Clinical Profile Of Persistent Pulmonary Hypertension In Neonates With Role Of Sildenafil In Its Outcome: Rural India NICU Experience

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 19 (47.5%), EOS 18 (45%) and MAS 12(30%). 20 (50%) responded to oral sildenafil and dobutamine therapy, 6 more responded with addition of milrinone. The overall survival rate was 26 (65%) and poor outcome in 14 (35%) in our study. Median duration of respiratory support was 1.5 (1 – 6) days in those with poor outcome and 6 (4 – 7) in those survived. Duration of hospital stay was 1.5 (1 – 6) days in poor outcome and 17 (13 – 22) in those survived.

Conclusions: Asphyxia, EOS and MAS are common causes of PPHN. Severity of respiratory distress on admission is correlated with mortality rather than etiological factors. 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.

Keywords: persistent pulmonary hypertension of newborn, Sildenafil, ventilation, asphyxia

INTRODUCTION

Persistence of pulmonary hypertension (PPHN) in neonates was described initially by Gersony and colleagues in 1969 as persistent fetal circulation[1]. Persistent pulmonary hypertension of the newborn can be defined as a failure of normal fall in pulmonary vascular resistance (PVR) at or shortly after birth, leading to shunting of unoxygenated blood into the systemic circulation across foramen ovale or ductus arteriosus[2]. Increased pulmonary vascular resistance and decreased pulmonary blood flow prevents adequate gas exchange in the lungs resulting in severe respiratory distress and hypoxemia in the neonate[3].

Its incidence is estimated at around 2 per 1 000 live births worldwide[4,5]. Despite the progress in treating PPHN, it remains a potentially fatal disease, especially in resource-limited settings[6].The reported overall mortality ranges from 4% to 33% in developed countries[4] and from 25% to 48% in developing countries[7,8].The mortality rate about 10-20% of affected infants despite of treatments such as nitric oxide, extracorporeal membrane oxygenation (ECMO) and advanced modes of mechanical ventilation[9].In addition, infants who survive PPHN at increased risks for long-term sequelae including chronic lung disease, seizures, and neurological developmental problems[10,11].

PPHN primarily affects full-term and near-term neonates[4,12]. Konduri *et al.* reported that meconium aspiration syndrome (MAS) was the leading cause of PPHN (42%), followed by idiopathic PPHN (27%), respiratory distress syndrome (RDS) (17%), pneumoniaor sepsis (13%) and, less frequently, lung hypoplasia[13]. Other potential risk factors for PPHN include perinatal asphyxia, polycythaemia, acidosis and hypothermia[5].

PPHN is suspected when there is a considerable difference between preductal and postductal 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.

MATERIAL AND METHODS

This is prospective observational study conducted in NICU (neonatal intensive care unit), Dhiraj Hospital, SBKS Medical Institute & Research Center, Waghodia Taluka, Vadodara district, Gujarat, India from March 2017 to August 2018 (18 months duration). Study was started after obtaining approval from institutional ethics committee. All the neonates both inborn and out born 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), with 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.

STATASTICAL ANALYSIS

Data collected was entered inMicrosoft excel sheet. Then it was analysed and summarized by percentage, mean & standard deviation; and median and IQR. 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.

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 out-born, out which 28 (6.1%) had PPHN16 (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).

Table 1: Demographic profile of cases with PPHN

	Total Number of Patients (n=40)
Place of Delivery	
Home	02 (05%)
Hospital	38 (95%)
Inborn	12 (30%)

Out born	28 (70%)
Sex	
Male	25 (62.5%)
Female	15 (32.5%)
Mode of delivery	
Vaginal	23 (57.5%)
LSCS (lower section cesarean section)	17 (42.5%)
Birth Weight	
LBW (low birth weight)	16 (40%)
NBW (normal birth weight)	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%)

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%).

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%)

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

Table 3: Therapy used for management of PPHN

Durationof 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%)

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.

Table 4: Outcome

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

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 5: Comparison between variousrisk 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%)	
Place of delivery				
Out-born	28	12 (42.9%)	16 (57.1%)	2.57 (95% ci 0.68 – 9.78), p = 0.17
In-born	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				
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 falring present)	14	1 (7.2%)	13 (92.8%)	
Birth asphyxia				
Present	19	08 (42.1%)	11 (57.9%)	1.47 (95 % CI 0.62 – 3.47), p = 0.37
Absent	21	06 (28.57%)	15 (71.43%)	
MAS				
Present	12	4 (33.33%)	8 (66.67%))	0.93 (95% CI 0.36 – 2.39), p = 0.88
Absent	28	10 (35.71%)	18 (64.29%)	
EOS				
Present	18	08 (44.44%)	10 (55.56%)	1.63 (95% CI 0.69 – 3.8), p = 0.26
Absent	22	06 (27.27%)	16 (72.73%)	
Pneumonia				
Present	6	2 (33.33%)	4 (66.7%)	0.94 (95% CI 0.28 – 3.19), p = 0.92
Absent	34	12 (35.29%)	22 (64.71%)	
RDS				
Present	3	0 (0%)	3 (100%)	0.33 (95% CI

Absent	37	14 (37.84%)	23 (62.16%)	0.024 – 4.52), p = 0.4
Hypolastic lung	1	01 (100%)	00	
Diaphragmatic hernia	1	00	01 (100%)	
Idiopathic	2	01 (50%)	01 (50%)	

Overall 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 out born 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. out born 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.

