Clinical profile of persistent pulmonary hypertension in new born: experience in an extramural institution

Harish S., Kamalarathnam C. N.*

INTRODUCTION
Persistent pulmonary artery hypertension of the new born was first described by Gersony et al in 1969 as persistent in fetal circulation. However, it was in 1977, when Fox and colleagues found out that desaturating neonates in the absence of congenital heart disease had right to left shunt through patent ductus arteriosus (PDA) or patent foramen ovale (PFO) discovered during cardiac catheterisation. The major hallmark of successful transition from fetal circulation to neonatal circulation involves reduction of pulmonary vascular resistance soon after birth. Failure of this smooth transition is termed as persistent pulmonary hypertension of new born (PPHN). A variety of factors can interfere this normal transition and they are generally grouped under 3 categories namely:
- Abnormally constricted vessels (meconium aspiration syndrome MAS, pneumonia, respiratory distress syndrome),
- Hypoplastic vasculature (Congenital diaphragmatic hernia, lung hypoplasia)

ABSTRACT
Background: Persistent pulmonary artery hypertension of the new born (PPHN) has an incidence of 1.9 per 1000 live births with a mortality of 12 to 29%. In our tertiary care referral institute, the mortality was relatively high. A department audit was undertaken which will help us to introspect and to reason out the factors favouring survival and mortality in our NICU.
Methods: Neonates with the diagnosis of PPHN from January 2016 to December 2016 were identified from our department database. After excluding cardiac causes of pulmonary hypertension, transport, prenatal, perinatal and post-natal data, treatment details and outcome information was collected from case records. The statistical analysis was calculated with SPSS software. Mean, standard deviation was calculated for continuous variables. Chi square test and Fischer’s exact test was used to test the association between categorical variables and t test for continuous variables.
Results: The incidence PPHN in our unit was 1.5%. The average duration of hospital stay was 17 days. Among the 45.7 % of babies, PPHN was secondary to MAS, followed by CDH (22.3 %). Based on oxygenation index, 15 babies, 42.3% had mild, 10 babies, 28.6% had moderate, 8 babies, 22.3% had severe PPHN and 3 babies, 8.6% had severe PPHN. Overall mortality was 42.3%. SpO2 on arrival at emergency room, adequacy of cardiorespiratory during transport and presence of shock is significantly associated with mortality.
Conclusions: This study show MAS and CDH are common causes of PPHN. Severity of illness at arrival was predictive of high mortality. Prior stabilization and adequate transport may improve outcomes.

Keywords: CDH, MAS, Neonates, PPHN
The overall incidence is 1.9 per 1000 live births and overall mortality is 12 to 29%. Although the overall mortality was high in the 1980s, prompt diagnosis, timely referral and management has shown to reduce death. In our tertiary care institute which serves as a referral centre for all the Specialised New Born Care Unit (SNCU) in neighbouring districts and Corporation EOC centres in Chennai as well as a number of private hospitals, the overall mortality was relatively high. Though referral bias was considered, we decided to undertake a study which will serve as a department audit to introspect and to reason out the factors favouring survival and mortality in our NICU in babies admitted with diagnosis of PPHN.

Aims and Objectives of this study were to determine incidence, mortality and survival rate of neonates with PPHN at our centre and to analyse possible factors influencing the severity and short-term outcomes in neonates with PPHN.

**METHODS**

Neonates with the diagnosis of PPHN from January 2016 to December 2016 were identified from our department database. Pulmonary artery hypertension (PAH) secondary to cardiac causes were excluded. Transport, prenatal, perinatal and post-natal data, treatment details and outcome information were collected from the case records.

**Maternal data**

Information on age, parity, birth number, booked/unbooked pregnancy, presence of risk factors such as diabetes, pregnancy induced hypertension, oligohydramnios, prolonged rupture of membranes, chorioamnionitis, intra uterine growth restriction and intake of drugs like Non-steroidal anti-inflammatory drugs and smoking were collected. Intrapartum details pertaining to mode of delivery, nature of amniotic fluid (clear, meconium stained, blood stained, foul smell), need for resuscitation at birth and birth weight, gestational age was obtained.

**Transport data**

The temperature on arrival, oxygen saturation, transport duration, age on referral and inadequacy of support during transport, defined as lack or respiratory and circulatory support during transport upon arrival for a baby with respiratory distress or shock were analysed.

