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Original Research Article

A RETROSPECTIVE STUDY ON PROFILE OF PERSISTENT PULMONARY HYPERTENSION OF NEWBORN IN NEONATES ADMITTED TO SICK NEWBORN CARE UNIT

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Abstract

Introduction: The normal intra uterine to extra uterine transition of a newborn consists of a rapid fall in pulmonary vascular resistance and simultaneous rise of pulmonary blood flow along with increase in systemic vascular resistance. Persistent pulmonary hypertension of newborn (PPHN) results when these circulatory adaptation fails leading to hypoxemic respiratory failure.

Materials& Methods: This is a Retrospective Observational Study which will be done at the Department of Pediatrics, Gulbarga Institute of medical Sciences, Kalaburagi, Karnataka.

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

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

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

Introduction

The normal intra uterine to extra uterine transition of a newborn consists of a rapid fall in pulmonary vascular resistance and simultaneous rise of pulmonary blood flow along with increase in systemic vascular resistance. Persistent pulmonary hypertension of newborn (PPHN) results when these circulatory adaptation fails leading to hypoxemic respiratory failure.[1]

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Incidence of PPHN varies across different neonatal units, so as the mortality associated with it, depending on the patient profile, quality of care and availability of high frequency oscillatory ventilation (HFOV), inhaled nitric oxide (iNO), or extracorporeal membrane oxygenation (ECMO). Only a few neonatal units in a developing country, like India, have facilities to provide HFOV or iNO and none has the facility for neonatal ECMO. Overall, the estimated incidence of PPHN varies from 0.4 to 6.8/1000 live births and mortality ranges from 4% to 33%.[2] However, mortality in developing country is much higher, ranging from 25% to 48%.[3,4]

The pathophysiologic mechanisms responsible for PPHN can be classified into maladaptation, maldevelopment, and underdevelopment.[5] Maladaptation of the normally developed pulmonary vasculature through excessive secretion and action of vasoactive mediators, as in sepsis, MAS, pneumonia, and asphyxia, is responsible for majority of the cases of PPHN. Maldevelopment of pulmonary vasculature is associated with chronic fetal hypoxia, fetal anemia, or intrauterine closure of ductus arteriosus from maternal medications like nonsteroidal anti-inflammatory drugs. Idiopathic PPHN also results from maldevelopment. Pulmonary hypoplasia with underdevelopment of pulmonary vasculature originates mostly from congenital diaphragmatic hernia or oligohydramnios from any cause. However, discrimination of maldevelopment from maladaptation requires histological examination and overlap between these mechanisms is a rule, rather than the exception.[6] There is a scarcity of data about PPHN from developing countries. The incidence, diagnostic modalities, treatment options, and outcome of PPHN are different from those in the developed countries.

Materials& Methods

This is a Retrospective Observational Study which will be done at the Department of Pediatrics, Gulbarga Institute of medical Sciences, Kalaburagi, Karnataka.

Inclusion criteria

All neonates admitted to Sick Newborn Care Unit of Gulbarga Institute of Medical Sciences Hospital between January 2021 to June 2022 will be included.

Exclusion criteria

Neonates with cyanotic congenital heart diseases.
Neonates with congenital anamolies.

- Study includes both inborn and outborn neonates admitted to SNCU.
- Data pertaining to the baby's details, maternal details (parity, gestational age, mode of delivery, pre-existing maternal illness, illness during pregnancy, drug intake, etc.), clinical conditions (primary diagnosis, APGAR score, requirement of ventilation, type of ventilation, duration of ventilation, types of drugs, duration of neonatal intensive care unit [NICU] stay, etc.), and outcome (discharged or expired) will be recorded.
-For the purpose of the study, Neonates were diagnosed with PPHN based on presentation with refractory hypoxemia plus one or more of the four following conditions: (1) echocardiographic evidence of elevated pulmonary pressure (right to left or bidirectional shunt at PDA and/or PFO level), (2) a pre-to-postductal partial pressure of oxygen gradient (PaO2) equal to or greater than 20 mmHg, (3) a pre-to-postductal pulse oximetry oxygen saturation (SpO2) gradient equal to or greater than 10%, and/or (4) a positive hyperoxia-hyperventilation test.

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-The primary outcomes of this study were the incidence (defined by probability of PPHN per 1000 live births based on the number of live births over the study period), etiologies (defined by the primary cause
of PPHN), diagnostic methods (defined by the method to diagnose PPHN (echocardiography versus non echo-cardiography), treatment options (defined by therapy related to PPHN), such as high frequency oscillation ventilation (HFOV), pulmonary vasodilators (iNO, sildenafil, iloprost, or milrinone), sedation (midazolam), analgesia (fentanyl or morphine), muscle relaxation, inotropic agents (dopamine, dobutamine, epinephrine, or norepinephrine), use of corticosteroids (hydrocortisone), and mortality outcomes of PPHN (defined by all-cause mortality during hospitalization).
-The secondary outcomes were durations of mechanical ventilation, supplemental oxygen and hospital stay, and number of infants who needed supplemental oxygen at 28 days of age.