Table 6: Correlation of various parameters between good outcome and poor outcome

	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
Out born	12 (85.71%)	16 (61.54%)	0.12
Inborn	02 (14.29%)	10 (38.46%)	0.12

VD	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 (Ventilation + CPAP) (days)	1.5 (1 – 6)*	6 (4 – 7)*	p = 0.00452#
	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

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.

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	
LOS / VAP (late onset sepsis / ventilator associated pneumonia)	00 (0%)	01 (10%)	0.4	
HIE 2 – 3 (hypoxic ischemic encephalopathy)	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 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 7B: Outcome in asphyxia with PPHN – analysis of effects of associated problem

Associated	Poor outcome (7)	Good outcome	P value	Relative risk

problem		(11)		
MAS	03 (42.86%)	04 (36.36%)	0.79	
EOS	03 (42.86%)	02 (18.18%)	0.27	
Pneumonia	0 (0%)	00 (0%)		
Hypolplastic 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	

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 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 (50%)	02 (28.57%)	0.5

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.

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%)

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.

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[29]. 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 vasodilator. Our findings are consistent with reports that assisted ventilation constitutes mainstay of PPHN 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 PPHN; 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 PPHN, which suggests that oral sildenafil may be effective in the treatment of PPHN[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 resource 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 out born 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 PPHN, but we had only one isolated MAS case and overall sample size was less to conclude.

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.

CONCLUSIONS

Asphyxia, EOS and MAS are common causes of PPHN. 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.

ETHICAL APPROVAL AND DISSEMINATION

Ethical approval was obtained for the study topicfrom 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 DISCLAIMER:

Authors have declared that no competing interests exist. 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.

REFERENCES:

1. Gersony WM, Duc GV, Sinclair JC. “PFC Syndrome” (Persistence of fetal circulation). Circulation 1969;40:87
2. Lakshminrusimha S, Steinhorn RH. Pulmonary vascular biology during neonatal transition. Clin Perinatol. 1999;26(3):601-619
3. Ostrea EM, Villanueva-Uy ET, Natarajan G, Uy HG. Persistent pulmonary hypertension of the newborn: Pathogenesis, etiology, and management. Paediatr Drugs 2006;8:179-88.
4. Walsh-Sukys MC, Tyson JE, Wright LL, et al. Persistent pulmonary hypertension of the newborn in the era before nitric oxide: Practice variation and outcomes. Pediatrics 2000;105(1 Pt 1):14-20. https://doi.org/10.1542/peds.105.1.14
5. D’cunha C, Sankaran K. Persistent fetal circulation. Paediatr Child Health 2001;6(10):744-750. https://doi.org/10.1093/pch/6.10.744
6. Agrawal A, Agrawal R. Persistent pulmonary hypertension of the newborn: Recent advances in the management. Int J Clin Pediatr 2013;2(1):1-11. https:// doi.org/10.4021/ijcp79w
7. Razzaq A, Quddusi AI, Nizami N. Risk factors and mortality among newborns with persistent pulmonary hypertension. Pak J Med Sci 2013;29(5):1099-1104. htps://doi.org/10.12669/pjms.295.3728.
8. Abdel Mohsen AH, Amin AS. Risk factors and outcomes of persistent pulmonary hypertension of the newborn in neonatal intensive care unit of Al-Minya University Hospital in Egypt. J Clin Neonatol 2013;2(2):78-82. https://doi. org/10.4103/2249-4847.116406