**PPHN diagnosis and severity**

In our centre, diagnosis of PPHN was made on a combination of clinical and echocardiographic grounds. Clinically, babies with labile saturation, delta saturation (SO2) between pre-ductal and post ductal >10%, central cyanosis and echocardiographic demonstration of right to left shunt or bidirectional shunt across PDA or PFO, tricuspid regurgitation and increased pulmonary pressures using pulse wave Doppler, flattening of septum or paradoxical septal motion were identified as PPHN. Severity of PPHN was based on Oxygenation Index (OI) in ventilated neonates and delta SO2 in non-ventilated neonates. An OI score of <15 was taken as mild, 15-25 as moderate, 25-40 as severe and > 0 as very severe. A delta saturation of 10-15% was taken as mild to moderate and >15% severe, provided the findings are consistent with clinical and echocardiographic criteria for PPHN.

**PPHN treatment strategies**

In our unit, PPHN was managed with minimal handling, oxygen to maintain SO2 within a target range of 90-95% (oxygen hood, HFNC, CPAP, mechanical ventilation), circulatory support to maintain mean arterial pressure >50 mm Hg and adequate cardiac contractility (dopamine, dobutamine, adrenaline, nor adrenaline, milrinone) when needed, vasodilators (sildenafil, bosentan) since iNO was unavailable at our locality, maintenance of temperature, euglycemia, electrolytes within normal range and haematocrit >40%.

The indications for mechanical ventilation were, respiratory distress with Downe’s score >8, failure to maintain SpO2 in target range with FiO2 <70%, shock not corrected with vaspressors and arterial blood gas values of pH <7.20, PCO2 >55 mm Hg, PO2 <50. The goal was to maintain PO2 between 60-90 mmHg and PCO2 between 35-50 mmHg to prevent oxidative stress and hypocapnia.

The nature of respiratory support and its duration, ventilation duration, maximum mean airway pressure and FiO2 reached, need for inotropes and vasodilator were recorded. Etiology for PPHN such as Meconium Aspiration Syndrome (MAS), Hypoxic Ischemic Encephalopathy (HIE), Congenital Diaphragmatic Hernia (CDH), sepsis/ pneumonia, Respiratory Distress Syndrome (RDS) and Bronchopulmonary Dysplasia (BPD) were analysed with respect to PPHN severity and mortality.

**Statistical analysis**

The statistical analysis was calculated with SPSS software. Mean, Standard deviation was calculated for continuous variables. Chi square test and Fischer’s exact test was used to test the association between categorical variables and t test for continuous variables.

**RESULTS**

In the year 2016, 2295 babies were admitted in the unit. 35 babies had non-cardiac causes of PPHN (1.5%).
Table 1: Demographics of study population (n = 35).

| Parameters                      | No. Percentage |
|-------------------------------|----------------|
| **Maternal**                  |                |
| Age (years), 18-34, n (%)     | 35 (100)       |
| Parity                        |                |
| Primi, n (%)                  | 12 (34.3)      |
| Multi                         | 23 (65.7)      |
| Maternal illness, n (%)       |                |
| Diabetes                      | 0              |
| PIH                           | 0              |
| Hypertension                  | 1 (2.9)        |
| Oligohydramnios               | 2 (5.7)        |
| PROM                          | 2 (5.7)        |
| Chorioamnionitis              | 0              |
| IUGR                          | 1 (2.9)        |
| **Neonatal**                  |                |
| Birth weight (g)              |                |
| 1500-2499                     | 11 (31.4)      |
| >2500                         | 24 (68.5)      |
| Gestational age (weeks)       |                |
| 34-36+6                       | 6 (17.1)       |
| >37                           | 29 (82.3)      |
| AGA                           | 27 (77)        |
| SGA                           | 8 (22.3)       |
| Male                          | 22 (62.9)      |
| Female                        | 13 (37.1)      |
| Mode of delivery              |                |
| Normal                        | 11 (31.4)      |
| LSCS                          | 24 (68.9)      |
| Cried at birth, n (%)         |                |
| Yes                           | 21 (60)        |
| No                            | 14 (40)        |
| Duration of hospital stay     | 14.3±2.6, 95% CI (9.1-19.5) |

Table 1 shows the demographics of study population. All the mothers were in the age group of 18-34 years. 68.9% of babies were delivered through LSCS. 29 babies (82.3%) were born at term and 6 babies (17.3%) were in the late preterm category.

Figure 1: PPHN-Etiologic distribution (n = 35).

24 babies (68.5%) weighed more than 2500 grams at birth and 11 babies (31.4%) weighed between 1500-2499 grams. The average duration of hospital stay was 14.3 days. The causes of PPHN are shown in Figure 1. In the present study population of 35 babies with PPHN, 45.7% was secondary to MAS followed by CDH at 22.3%. Table 2 shows incidence of PPHN among the population at risk in our hospital, which was 4.9%. The etiologic distribution of PPHN based on severity is shown in Table 3.

