Title: Clinical Profile of Persistent Pulmonary Hypertension in Neonates with Role of Sildenafil in its Outcome: Rural India NICU Experience

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Authors’ contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

ABSTRACT

Background: Persistent pulmonary hypertension of newborn (PPHN) result from failure of normal fall in pulmonary vascular resistance at or shortly after birth. It is associated with high mortality and morbidity.

Objectives: To estimate incidence, risk factors; and outcome within limited resources – conventional ventilation, sildenafil, dobutamine and milrinone therapy.

Methods: This prospective study was carried out on cases of PPHN admitted between March 2017 to August 2018. PPHN was suspected clinically, and then confirmed by echocardiography.

Results: Out of 2811 inborn live births 12 (0.43%) developed PPHN. Out of total 942 NICU admissions, PPHN was diagnosed in 40(4.2%). 32 (80%) were full term, 6 (15%) were late preterm and 2(5%) were post term neonates. 25(62.5%) were male. Major etiological factors were asphyxia

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PPHN is suspected when there is a considerable difference between preductal and post-ductal oxygen saturation, in combination with severe hypoxaemia that does not improve when the infant is subjected to 100% supplemental oxygen. As it is difficult to differentiate PPHN from cyanotic congenital heart disease on clinical grounds alone, echocardiography is usually required to confirm a diagnosis of PPHN [5,14].

The main goals of treatment of PPHN are to decrease pulmonary vascular resistance and increase pulmonary blood flow. This is carried out by correcting the underlying disease, good supportive care, and selective pulmonary vasodilators such as inhaled nitric oxide (iNO), Magnesium sulphate (MgSO4) and Oral sildenafil [15]. In resource-limited facilities, sildenafil, milrinone and magnesium sulphate have been shown to be safe, effective pulmonary vasodilators for improving oxygenation when iNO is not available [16,17,18,19]. The current mainstay of PPHN treatment when conventional ventilatory support alone fails, consists of a combination of high frequency oscillatory ventilation (HFOV) and administering iNO. ECMO is used as a rescue therapy for neonates in respiratory failure and who are unresponsive to other therapies [20,21,22,23].

As there were no outcome data from our centre, we conducted a prospective study to determine incidence, risk factors, etiological factors & survival rate. We also aimed to analyse role of sildenafil, dobutamine, milrinone and conventional ventilation in management of PPHN, as also factors influencing outcome.

2. MATERIALS AND METHODS

This is prospective observational study conducted in NICU (neonatal intensive care unit), Dhiraj Hospital, SBKS Medical Institute &

Keywords: Persistent pulmonary hypertension of newborn; sildenafil; ventilation; asphyxia.
Research Center, Waghodia Taluka, Vadodara district, Gujarat, India from March 2017 to August 2018 (18 months duration). All the neonates both inborn and outborn with echocardiographic confirmed diagnosis of PPHN were included in this study. Neonates with congenital heart diseases and those with pulmonary hypertension secondary to cardiac conditions were excluded from this study. Sick neonates with clinical diagnosis of PPHN (based on history, examination, SpO2, hyperoxia test) were subjected to echocardiography. Echocardiography was done by cardiologist. Diagnostic criteria for echocardiography used were increased pulmonary artery pressure (measured by tricuspid regurgitation jet), right to left shunt or bidirectional shunt across patent ductus arteriosus (PDA) or persistent foramen ovale (PFO) or paradoxical ventricular septal movement. All the neonates with PPHN started with head box oxygen, oral sildenafil and dobutamine infusion along with specific therapy based on etiology, and other supportive management based on standard protocol guidelines. Conventional ventilation was given based on oxygen saturation (SpO2) / arterial blood gas (ABG) &/or clinically based on respiratory distress severity. In poor responders milrinone infusion was added.

2.1 Statistical Analysis

Data collected was entered in Microsoft excel sheet. Then it was analysed and summarized by percentage, mean & standard deviation; and median and IQR (inter quartile range). Relative risk and p value calculation was done to find association between variables. Mann Whitney U test was used to find out p value from median.

