: not recommended because of potential to impair brain perfusion , increased requirement of ECMO and increased incidence of deafness (sensory-neural) [23].
- Recommendation is to maintain pH>7.25, (7.35-7.45) throughout acute phase of PPHN [24].
- Correct hematological abnormalities viz anemia and polycythemia.

Fluids and electrolytes

- Management of fluid volume, blood glucose, electrolytes and calcium.
- Nutritional requirement of the neonate must be taken care.
- Total parenteral nutrition may be considered especially in preterm and growth retarded neonates [25].

Sepsis

- Early recognition and treatment of sepsis through recommended antibiotics is essential, corticosteroids are relatively contraindicated in case of sepsis [14].

Conclusion

Based upon the discussion above the closing points are:

1. PPHN is more common in term/near-terms
2. Supportive measures followed by oxygen therapy should be started immediately pre- ductal SPO2 should be aimed at low-to-min 90s.
3. Inhaled nitric-oxide is the mainstay of treatment and should be started at 20ppm and dose adjusted accordingly. Sometimes lung expansion is necessary for optimal oxygenation and adequate iNO delivery, hence mechanical ventilation may be needed.
4. Phosphodiestrase inhibitors viz Sildenafil are used in cases where iNO and HFV are not able to achieve /maintain optimal oxygenation. It can be tried in centers where iNO is not available.
5. Endothelin-1 receptor antagonist (Bosentan) seems to be an effective drugs but not studied extensively in neonates.
6. The systemic hypotension without cardiac dysfunctions in PPHN should be managed with catecholamine (Dopamine, noradrenaline etc) and vasopressin.
7. Milrinone is inotrope of choice for PPHN with left ventricular dysfunction.

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