9. Greenough A, Khetriwal B. Pulmonary hypertension in the newborn. Paediatr Respir Rev 2005;6:111-6.
10. Abman SH. Neonatal pulmonary hypertension: A physiologic approach to treatment. Pediatr Pulmonol Suppl 2004;26:127-8.
11. Latini G, Del Vecchio A, De Felice C, Verrotti A, Bossone E. Persistent pulmonary hypertension of the newborn: Therapeutical approach. Mini Rev Med Chem 2008;8:1507-13.
12. Suesaowalak M, Cleary JP, Chang AC. Advances in diagnosis and treatment of pulmonary arterial hypertension in neonates and children with congenital heart disease. World J Pediatr 2010;6:13-31.
13. Konduri GG, Kim UO. Advances in the diagnosis and management of persistent pulmonary hypertension of the newborn. Pediatr Clin N Am 2009;56:579-600. https://doi.org/10.1016/j.pcl.2009.04.004
14. Lakshminrushimha S, Kumar VH. Diseases of pulmonary circulation. In: Fuhrman BP, Zimmerman JJ, eds. Pediatric Critical Care. 4th ed. Philadelphia: Elsevier, 2011:638-645.
15. Vargas-Origel A, Gómez-Rodríguez G, Aldana-Valenzuela C, Vela-Huerta MM, Alarcón-Santos SB, Amador-Licona N. The use of sildenafil in persistent pulmonary hypertension of the newborn. Am J Perinatol 2010;27:225-30.
16. Abu-Osba YK, Galal O, Manasra K, Rejjal A. Treatment of severe persistent pulmonary hypertension of the newborn with magnesium sulphate. Arch Dis Child 1992;67(1 Spec No):31-35. https://doi.org/10.1136/adc.67.1_spec_no.31.
17. Daffa SH, Milaat WA. Role of magnesium sulphate in treatment of severe persistent pulmonary hypertension of the neoborn. Saudi Med J. 2002;23(10):1266-1269.
18. Porta NFM, Steinhorn RH. Pulmonary vasodilator therapy in the NICU: Inhaled nitric oxide, sildenafil, and other pulmonary vasodilating agents. Clin Perinatol 2012;39(1):149-164. https://doi.org/10.1016/j.clp.2011.12.006
19. Baquero H, Soliz A, Neira F, Venegas ME, Sola A. Oral sildenafil in Neonates with persistent pulmonary hypertension of the newborn: A pilot randomized blinded study. Pediatrics 2006;117(4):1077-1083. https://doi.org/10.1542/peds.2005-0523
20. Nair J, Lakshminrusimha S. Update on PPHN: Mechanisms and treatment. Semin Perinatol 2014;38(2):78-91. https://doi.org/10.1053/j.semperi.2013.11.004 .

21. Teixeira-Mendonc C, Henriques-Coelhob T. Pathophysiology of pulmonary hypertension in newborns: Therapeutic indications. Rev Port Cardiol 2013;32(12):1005-1012. https://doi.org/10.1016/j.repce.2013.06.026.
22. Ichiba S, Bartlett RH. Current status of extracorporeal membrane oxygenation for severe respiratory failure. Artif Organs 1996;20(2):120-123. https://doi. org/10.1111/j.1525-1594.1996.tb00712.x.
23. Maslach-Hubbard A, Bratton SL. Extracorporeal membrane oxygenation for pediatric respiratory failure: History, development and current status. World J Crit Care Med 2013;2(4):29-39. https://doi.org/10.5492/wjccm.v2.i4.29
24. Rocha G, Baptista MJ, Guimaraes H. Persistent pulmonary hypertension of non cardiac cause in a neonatal intensive care unit. Pulm Med 2012;10:818971. https://doi.org/10.1155/2012/818971, REF 11,
25. Hsieh WS, Yang PH, Fu RH. Persistent pulmonary hypertension of the newborn: Experience in a single institution. Acta Paediatr Taiwan 2001;42(2):94-100. REF 22,11,23)
26. 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.
27. Harish S., Kamalarathnam C. N. Clinical profile of persistent pulmonary hypertension in new born: experience in an extramural institution. International Journal of Contemporary Pediatrics 2018 Nov;5(6):2193-2198.
28. de Araujo OR, Andrea de Cdssia Stefano, Vanessa Aparecida. Cesarean deliveries and other risks for persistent pulmonary hypertension of the newborn. Bras Ter Intensiva 2008; 20: 394-7.
29. I Harerimana, D E Ballot, P A Cooper. Retrospective review of neonates with persistent pulmonary hypertension of the newborn at Charlotte Maxeke Johannesburg Academic Hospital. *S Afr J Child Health* 2018;12(1):29-33. DOI:10.7196/SAJCH.2018.v12i1.1245
30. Abman SH. Recent advances in the pathogenesis and treatment of persistent pulmonary hypertension of the newborn. Neonatology 2007;91:283-290. https:// doi.org/10.1159/000101343

31. Bendapudi P, Barr S. Diagnosis and management of pulmonary hypertension of the newborn. Paediatr Child Healt 2013;24(1):12-16. https://doi.org/10.1016/j. paed.2013.05.021
32. Konduri GG. New approaches for persistent pulmonary hypertension of newborn. Clin Perinatol 2004;31:591-611. https://doi.org/10.1016/j.clp.2004.04.001
33. Arturo Vargas-Origel, Guadalupe Gómez-Rodríguez, Carlos Aldana-Valenzuela, Ma Martha Vela-Huerta, Salvador Benjamín Alarcón-Santos, Norma Amador-Licona. The Use of Sildenafil in Persistent Pulmonary Hypertension of the Newborn. Amer J Perinatol 2010; 27(3): 225-230. DOI: 10.1055/s-0029-1239496
34. Dinakara Prithviraj, Bharath Reddy, Abhijitshetty, Deepthi, Radha Reddy. Oral Sildenafil in Persistent Pulmonary Hypertension of the Newborn in Invasive and Non-invasive Ventilated Babies-its Effect on Oxygenation Indices. International Journal of Scientific Study | May 2016 | Vol 4 | Issue 2, 203 – 209. DOI: 10.17354/ijss/2016/285
35. Khorana M, Yookaseam T, Layangool T, Kanjanapattanakul W, Paradeevisut H. Outcome of oral sildenafil therapy on persistent pulmonary hypertension of the newborn at Queen Sirikit National Institute of Child Health. J Med Assoc Thai 2011;94 Suppl 3:S64-73.