3. RESULTS

This study was conducted over a period of one and half year, from March 2017 to August 2018, in NICU of Dhiraj Hospital, S.B.K.S. M.I.R.C., Waghodiya taluka, Vadodara district. During the period of our study, there were 2811 inborn live births, of which 12 (0.43%) had PPHN. Total 942 patients were admitted in NICU, among them 40 patients (4.2%) had PPHN. Inborn admissions were 489, of which 12 (2.4%) had PPHN. 453 patients were outborn, out which 28 (6.1%) had PPHN.16 (40%) were low birth weight (all were between 1.5 kg to 2.5 kg), 24 (60%) were normal birth weight. 6 (15%) were preterm (all were late preterm), 32 (80%) were term and 2 (5%) were post term. 33 (82.5%) were AGA (appropriate for gestational age), and 7 (17.5%) were SGA (small for gestational age).

Major risk factors were MSAF (meconium stained amniotic fluid) in 20 (50%), PROM (premature rupture of membrane) in 12 (30%), use of NSAIDs (non-steroid anti-inflammatory drugs) in 7 (17.5%) and SGA in 7 (17.5%). Major etiological factors were asphyxia in 19 (47.5%), EOS (early onset sepsis) in 18 (45%), MAS in 12 (30%) and pneumonia in 6 (15%).

Risk of PPHN was 3.7% in inborn asphyxiated neonates, while it was 16.49% in outborn asphyxiated. Risk among MAS cases was 23.08% in inborn while 45% in outborn. Risk of PPHN among EOS cases was 10.42% in inborn and 13.33% in outborn.

All the neonates required ventilator therapy (conventional ventilator). Out of 26 neonates who showed good response, post extubation CPAP (continuous positive airway pressure ventilation) was required in 17 (42.5%) neonates. 9 were directly extubated to head box oxygen. All (40) the neonates were given sildenafil and dobutamine, of which 20 showed good response, and remaining 20 did not show good response. of which milrinone was added in 17 neonates.

26 (65%) were successfully discharged. 9 (22.5%) were expired. 5 (12.5%) left against medical advice (LAMA), they left NICU in moribund state.

| Table 1. Demographic profile of cases with PPHN |
|-----------------------------------------------|
| Place of Delivery | Total Number of Patients (n=40) |
|-------------------|-------------------------------|
| Home              | 02 (05%)                      |
| Hospital          | 38 (95%)                      |
| Inborn            | 12 (30%)                      |
| Outborn           | 28 (70%)                      |
| Sex               |                               |
| Male              | 25 (62.5%)                    |
| Female            | 15 (32.5%)                    |


|                  | Total Number of Patients (n=40) |
|------------------|---------------------------------|
| **Mode of delivery** |                                 |
| Vaginal          | 23 (57.5%)                      |
| LSCS             | 17 (42.5%)                      |
| **Birth Weight**  |                                 |
| LBW              | 16 (40%)                        |
| NBW              | 24 (60%)                        |
| Large Birth Weight | 00                              |
| **Gestational Age** |                                |
| Preterm (all late preterm) | 06 (15%)                        |
| Term             | 32 (80%)                        |
| Post term        | 02 (05%)                        |
| **Weight for Gestational Age** |                            |
| AGA              | 33 (82.5%)                      |
| SGA              | 07 (17.5%)                      |
| LGA (large for gestational age) | 00                              |
| **Age on admission** |                                |
| < 24 hours       | 28 (70%)                        |
| >24 hours        | 12 (30%)                        |