Table 2: PPHN-risk factor distribution.

| Risk factors                  | No. of cases (n) | No. of PPHN, (n) | Incidence, % |
|-------------------------------|------------------|------------------|--------------|
| MAS                           | 43               | 16               | 37           |
| CDH                           | 12               | 8                | 66           |
| Congenital pneumonia          | 30               | 3                | 10           |
| Sepsis                        | 246              | 3                | 1.2          |
| HIE                           | 192              | 2                | 2.6          |
| RDS                           | 75               | 1                | 1.3          |
| TTN                           | 109              | 2                | 1.8          |
| Total                         | 707              | 35               | 4.9          |

Table 3: Etiologic and mortality distribution based on severity.

| Etiology                      | PPHN (n=35) | Mild (OI <15) | Moderate (OI 15-25) | Severe (OI 25-40) | Very severe (OI >40) |
|-------------------------------|-------------|---------------|---------------------|------------------|----------------------|
|                               | Total, n    | Death n (%)   | Total n (%)         | Death n (%)      | Total n (%)          | Death n (%)          |
| MAS                           | 16 (45.7)   | 6 (37.5)      | 8 (50)              | 0                | 3 (18.9)             | 0                    |
| CDH                           | 8 (22.3)    | 7 (87.5)      | 1 (12.5)            | 2 (25)           | 2 (100)              | 2 (100)              |
| Congenital Pneumonia          | 3 (11.4)    | 0 (33)        | 1 (33)              | 0                | 1 (33)               | 0                    |
| Sepsis                        | 3 (11.4)    | 0 (33)        | 0 (33)              | 0                | 0                    | 0                    |
| HIE                           | 2 (5.7)     | 1 (50)        | 0 (0)               | 1 (50)           | 0 (50)               | 0                    |
| RDS                           | 1 (2.8)     | 0 (100)       | 0 (0)               | 0                | 0                    | 0                    |
| Others (TTN, IUGR)            | 2 (5.7)     | 1 (50)        | 0 (0)               | 1 (50)           | 1 (100)              | 0 (0)                |
| Total                         | 35           | 15 (42.3)     | 14 (40)             | 10 (28.5)        | 6 (60)               | 8 (22.8)             | 6 (75)              | 3 (8.5)             | 3 (100)             |
Table: 4 Treatment characteristics

| Respiratory support       |            |            |            |
|---------------------------|-----------|-----------|-----------|
| Conventional ventilation  | 29 (82.3)|           |           |
| CPAF, n (%)               | 1 (2.8)  |           |           |
| Oxygen hood, n (%)        | 13 (37)  |           |           |
| Surfactant, n (%)         | 1 (2.8)  |           |           |
| Ventilation days, median  | 5 (1-49) |           |           |
| Oxygen days, median (min-max) | 10 (3-34) |           |

| Circulatory support       |            |            |            |
|---------------------------|-----------|-----------|-----------|
| Dopamine, n (%)           | 25 (71.4)|           |           |
| Dobutamine, n (%)         | 24 (68.6)|           |           |
| Adrenalin, n (%)          | 9 (25.7) |           |           |
| Vasodilator support       | Sildenafil| 19 (54.2)|           |

Pulmonary hypertension severity was classified based on [1] of mild (15, 42.3%), moderate (10, 28.6%), severe (8, 22.3%) and very severe PPHN (3, 8.6%). 15 babies (42.3%) died (10 males, 5 females), 6 among 10 babies (60%) died with moderate, 6 among 8 babies (75%) died in severe PPHN and all 3 babies (100%) died with very severe PPHN. The average duration from admission to death was 3.6 days, 3 out of 35 (8.5%) babies with PPHN developed pneumothorax of which 2 (66.7%) died. The treatment characteristics of our study group are shown in Table 4. Sildenafil was the vasodilator of choice in our unit and with the unavailability of HFOV; conventional ventilation was the mainstay ventilator therapy. The overall survival rate of our population was 57.1%. Factors favouring survival and mortality is shown in Table 5.

