A retrospective study of predisposing factors and outcome of persistent pulmonary hypertension among newborns at rural tertiary care centre

B. C. Yelamali, Gangadhar S. Mirji, Mirnalini Rajput*

Department of Paediatrics, S. Nijalingapppa Medical College, Bagalkot, Karnataka, India

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*Correspondence:
Dr. Mirnalini Rajput,
E-mail: Mirnalinirajput2010@gmail.com

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ABSTRACT

Background: Persistent pulmonary hypertension in newborns (PPHN) remains a significant cause of perinatal morbidity and mortality. Early recognition of factors that increase the risk of PPHN is of great importance in either to prevent or to treat PPHN optimally. Aim was to study the neonatal predisposing factors, profile and outcome of PPHN.

Methods: This retrospective study was conducted in level III neonatal care unit, a rural referral centre of North Karnataka, India from January 2018 to April 2020.

Results: During the study period a total of 50 infants with PPHN were identified with the incidence of 5.43/1000 live births. Mean gestation age (±SD) was 38.28±2.49 weeks and mean birth weight (±SD) was 2624±512 gm. The most noted risk factors were meconium aspiration syndrome (42%), birth asphyxia (16%), RDS (10%), positive pressure ventilation at birth (52%) and male gender (62%). Out of 50 infants with PPHN, high mortality was seen in low birth weight babies (66.6%). Use of sildenafil showed increased mortality (56.2%) whereas use of surfactant scored better with decreased mortality of 42.8%.

Conclusions: Major risk factors for PPHN are MAS, birth asphyxia, RDS and low birth weight. Poor prognosis is seen in male gender, prematurity and CDH with increased risk of mortality. The use of systemic pulmonary vasodilators can be considered with caution and use of surfactant has a role in management of PPHN.

Keywords: Birth asphyxia, Meconium aspiration syndrome, Persistent pulmonary hypertension of newborn, Positive pressure ventilation

INTRODUCTION

Persistent pulmonary hypertension in newborn (PPHN) is a serious and possibly a fatal syndrome characterized by sustained foetal elevation of pulmonary vascular resistance at birth. Failure on part of neonate to a normal transition from intrauterine to extra uterine physiology leads to PPHN.

In utero, the foetus is in a state of physiological pulmonary hypertension. The foetus obtains oxygen through the low-resistance placental circulation and its pulmonary vascular resistance (PVR) is high as the lungs are fluid-filled. At birth, after first breath and after umbilical cord is clamped, neonate makes postnatal transition from a high resistance foetal pulmonary circulatory state to a low resistance pulmonary circulation.

In persistent pulmonary hypertension of the newborn (PPHN) this transition is disturbed, resulting in sustained elevation of PVR. This increased pulmonary vascular...
resistance leads to right-to-left extrapulmonary shunting of blood flow across the ductus arteriosus and/or patent foramen ovale. Thus this decreased pulmonary blood flow prevents adequate gas exchange in the lungs resulting in severe respiratory distress and hypoxemia in the neonate. Basic pathology in PPHN is the altered foetal pulmonary vasculature. Based on etiology, PPHN can be categorized into seven broad groups. 

Idiopathic: No lung disease is present and pulmonary vascular blood flow is decreased due to abnormal vascular remodelling leading to pulmonary vasoconstriction.

Abnormal transition at birth: Perinatal asphyxia, RDS, and transient tachypnea of newborn (TTN) resulting in impaired pulmonary vasodilation at birth.

Parenchymal disorders (also known as “secondary PPHN”): Such as due to meconium aspiration syndrome (MAS) and pneumonia.

Abnormal lung development: Pulmonary hypoplasia due to oligohydramnios secondary to renal dysfunction/anomalies or prolonged rupture of membranes or congenital diaphragmatic hernia (CDH) and other pulmonary malformations.

Intravascular obstruction due to hyperviscosity: Polycythemia.

Pulmonary hypertension (PH) in preterm infants in the initial phase of RDS.  

Pulmonary venous hypertension.

In a previous multicenter study from USA, the overall incidence of PPHN was estimated to be 1.9 per 1000 live births, with wide variability across referral centers. Mortality has been reported at 12% to 29%. There are very few studies which have examined the incidence of PPHN in Asian countries. A study from Thailand reported an incidence of PPHN of 2.8 per 1000 live births which was higher than the incidence in USA. And also the mortality and morbidity may be higher in developing countries compared to developed regions. This difference can be explained due to the high percentage of established risk factors for PPHN in developing countries like prematurity, neonatal sepsis, meconium aspiration, pneumonia, low birth weight and other associated factors like poor socioeconomic conditions. 