Table 2a. Risk factors & etiological factors of PPHN

| Risk Factor                  | Total Cases (n=40) |
|------------------------------|--------------------|
| Diabetes                     | 0                  |
| Toxemia                      | 04 (10%)           |
| NSAIDs in 3rd trimester      | 07 (17.5%)         |
| PROM > 24 hours              | 12 (30%)           |
| MSAF                         | 20 (50%)           |
| Post maturity                | 02 (5%)            |
| SGA                          | 07 (17.5%)         |
| **Etiology**                 |                    |
| Asphyxia                     | 19 (47.5%)         |
| MAS                          | 12 (30%)           |
| EOS                          | 18 (45%)           |
| Pneumonia                    | 06 (15%)           |
| RDS                          | 03 (7.5%)          |
| Hypoplastic lungs            | 01 (2.5%)          |
| Diaphragmatic hernia         | 01 (2.5%)          |
| Idiopathic                   | 02 (5%)            |

Table 2b. Risk of PPHN among common etiological factors

| Inborn                 | Risk of PPHN |
|------------------------|--------------|
| Asphyxia (n=81)        | 03 (3.7%)    |
| MAS (n=13)             | 03 (23.08%)  |
| EOS (n=48)             | 05 (10.42%)  |
| **Outborn**            |              |
| Asphyxia (n=97)        | 16 (16.49%)  |
| MAS (n=20)             | 09 (45%)     |
| EOS (n=87)             | 13 (14.94%)  |
| **Inborn + Outborn**   |              |
| Asphyxia (n=178)       | 19 (10.67%)  |
| MAS (n=33)             | 12 (36.36%)  |
| EOS (n=135)            | 18 (13.33%)  |
Table 3. Therapy used for management of PPHN

| Duration of Oxygen therapy including ventilation | Number of Cases (n = 40) |
|------------------------------------------------|-------------------------|
| 0 - 7 days                                      | 20 (50%)                |
| 8 – 14 days                                     | 19 (47.5%)              |
| >14 days                                        | 01 (2.5%)               |

| Duration of ventilation therapy                | 40                       |
|-----------------------------------------------|--------------------------|
| 0 – 3 days                                     | 21 (52.5%)               |
| 4 – 7 days                                     | 17 (42.5%)               |
| >7 days                                        | 02 (5%)                  |

| Duration of CPAP therapy (post extubation)    | 17                       |
|-----------------------------------------------|--------------------------|
| 0 – 3 days                                     | 13 (32.5%)               |
| 4 – 7 days                                     | 04 (10%)                 |
| Not given                                      | 23 (57.5%)               |

| Pulmonary vasodilator drugs                   |                          |
|-----------------------------------------------|--------------------------|
| Sildenafil                                     | 40 (100%)                |
| Dobutamine                                     | 40 (100%)                |
| Milrinone                                      | 17 (42.5%)               |

Table 4. Outcome

| Outcome                        | Total Cases (n=40) |
|--------------------------------|--------------------|
| Discharge                      | 26 (65%)           |
| LAMA non moribund              | 05 (12.5%)         |
| LAMA moribund                  | 00                 |
| Death                          | 09 (22.5%)         |

Over all 26 (65%) had good outcome in the form of discharge. 14 (35%) had poor outcome; either they expired or left against medical advice in severely moribund state. Good outcome was noted in 10 (83.4%) of inborn admissions, 5 (83.33%) of late preterm, 11 (57.9%) of asphyxiated neonates, 8 (66.67%) of MAS, 10 (55.56%) of EOS, 4 (66.67%) of pneumonia cases with PPHN. Poor outcome was noted in 12 (42.9%) of outborn admissions, 13 (38.23%) of neonates with gestational age ≥ 37 weeks, 8 (42.1%) of asphyxia, 4 (33.3%) of MAS, 8 (44.44%) of EOS and 2 (33.33%) of pneumonia with PPHN cases.

We analyzed relative risk of poor outcome among various factors, e.g. outborn Vs inborn, LSCS delivered Vs vaginally delivered, born before 37 weeks Vs born after 37 weeks, PPHN due to asphyxia Vs PPHN due to cause other than asphyxia, etc. We were not able to find any significance among them. We found statistically significant increased risk of poor outcome among those who presented with severe respiratory distress than those who presented with mild/moderate respiratory distress; RR 7.0 (95% CI 1.02 – 3.43), p = 0.048.