Table: 5 Risk analysis-survival versus mortality.

| Risk factors | Survival (n = 20) | Death (n = 15) | P value |
|--------------|-------------------|---------------|---------|
| Transport    |                   |               |         |
| Arrival temp, mean, SD, 95% CI | 36.1, 1.05, (35.6-36.6) | 36.5, 0.57, (35.9-37.07) | 0.100* |
| Arrival SpO2 mean, SD, 95% CI | 87.15, 13 (81.1-93.3) | 76.47, 7.7 (72.2-80.6) | 0.0042* |
| Need for intubation on arrival, n (%) | 3 (15) | 14 (93) | 0.0003+ |
| Shock, n (%) | 1 (5) | 10 (66.6) | 0.0018+ |
| Duration of travel, median (min-max) | 1 (0.5-6) | 1 (0.5-6) | 0.43* |
| Age at referral, median (min-max) | 10.5 (1-192) | 12 (3.5-144) | 0.65* |
| Gender       |                   |               |         |
| Male, n (%)  | 12 (34.2) | 10 (28.6) | 0.6+ |
| Female, n (%)| 8 (22.9)  | 5 (14.3)  |         |
| Gestational age |           |               |         |
| >37 weeks, n (%) | 17 (48.9) | 10 (28.6) | 0.2+ |
| <37 weeks, n (%) | 3 (8.5) | 5 (14.3) |         |
| Gestational age distribution | SGA, n (%) | 3 (8.5) | 5 (14.3) | 0.2+ |
| AGA, n (%) | 17 (48.9) | 10 (28.9) |         |
| Birth weight |                   |               |         |
| <2500 g, n (%) | 4 (11.4) | 6 (17.1) | 0.2+ |
| >2500 g, n (%) | 16 (45.7) | 9 (25.7) |         |

On evaluating transport and clinical condition on arrival at ER status, admission SpO2, need for intubation and presence of shock on arrival was significantly associated with mortality. Mortality in PPHN was also associated with various risk factors such as, <37 weeks gestation, SGA, <2500 and male gender. However, the results were statistically insignificant.

DISCUSSION

Our overall incidence of PPHN in the year of 2016 was 1.5%. The incidence of PPHN in our study population with risk factors was 4.9%. This when compared to reported incidence by Sukys et al of 1.9 per 1000 and Malik et al of 0.43 to 6.8 per 1000 live births is high. However, our incidence cannot be taken to represent the general population as ours was a referral centre for sick neonates and the incidence would have been influenced by referral bias. Our population showed a male preponderance and similar observations were also shown by Choudhary et al with 63% and 62.5% in Hsieh et al. LSCS delivery rate was high in our group which could have played a role in development of PPHN, following interference with secretion of endogenous catecholamine thereby leading to delayed transition. In contrast to general incidence of PPHN being high among late preterm as in Steurer et al, in the present study more term infants (82.3%) were diagnosed with PPHN. Similar findings were seen with Gustav et al with 82.6% term infants as opposed to 20% preterm. In the present study, apart from identifying various etiological factors, we attempted to classify PPHN into mild, moderate, severe and very severe and analyse the distribution of etiology under severity and their respective mortality rates.

The overall mortality of PPHN in our population was 42.3%. The mortality of PPHN among the at-risk population in our hospital was 4.9%. Hsieh et al reported a mortality of 26.7%, 11% in Sukys et al. In our population, mortality was high, reaching 75% in severe
and 100% in very severe PPHN. This could be due to the fact that these babies could not be managed with iNO, HFOV or ECMO, and was only managed with sildenafil and conventional ventilation. MAS was the major cause of PPHN. Similar finding was reported by Konduri et al in his iNO study and Choudhary et al.\textsuperscript{2,8}

The second common cause of PPHN in our group was CDH. Majority of the CDH in our group belonged to moderate and severe PPHN, which accounted for the high mortality. Brownlee et al reported that, the true mortality of CDH was high when foetuses with CDH were also included.\textsuperscript{13} Boloker et al however reported a mortality rate of 26.2% when CDH babies were managed with permissive hypercapnia and elective surgery.\textsuperscript{14}

The third most common cause in our group was congenital pneumonia and sepsis. The endotoxins released by the infecting organism accompanied by the release of cytokines, endothelin and tumour necrosis factor alpha.\textsuperscript{15} The other causes of PPHN in our population were HIE, IUGR and TTN. In utero hypoxia, acute and chronic and placental dysfunction along with nutrient delivery defect resulting in IUGR also contributes to development of PPHN.\textsuperscript{16,17}

We attempted to analyse factors that could possibly contribute to mortality and in doing we recognised a possible association between quality of transport and death. Cardiovascular support during transport/referral, in particular stabilisation of circulatory status significantly contributed to survival, whereas shock on arrival in ER despite being transported by ambulance services was associated with unfavourable outcome.

Present study is limited by the fact that it is a retrospective single centre study with a small sample size and referral bias. However, it has given us insight into PPHN in our hospital newborn population. Further prospective studies are needed to evaluate various therapeutic efficacies and survival.