In high income countries lower percentage of complications and better outcomes are observed with the availability of both iNO and ECMO and also mortality in PPHN has reduced from 25–50% to 10–15%. At the same time, many nurseries around the world cannot afford proven but expensive therapies such as iNO and ECMO. Many developing countries and resource-limited centres use readily available treatment modalities but less effective pulmonary vasodilators like sildenafil, magnesium sulphate along with surfactant, gentle ventilation and sedation. The infants with PPHN who survive and are discharged from the NICU have long-term consequences, such as neurodevelopment, cognitive, and hearing abnormalities. In our centre, as iNO and ECMO are not available, hence the mortality and morbidity will be higher.

PPHN is a serious neonatal illness, identifying neonates who are at higher risk for PPHN and understanding underlying pathophysiology of PPHN is very essential as these infants are at increased risk for rapid clinical deterioration. In turn this may help to identify targeted therapies and prevention strategies.

As there is limited data available from local studies, this study was planned. The aim of our study was to study expanded profile of predisposing factors, treatment options and outcome of PPHN infants in low resource settings. The data search showed us the aetiologies, predisposing factors, profile of PPHN, treatment options and the outcomes in infants with PPHN.

METHODS

This study was a retrospective study involving Neonatal intensive care unit of S Nijalingappa Medical College and HSK Hospital, Bagalkot, Karnataka which is a rural referral centre. Data were collected from records review of neonates diagnosed with PPHN admitted to NICU from January 2018 to April 2020. The study protocol was approved by Institutional Ethics Committee.

Definition of PPHN, inclusion and exclusion criteria

Persistent pulmonary hypertension of the newborn (PPHN) is secondary to failure of normal circulatory transition at birth and is a syndrome characterized by elevated pulmonary vascular resistance (PVR) that causes labile hypoxemia due to decreased pulmonary blood flow and right-to-left shunting of blood across the fetal channels (patent ductus arteriosus and/or patent foramen ovale).

We included preterm, term and post term babies which were diagnosed with PPHN based on clinical presentation and on echocardiography criteria. Neonates with PPHN were managed as per unit protocol, as our NICU does not have facility for iNO and ECMO, newborns were put on respiratory support either non-invasive or invasive mechanical ventilation.

Clinical criteria were severe hypoxemia (SpO2) and differential pulse oximetry oxygen saturation gradient equal to or more than 10% between preductal and postductal sites.

Confirmatory echocardiography findings include elevated pulmonary pressure (right to left or bidirectional shunt at
PFO and/or PDA), right ventricular hypertrophy, deviation of interventricular septum towards left, jet of tricuspid regurgitation with jet pressure of >40 mmol of Hg. Neonates with congenital cyanotic heart disease or chromosomal anomalies were excluded. The neonates with PPHN were grouped into two groups: Pre term (from 28 to <37 weeks) and term and post term neonates (37 weeks to >42 weeks of gestation) to control the confounding variables.

The primary outcomes of this study were the incidence, aetiologies, risk factors, diagnostic options, various management modalities such as pulmonary vasodilators (sildenafil, milrinone), inotropes (dopamine, dobutamine, epinephrine or norepinephrine), sedation and analgesia (midazolam, morphine or fentanyl), muscle relaxants and final outcome as survived or death. The secondary outcomes were need for oxygen supplementation, requirement and period of mechanical ventilation and duration of hospital stay.

**Statistical analysis**

Statistical analysis was done using SPSS statistical package for social sciences, IBM, SPSS Statistics, USA version 19.0. Data obtained was tabulated in the Excel sheet and was analyzed. All values were expressed as mean + standard deviation or number and percentages. Chi-square test for proportions in qualitative data was applied. P<0.05 was considered as statistically significant.

**RESULTS**

A total of 50 neonates with PPHN, both inborn and out born were included in the study period of 26 months.