We were not able to find correlation of any factor associated with either good or poor outcome except post maturity; which was associated with poor outcome; p value of 0.05. Mean gestational age was 37.62 (1.11) in neonates with good outcome, as against mean gestational age of 38.57 (1.4) in neonates with poor outcome; p value 0.024.

Duration of hospital stay was statistically very significant between the two outcome groups, with mean duration of 3.36 days in those with poor outcome and of 17.77 days in those with good outcome. As also duration of respiratory support was significantly different between the two outcome groups. Those with poor outcome, outcome came very early with mean 3.36 (3.41) days and median days of 1.5 (1 – 6) days of admission.

One case with associated surgical condition – esophageal atresia with tracheoesophageal fistula in whom surgery was done was removed from analysis. Thus, total 17 cases of EOS with PPHN were analyzed.

We could not find any effect of associated problem along with EOS in relation with either poor or good outcome. We also could not find any statistically increased relative risk of poor outcome when EOS is associated with other conditions causing PPHN.
Table 5. Comparison between various risk factors and etiological factors with outcome

| Etiological factor                          | Total number of patients (n) | Outcome (number of patients) | Relative risk  |
|--------------------------------------------|------------------------------|------------------------------|----------------|
|                                            |                              | Poor outcome (LAMA (moribund) / death) | Good outcome |                  |
| Overall outcome                            | 40                           | 14 (35%)                     | 26 (65%)      | 2.57 (95% CI 0.68 – 9.78), p = 0.17 |
| Place of delivery                          |                              |                              |               |                   |
| Outborn                                    | 28                           | 12 (42.9%)                   | 16 (57.1%)    | 2.57 (95% CI 0.68 – 9.78), p = 0.17 |
| Inborn                                     | 12                           | 2 (16.6%)                    | 10 (83.4%)    |                   |
| Mode of delivery                           |                              |                              |               |                   |
| LSCS                                       | 17                           | 6 (35.3%)                    | 11 (64.7%)    | 1.01 (95% CI 0.43 – 2.38), p = 0.97 |
| NVD (normal vaginal delivery)              | 23                           | 8 (34.7%)                    | 15 (65.3%)    |                   |
| Toxemia of pregnancy                       |                              |                              |               |                   |
| Present                                    | 4                            | 0 (0%)                       | 4 (100%)      | 0.26 (95% CI 0.018 – 3.65), p = 0.31 |
| Absent                                     | 36                           | 14 (38.9%)                   | 22 (61.1%)    |                   |
| NSAIDS in third trimester                  |                              |                              |               |                   |
| Present                                    | 7                            | 1 (14.2%)                    | 6 (85.7%)     | 0.36 (95% CI 0.056 – 2.34), p = 0.29 |
| Absent                                     | 33                           | 13 (39.4%)                   | 20 (60.6%)    |                   |
| PROM                                       |                              |                              |               |                   |
| >24 HRS                                    | 12                           | 3 (25%)                      | 9 (75%)       | 0.64 (95% CI 0.22 – 1.88), p = 0.41 |
| <24 HRS                                    | 28                           | 11 (39.2%)                   | 17 (60.7%)    |                   |
| Color of liquor                            |                              |                              |               |                   |
| Meconium stained                           | 20                           | 9 (45%)                      | 11 (55%)      | 1.8 (95% CI 0.73 – 4.43), p = 0.2 |
| Clear                                      | 20                           | 5 (25%)                      | 15 (75%)      |                   |
| Maturity                                   |                              |                              |               |                   |
| < 37 weeks                                 | 06                           | 1 (16.66%)                   | 5 (83.33%)    | 0.44 (95% CI 0.069 – 2.74), p = 0.38 |
| ≥ 37 weeks                                 | 34                           | 13 (38.23%)                  | 21 (61.76%)   |                   |
| Weight for gestational age                 |                              |                              |               |                   |
| SGA                                        | 7                            | 3 (42.8%)                    | 4 (57.2%)     | 1.28 (95% CI 0.48 – 3.43), p = 0.62 |
| AGA                                        | 33                           | 11 (33.3%)                   | 22 (66.7%)    |                   |
| Severity of respiratory distress on admission |                        |                              |               |                   |
| Severe (grunting and/or gasping present)   | 26                           | 13 (50%)                     | 13 (50%)      | 7.0 (95% CI 1.02 – 48.1), p = 0.048 |
| Mild to moderate (retractions and nasal flaring present) | 14                           | 1 (7.2%)                     | 13 (92.8%)    |                   |
| Condition                  | Present | Absent | Odds Ratio 95% CI | p-value |
|----------------------------|---------|--------|------------------|---------|
| Birth asphyxia             |         |        |                  |         |
| Present                    | 19      | 21     | 1.47 (0.62 – 3.47) | 0.37    |
| Absent                     | 08 (42.1%) | 06 (28.57%) |               |          |
| MAS                        |         |        |                  |         |
| Present                    | 12      | 28     | 0.93 (0.36 – 2.39) | 0.88    |
| Absent                     | 04 (33.33%) | 10 (35.71%) |               |          |
| EOS                        |         |        |                  |         |
| Present                    | 12      | 28     | 1.63 (0.69 – 3.8)  | 0.26    |
| Absent                     | 04 (33.33%) | 10 (35.29%) |               |          |
| Pneumonia                  |         |        |                  |         |
| Present                    | 6       | 34     | 0.94 (0.28 – 3.19) | 0.92    |
| Absent                     | 02 (33.33%) | 12 (35.29%) |               |          |
| RDS                        |         |        |                  |         |
| Present                    | 03      | 14     | 0.33 (0.024 – 4.52) | 0.4     |
| Absent                     | 04 (0%) | 23 (37.84%) |             |          |
| Hypoplastic lung           |         |        |                  |         |
| Present                    | 01 (100%) | 00     |                 |          |
| Absent                     | 00 (0%) | 01 (100%) |             |          |
| Diaphragmatic hernia       |         |        |                  |         |
| Present                    | 01 (100%) | 00     |                |          |
| Absent                     | 00 (0%) | 01 (100%) |             |          |
| Idiopathic                 |         |        |                  |         |
| Present                    | 02      | 04     |                 |          |
| Absent                     | 04 (50%) | 01 (50%) |             |          |
Table 6. Correlation of various parameters between good outcome and poor outcome