**CONCLUSION**

To conclude, this study shows MAS and CDH are common causes of PPHN. Severity of illness at arrival is predictive of high mortality. Prior stabilisation and adequate transport may improve outcomes.

**ACKNOWLEDGEMENTS**

Authors thank the Medical Records Department at their Institute for helping them in accessing the patient’s records with ease.

**Funding:** No funding sources  
**Conflict of interest:** None declared  
**Ethical approval:** The study was approved by the Institutional Ethics Committee

**REFERENCES**

1. Goldsmith JP, Karotkin E. Assisted ventilation of the neonate. Elsevier Health Sciences; 2016:658.
2. Fox WW, Gewitz MH, Dinwiddie R, Drummond WH, Peckham GI. Pulmonary hypertension in the perinatal aspiration syndromes. Pediatr. 1977;59(2):205-11.
3. Steurer MA, Jelliffe-Pawlowski LL, Baer RJ, Partridge JC, Rogers EE, Keller RL. Persistent pulmonary hypertension of the newborn in late preterm and term infants in California. Pediatrics. 2017;139(1):e20161165.
4. Walsh-Sukys MC, Tyson JE, Wright LL, Bauer CR, Korones SB, Stevenson DK, et al. Persistent pulmonary hypertension of the newborn in the era before nitric oxide: practice variation and outcomes. Pediatr. 2000;105(1):14-20.
5. Konduri GG, Kim UO. Advances in the Diagnosis and Management of Persistent Pulmonary Hypertension of the Newborn. Pediatr Clin North Am. 2009;56(3):579-600.
6. Roofthoofd MT, Elena A, Bergman KA, Berger RM. Patient characteristics in persistent pulmonary hypertension of the newborn. Pulmonary Medicine. 2011:2011.
7. Malik M, Nagpal R. Emerging role of sildenafil in neonatology. Indian Pediatr. 2011;48(1):11-3.
8. Choudhary M, Meena MK, Chhangani N, Sharma D, Choudhary JS, Choudhary SK. To study prevalence of persistent pulmonary hypertension in newborn with meconium aspiration syndrome in western Rajasthan, India: a prospective observational study. J Matern Fetal Neonatal Med. 2016;29(2):324-7.
9. Hsieh WS, Yang PH, Fu RH. Persistent pulmonary hypertension of the newborn: experience in a single institution. Acta Paediatr Taiwanica Taiwan Er Ke Yi Xue Hui Za Zhi. 2001;42(2):94-100.
10. Heritage CK, Cunningham MD. Association of elective repeat cesarean delivery and persistent pulmonary hypertension of the newborn. Am J Obstet Gynecol. 1985;152(6)(1):627-9.
11. Gustav R, Baptista MJ, Guimarães H. Persistent pulmonary hypertension of non-cardiac cause in a Neonatal Intensive Care Unit. Pulmonary Med. 2012; 818971.
12. Konduri GG, Solimano A, Sokol GM, Singer J, Ehrenkranz RA, Singhal N, et al. A randomized trial of early versus standard inhaled nitric oxide therapy in term and near-term newborn infants with hypoxic respiratory failure. Pediatr. 2004;113(3):559-64.
13. Brownlee EM, Howatson AG, Davis CF, Sabharwal AJ. The hidden mortality of congenital diaphragmatic hernia: a 20-year review. J Pediatr Surg. 2009;44(2):317-20.
14. Boloker J, Bateman DA, Wung JT, Stolar CJH. Congenital diaphragmatic hernia in 120 infants treated consecutively with permissive
hypercapnea/spontaneous respiration/elective repair. J Pediatr Surg. 2002;37(3):357-66.

15. Navarrete CT, Devia C, Lessa AC, Hehre D, Young K, Martinez O, et al. The role of endothelin converting enzyme inhibition during group b streptococcus–induced pulmonary hypertension in newborn piglets. Pediatr Res. 2003;54(3):387-92.

16. Srinivas SK, Edlow AG, Neff PM, Sammel MD, Andrela CM, Elovitz MA. Rethinking IUGR in preeclampsia: dependent or independent of maternal hypertension? J Perinatol. 2009;29(10):680-4.

17. Kaufmann P, Black S, Huppertz B. Endovascular trophoblast invasion: implications for the pathogenesis of intrauterine growth retardation and preeclampsia. Biol Reprod. 2003;69(1):1-7.

Cite this article as: Harish S, Kamalarathnam CN. Clinical profile of persistent pulmonary hypertension in new born: experience in an extramural institution. Int J Contemp Pediatr 2018;5:2193-8.