| Table 1: Perinatal risk factors and characteristics of the newborn with PPHN. |
|--------------------------------------------------|
| Characteristics | Over all (n=50) | Pre term (n=9) | Term and Post term (n=41) |
|------------------|----------------|---------------|--------------------------|
| Gender of neonates |                |               |                          |
| Male             | 31 (62.0)      | 7 (77.8)      | 24 (58.5)                |
| Female           | 19 (38.0)      | 2 (22.2)      | 17 (41.5)                |
| Mode of delivery |                |               |                          |
| NVD*             | 27 (54.0)      | 4 (44.4)      | 23 (56.0)                |
| C-section        | 23 (46.0)      | 5 (55.5)      | 18 (43.9)                |
| PIH              | 7 (14.0)       | 3 (33.3)      | 4 (9.9)                  |
| PROM/PPROM       | 8 (16.0)       | 3 (33.3)      | 5 (12.1)                 |
| Birth asphyxia   | 8 (16.0)       | 1 (11.1)      | 7 (17.0)                 |
| MAS              | 21 (42.0)      | 1 (11.1)      | 20 (48.7)                |
| RDS              | 5 (10.0)       | 5 (55.5)      | 0                        |
| TTNB             | 6 (12.0)       | 1 (11.1)      | 5 (12.1)                 |
| CDH              | 4 (08.0)       | 1 (11.1)      | 3 (07.3)                 |
| Sepsis           | 3 (06.0)       | 0             | 3 (07.3)                 |
| Congenital pneumonia | 3 (06.0)    | 0             | 3 (07.3)                 |
| Resuscitation done |              |               |                          |
| Routine care     | 24 (48.0)      | 4 (44.4)      | 20 (48.7)                |
| PPV**            | 26 (52.0)      | 5 (55.5)      | 21 (51.2)                |
| APGAR at 5 minute |              |               |                          |
| Normal           | 13 (26.0)      | 2 (22.2)      | 11 (26.8)                |
| Moderate         | 2 (04.0)       | 1 (11.1)      | 1 (02.4)                 |
| Severe           | 1 (02.0)       | 0             | 1 (02.4)                 |
| Unknown          | 34 (68.0)      | 6 (66.6)      | 28 (68.2)                |
| Echocardiography |              |               |                          |
| Mild PPHN        | 10 (20.0)      | 2 (22.2)      | 8 (19.5)                 |
| Moderate PPHN    | 24 (48.0)      | 3 (33.3)      | 21 (51.2)                |
| Severe PPHN      | 16 (32.0)      | 4 (44.4)      | 12 (29.2)                |
| Respiratory support |           |               |                          |
| Oxygen           | 3 (06.0)       | 0             | 3 (07.3)                 |
| CPAP (initially) | 21 (42.0)      | 2 (22.2)      | 19 (46.3)                |
| HFNC (initially) | 4 (08.0)       | 1 (11.1)      | 3 (07.3)                 |
| Mechanical ventilation | 22 (44.0) | 6 (66.6)     | 16 (39.0)                |

*Normal vaginal delivery, **Positive pressure ventilation
The incidence of PPHN among both in born and out born babies were 5.43/1000 live birth. Out of these 50 neonates with PPHN, 35 cases were out born and 15 cases were inborn, with male preponderance, 31 males (62%) and 19 females (38%). 9 were preterm (from 28 weeks to <37 weeks of gestation) and 41 (82%) were term and post term (from 37 weeks to >42 weeks of gestation) babies. Mean gestation age (±standard deviation (SD)) was 38.28±2.49 weeks and mean birth weight (±SD) was 2624±512 gm. The characteristics and profile of the newborn with persistent pulmonary hypertension is shown in Table-1. Infant risk factors were predominantly male gender (62%), gestation age wise term and post term babies (82%) were more affected. Meconium aspiration syndrome (42%), birth asphyxia (16%), positive pressure ventilation at birth (52%) were the other observed major risk factors. The preterm babies with PPHN were predominantly male sex (77.8%), birth by caesarean section (55.5%), RDS (55.5) and resuscitation at birth with positive pressure ventilation (55.5%). Almost all neonates were on respiratory support and those initially who were on CPAP and HFNC, went in for mechanical ventilation 47 (94%).

Table 2 compares the demographic characters, aetiologies and out comes with survivors and non-survivor group of neonates with PPHN. Out of 50 neonates with PPHN, 35 (70%) of them were out born, among them 54% expired. Male preponderance was seen 31 (61%) and mortality was 52%. 18 (38.2%) babies were less than 2500 gms and with high mortality of 66.6%. Multiple aetiologies were noted in neonates with PPHN, most common cause was meconium aspiration syndrome 21 (42%) with survival rate of 42%. Among congenital anomalies CDH was seen in 4 babies with mortality of 75%.

Table 3: Comparison of treatment options and their outcome in babies with PPHN.

| Treatment given          | Total n=50 | Survivors n (%) | Non survivors n (%) |
|-------------------------|------------|-----------------|---------------------|
| Mechanical ventilation  | 47 (94)    | 23 (48.9)       | 24 (51.0)           |
| Sildenafil              | 32 (64)    | 14 (43.7)       | 18 (56.2)           |
| Inotropes               | 47 (94)    | 23 (48.9)       | 24 (51.0)           |
| Surfactant              | 07 (14)    | 04 (57.1)       | 03 (42.8)           |
| Sedation                | 45 (90)    | 22 (48.8)       | 23 (51.1)           |
| Milrinone               | 02 (04)    | 01 (50.0)       | 01 (50.0)           |

The treatment options and their outcomes comparison is shown in Table 3. Nearly 94% of neonates were treated with gentle ventilation with almost equal survival and death percentage. The mean duration of ventilation was 4.28±2.9 days. Sildenafil and milrinone were used as pulmonary vasodilators; increased mortality was noticed in neonates who required inotropes and sildenafil. While use of surfactant showed decreased mortality.