| Parameter                             | Poor outcome (n=14) | Good outcome (n=26) | p value |
|---------------------------------------|---------------------|---------------------|---------|
| Birth weight (kg)                     | 2.453 (0.42)        | 2.469 (0.36)        | 0.9     |
| Gestational age (weeks)               | 38.57 (1.4)         | 37.62 (1.11)        | 0.024   |
| Outborn                               | 12 (85.71%)         | 16 (61.54%)         | 0.12    |
| Inborn                                | 02 (14.29%)         | 10 (38.46%)         | 0.12    |
| Vaginal Delivery                      | 08 (57.14%)         | 15 (57.69%)         | 0.97    |
| LSCS                                  | 06 (42.86%)         | 11 (42.31%)         | 0.97    |
| Male                                  | 07 (50%)            | 18 (69.23%)         | 0.24    |
| Female                                | 07 (50%)            | 08 (30.77%)         | 0.24    |
| Preterm                               | 01 (7.14%)          | 05 (19.23%)         | 0.31    |
| Full term                             | 11 (78.57%)         | 21 (80.77%)         | 0.87    |
| Post term                             | 02 (14.29%)         | 00 (0%)             | 0.05    |
| AGA                                   | 11 (78.57%)         | 22 (84.62%)         | 0.64    |
| SGA                                   | 03 (21.43%)         | 04 (15.38%)         | 0.64    |
| Asphyxia                              | 08 (57.14%)         | 11 (42.31%)         | 0.38    |
| MAS                                   | 04 (28.57%)         | 08 (30.77%)         | 0.89    |
| EOS                                   | 08 (57.14%)         | 10 (38.46%)         | 0.26    |
| Pneumonia                             | 02 (14.29%)         | 04 (15.38%)         | 0.93    |
| RDS                                   | 00 (0%)             | 03 (11.54%)         | 0.19    |
| Idiopathic                            | 01 (7.14%)          | 01 (3.85%)          | 0.65    |
| Duration of respiratory support       | 1.5 (1 – 6)*        | 6 (4 – 7)*          | p = 0.00452# |
| support (Ventilation + CPAP) (days)   |                     |                     |         |
|                                       | 3.36 (3.41)**       | 6.04 (2.64)**       | p = 0.009 |
| Duration of hospital stay (days)      | 1.5 (1 – 6)*        | 17 (13 – 22)*       | p < 0.00001# |
|                                       | 3.36 (3.41)**       | 17.77 (6.39)**      | < 0.0001 |

*data as median and IQR, **data as mean and SD, #Mann-Whitney U test

Table 7a. Outcome in EOS with PPHN – analysis of effects of associated problem

| Associated problem                              | Poor outcome (7) | Good outcome (10) | P value | Relative risk |
|------------------------------------------------|------------------|-------------------|---------|---------------|
| MAS                                            | 02 (28.57%)      | 04 (40%)          | 0.51    |               |
| Asphyxia                                       | 03 (42.86%)      | 02 (20%)          | 0.19    |               |
| Pneumonia                                      | 01 (14.29%)      | 01 (10%)          | 0.87    |               |
| RDS                                            | 00 (0%)          | 01 (10%)          | 0.37    |               |
| EOS with other conditions of PPHN              | 05 (71.43%)      | 06 (60%)          | 0.64    | 1.36 (95%) CI 0.37 – 5.02, p = 0.64 |
| Isolated EOS as a cause of PPHN                | 02 (28.57%)      | 04 (40%)          | 0.51    | 5.02, p = 0.64 |
| Late onset sepsis/ventilator associated pneumonia(LOS / VAP) | 00 (0%)          | 01 (10%)          | 0.4     |               |
| Hypoxic ischemic encephalopathy 2-3 (HIE)      | 03 (42.86%)      | 01 (10%)          | 0.13    |               |

One case with associated surgical condition – esophageal atresia with tracheoesophageal fistula in whom surgery was done was removed from analysis. Thus, total 18 cases of asphyxia with PPHN were analyzed.

We could not find any effect of associated problem along with asphyxia in relation with either poor or good outcome. We also could not find any statistically increased relative risk of poor outcome when asphyxia is associated with other conditions causing PPHN.
Table 7. Outcome in asphyxia with PPHN – analysis of effects of associated problem

| Associated problem | Poor outcome (7) | Good outcome (11) | P value | Relative risk |
|--------------------|------------------|-------------------|---------|---------------|
| MAS                | 03 (42.86%)      | 04 (36.36%)       | 0.79    |               |
| EOS                | 03 (42.86%)      | 02 (18.18%)       | 0.27    |               |
| Pneumonia          | 0 (0%)           | 00 (0%)           |         |               |
| Hypoplastic lungs  | 01 (14.29%)      | 00 (0%)           | 0.21    |               |
| Asphyxia with other conditions of PPHN | 06 (85.71%) | 06 (54.54%) | 0.18 | 3.0(95% CI 0.46 – 19.59), p = 0.25 |
| Isolated asphyxia as a cause of PPHN | 01 (14.29%) | 05 (45.45%) | 0.18 |               |
| HIE 2 – 3         | 05 (71.43%)      | 08 (72.72%)       | 0.95    |               |
| LOS / VAP         | 02 (28.57%)      | 03 (27.27%)       | 0.95    |               |