DISCUSSION

Although recognized for decades, the persistant pulmonary hypertension is a leading cause for respiratory failure in the newborn. Little is known about the direct aetiology, physiopathology and preventive strategies of persistent pulmonary hypertension of the newborn (PPHN) and its treatment remains a major challenge for neonatologists.16

In this current study, we evaluated the predisposing risk factors and their outcomes in neonates with persistent pulmonary hypertension. We made an attempt to note similarities and differences between current study and studies by others. Ours being a rural referral centre, out born babies 35 (70%) were more than the inborn babies. As observed in other studies PPHN is a disease of term and post term neonates in our study 41 (82%) babies belonged to this group as compared to pre term neonates 9 (18%).17-18 Of the 50 babies in our study, majority were male (62%). Several previous studies found an increased incidence of PPHN in male, term and post term babies.17,18

Regarding aetiology, MAS (42%) was the most common aetiology followed by birth asphyxia (16%) and TTNB (12%). Rest of the cases were due to RDS (10%), CDH (8%), sepsis and congenital pneumonia (6%). MAS has been repeatedly reported as the most common cause of PPHN.19,20

In our study, ventilation, milrinone, combined use of pulmonary vasodilators and inotropes were all associated
with increased mortality. These findings are similar to those noted by Sardar et al a study from eastern India.\textsuperscript{19} Inhaled NO is the treatment of choice in PPHN. Use of other pulmonary vasodilators (sildenafil, milrinone etc) in the absence of iNO have inconsistent results. Major reason being that these pulmonary vasodilators lack selective effect of inhaled NO and thus leads to systemic adverse effects (hypotension) and worsen the PPHN further. In developed countries, iNO delivered through HFOV is associated with better survival and less need of ECMO.\textsuperscript{20}

Sildenafil is the first line pulmonary vasodilator in our NICU, in the absence of iNO. However, in cases of patients with left ventricular dysfunction, sildenafil is replaced with milrinone. Inotropes were used in hypotensive babies. Ventilation and sedation were also used. Use of multiple treatment modalities simultaneously implies sick babies who had less survival chance and thus associated with increased mortality. Although Cochrane meta-analysis by Kelly et al. noted decreased mortality in PPHN patients with sildenafil, the only intervention that was associated with better survival was use of surfactant, which can be explained by the better lung recruitment with surfactant and concomitant ventilation which improves the oxygenation.\textsuperscript{21} Also the most common aetiologies in our NICU were MAS and TTNB, where surfactant has a role in management.\textsuperscript{19,22}

The mortality in our study was 58%. The mortality with PPHN ranges from 4% to 33%. However, mortality in developing countries is much higher, ranging from 25% to 48%.\textsuperscript{6,12,19} Reported mortality in PPHN varies in different countries, such as 20.6% in Asian countries, 32% in Portugal, 4%-33% in the USA and 26.6% in Pakistan.\textsuperscript{6,8,18,23} In our study increased risk of mortality was noticed in premature infants (6 infants out of 9) who all required mechanical ventilation and those with CDH.

In spite of progress in understanding the pathophysiology and treatment of PPHN, prognosis remains poor in developing countries, mostly because of non-availability of newer treatment modalities, such as HFOV, inhaled NO or ECMO.

Our study has few limitations, first because of retrospective nature, few essential data were lost. Second, is the small sample size of the study and lastly non-availability of iNO, HFOV and ECMO for quality care. On the other hand, strength of our study being that diagnosis of PPHN was confirmed in each and every case with echocardiography and was not solely based on clinical assessment.

**CONCLUSION**

In conclusion major risk factors for PPHN are MAS, birth asphyxia, low birth weight and RDS. Male sex, prematurity and CDH have poor prognosis and are associated with increased mortality in these infants. The detailed profile of risk factors may help in identification of at risk PPHN neonates before they clinically deteriorate. In the non-availability of inhaled NO, the drug of choice for treatment of PPHN, use of systemic pulmonary vasodilators can be considered with caution because of adverse effects of such drugs. The use of surfactant has a role in management of PPHN.

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