Table 7c. Outcome of MAS with PPHN – analysis of effects of associated problem

| Associated Problem | Poor Outcome (4) | Good Outcome (7) | p value | Relative Risk |
|--------------------|------------------|------------------|---------|---------------|
| Asphyxia           | 02 (50%)         | 05 (71.43%)      | 0.5     |               |
| EOS                | 02 (50%)         | 04 (57.14)       | 0.83    |               |
| MAS with other causes of PPHN | 03 (75%) | 07 (100%) | 0.19 | 0.3 (95% CI 0.12 – 0.77), p = 0.013 |
| Isolated MAS as a cause of PPHN | 01 (25%) | 00 (0%) | 0.19 |               |
| LOS/VAP            | 00 (0%)          | 01 (14.29)       | 0.45    |               |
| HIE 2 – 3         | 02 (28.57%)      | 02 (28.57%)      | 0.5     |               |

Table 8. Pulmonary vasodilator drugs and outcome

| Drug               | Poor Response | Poor Outcome | Good Outcome |
|--------------------|---------------|--------------|--------------|
| Sildenafil with Dobutamine (n=40) | 20 (50%) | 03 | 20 (50%) |
| Sildenafil, Dobutamine, Milrinone (n=17) | 11 (64.71%) | 11 | 06 (35.29%) |
| Total Cases (n=40) | 14 (35%) | 26 | 65 (65%) |

One case with associated surgical condition – diaphragmatic hernia in whom surgery was done was removed from analysis. Thus, total 11 cases of MAS with PPHN were analyzed.

We could not find any effect of additional associated conditions along with MAS in relation with either poor or good outcome. We found relatively low risk of poor outcome when MAS is associated with other conditions causing PPHN, but we had only one isolated MAS case and overall sample size was less to conclude.

All (40) the neonates were given sildenafil and dobutamine, of which 20 (50%) showed good response & survived. Remaining 20 (50%) did not show good response; of which 3 neonates expired before we could add on milrinone. In 17 sildenafil and dobutamine poor responders milrinone was added, of which 06 (35.29%) showed good response & outcome, and 11 (64.71%) had poor outcome.

4. DISCUSSION

During 18 months of study period total 40 neonates with diagnosis of PPHN were admitted, accounted for 4.2% of NICU admissions. 80% were full term, 15% were late preterm and 5% were post term neonates with mean gestational age of 37.95 weeks. These results are consistent with evidence that PPHN affects mainly term and post term neonates [13,24,25]. 62. 5% were male, similar male preponderance was observed by Choudhary et al. with 63%, Hsieh et al with 62.5% and Harish et al with 62.9% [25,26,27]. 57.5% were vaginally delivered, which is not
consistent with most other studies showing preponderance with caesarian deliveries [8,28]. It is near similar to study by Harerimana et al showing 52.8% vaginally delivered. 17.5% were SGA. In study by Harish et al. 22% 3% were SGA, while in study by Harerimana et al and in another study by Abdel et al 12.5% were SGA [8,27,29].

Major etiological factors were asphyxia (47.5%), EOS (45%) and MAS (30%). In study by Abdel et al common causes were MAS (50%), asphyxia (43.75%) and EOS (43.75%) [8]. In a study by Harish et al common causes were MAS (45.7%), congenital diaphragmatic hernia (22.3%), sepsis (11.4%), congenital pneumonia (11.4%), HIE (5.7%) [27]. In a study by Harerimana et al common causes were MAS (59.7%), congenital pneumonia (12.5%), RDS (8.3%) [29].

All (100%) the neonates in our study were mechanically ventilated with CMV. And dobutamine and oral sildenafil were started in all (100%) as a pulmonary vasoconstrictor. Our findings are consistent with reports that assisted ventilation constitutes mainstay of PPNN management [14,21,30,31,32]. The high proportion of neonates treated with mechanical ventilation in our study may reflect the severity of their disease, although we were unable to calculate the neonates’ oxygenation indices as a measure of the severity of respiratory failure. None of the neonates were treated with HFOV, iNO or ECMO as our we did not have these treatment modalities. 20 (50%) responded to oral sildenafil and dobutamine therapy. In 17 (42.5%) non-responders we added milrinone, of which 6 (35.29%) responded. In study by Abdel et al 62.5% responded with oral sildenafil [8].

Columbian pilot study by Baquero et al. stated that oral sildenafil was administered easily and tolerated well and improved oxygenation index in infants with severe PPNN; showed 6/7 survival in sildenafil group vs 1/6 survival in placebo group [19]. In a study by Arturo et al observed better oxygenation parameters after 7 hours of sildenafil treatment, but no significant changes were found in the placebo group. Mortality was higher in the placebo group (40%) than in those infants who received sildenafil (6%; $p = 0.004$). concluded that sildenafil may be a useful adjuvant therapy for term infants with pulmonary hypertension in centers lacking inhaled nitric oxide and extracorporeal membrane oxygenation [33]. In a study by Dinakara et al. oral sildenafil was administered easily and tolerated improved OI in infants with severe PPNN, which suggests that oral sildenafil may be effective in the treatment of PPNN [34]. All of our cases tolerated sildenafil well, and none of them developed any adverse events suspected to be due to sildenafil. Khorana et al in a retrospective study concluded that sildenafil may be useful adjuvant therapy for term infants with pulmonary hypertension in centers lacking iNO and ECMO [35].

The overall survival rate was 65% and poor outcome in 35% in our study. Harish et al noted 57.1% survival having similar kind of resource limited instrumental facilities [27]. In study by Harerimana et al 34.7% did not survive [29]. Similar kind of high mortality is reported from other limited settings [6,7,8]. High mortality rate in resource limited settings may be attributed to non-availability of newer modalities of therapy [5,20,21]. In our case it was also attributed to late presentation of many of outborn neonates with severe respiratory distress. The duration of both ventilation and hospital stay was longer for those having good outcome than those with poor outcome ($p = 0.00452$ & <0.0001 respectively), probably because of early poor outcome. Those having poor outcome had poor outcome very early with mean 3.36 (3.41) days and median days of 1.5 (1 – 6) days of admission. We tried to analyze various factors probably associated with either good or poor outcome. Out of many factors only post maturity and higher gestational age was found to be associated with significantly poor outcome. We analyzed relative risk of poor outcome between various risk factors and etiological factors, but could not find any statistically significant difference. Those presented with severe respiratory distress had significantly higher risk of poor outcome compared to presented with mild to moderate distress. We tried to find association of additional problems or those having multiple etiologies with increased risk of poor outcome than those having single etiology (isolated asphyxia or EOS or MAS as a cause) without additional problem. But we could not find any such association. Surprisingly we found relatively low risk of poor outcome when MAS is associated with other additional conditions causing PPNN, but we had only one isolated MAS case and overall sample size was less to conclude.

5. CONCLUSION

Asphyxia, EOS and MAS are common causes of PPNN. Severity of respiratory distress on
admission is correlated with mortality rather than etiological factors. Prevention of asphyxia, EOS and MAS by good antenatal and intrapartum obstetric care, & reducing post term births helps in reduction of PPHN cases. Conventional ventilation, dobutamine, sildenafil and milrinone therapy are mainstay of treatment of PPHN cases in resource limited settings, and helps to reduce mortality to some extent.

6. LIMITATIONS OF STUDY

We had service of visiting pediatric cardiologist. Cardiologists who were on regular service were adult cardiologist. Echocardiography was done by any of the available cardiologist. Though echocardiography was done in all, in many of the patients echocardiography was done after management of PPHN was started on clinical grounds. ABG could not be done frequently. So, we were not able to measure severity of PPHN based on echocardiographic findings or oxygenation index.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT AND ETHICAL APPROVAL

Ethical approval was obtained for the study topic from Sumandeep Vidyapeeth Institutional Ethics Committee (SVIEC/UN/MEDI/BNPG16). Those are involved in the study, were asked to read and willingly sign on the informed consent form.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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