Results

A total of 50 neonates with PPHN, both inborn and out born were included in the study period of 26 months The incidence of PPHN among both in born and out born babies were 5.43/1000 live birth. Out of these 50 neonates with PPHN, 35 cases were out born and 15 cases were inborn, with male preponderance, 31 males (62%) and 19 females (38%). 9 were preterm (from 28 weeks to <37 weeks of gestation) and 41 (82%) were term and post term (from 37 weeks to >42 weeks of gestation) babies. Mean gestation age (±standard deviation (SD) was 38.28±2.49 weeks and mean birthweight (±SD) was 2624±512 gm.

The characteristics and profile of the newborn with persistent pulmonary hypertension is shown in Table-1. Infant risk factors were predominantly male gender (62%), gestation age wise term and post term babies (82%) were more affected. Meconium aspiration syndrome (42%), birth asphyxia (16%), positive pressure ventilation at birth (52%) were the other observed major risk factors. The preterm babies with PPHN were predominantly male sex (77.8%), birth by caesarean section (55.5%), RDS (55.5) and resuscitation at birth with positive pressure ventilation(55.5%).
Almost all neonates were on respiratory support and those initially who were on CPAP and HFNC, went in for mechanical ventilation 47 (94%). Table 2 compares the demographic characters, aetiologies and out comes with survivors and non-survivor group of neonates with PPHN. Out of 50 neonates with PPHN, 35 (70%) of them were out born, among them 54% expired. Male preponderance was seen 31 (61%) and mortality was 52%. 18 (38.2%) babies were less than 2500 gms and with high mortality of 66.6%. Multiple aetiologies were noted in neonates with PPHN, most common cause was meconium aspitation syndrome 21 (42%) with survival rate of 42%. Among congenital anomalies CDH was seen in 4 babies with mortality of 75%. The treatment options and their outcomes comparison is shown in Table 3. Nearly 94% of neonates were treated with gentle ventilation with almost equal survival and death percentage. The mean duration of ventilation was 4.28±2.9 days. Sildenafil and milrinone were used as pulmonary vasodilators; increased mortality was noticed in neonates who required inotropes and sildenafil. While use of surfactant showed decreased mortality.

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Table 1: Perinatal risk factors and characteristics of the newborn with PPHN.

Characteristics	Over all (n=50)	Pre term (n=9)	Term and Post term (n=41)
	N (%)	N (%)	N (%)
Gender of neonates			
Male	31 (62.0)	7 (77.8)	24 (58.5)
Female	19 (38.0)	2 (22.2)	17 (41.5)
Mode of delivery			
NVD*	27 (54.0)	4 (44.4)	23 (56.0)
C-section	23 (46.0)	5 (55.5)	18 (43.9)
PIH	7 (14.0)	3 (33.3)	4 (09.7)
PROM/PPROM	8 (16.0)	3 (33.3)	5 (12.1)
Birth asphyxia	8 (16.0)	1 (11.1)	7 (17.0)
MAS	21 (42.0)	1 (11.1)	20 (48.7)
RDS	5 (10.0)	5 (55.5)	0
TTNB	6 (12.0)	1 (11.1)	5 (12.1)
CDH	4 (08.0)	1 (11.1)	3 (07.3)
Sepsis	3 (06.0)	0	3 (07.3)
Congenital pneumonia	3 (06.0)	0	3 (07.3)
Resuscitation done			
Routine care	24 (48.0)	4 (44.4)	20 (48.7)
PPV**	26 (52.0)	5 (55.5)	21 (51.2)
APGAR at 5 minute			
Normal	13 (26.0)	2 (22.2)	11 (26.8)
Moderate	2 (04.0)	1 (11.1)	1 (02.4)
Severe	1 (02.0)	0	1 (02.4)
Unknown	34 (68.0)	6 (66.6)	28 (68.2)
Echocardiography			
Mild PPHN	10 (20.0)	2 (22.2)	8 (19.5)
Moderate PPHN	24 (48.0)	3 (33.3)	21 (51.2)
Severe PPHN	16 (32.0)	4 (44.4)	12 (29.2)
Respiratory support			
Oxygen	3 (06.0)	0	3 (07.3)
CPAP (initially)	21 (42.0)	2 (22.2)	19 (46.3)
HFNC (initially)	4 (08.0)	1 (11.1)	3 (07.3)
Mechanical ventilation	22 (44.0)	6 (66.6)	16 (39.0)
(first option)			

*Normal vaginal delivery, **Positive pressure ventilation

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Table 2: Comparison of survivor and non-survivor groups of PPHN neonates with respect to characters.

Characteristics	Total (n=50)	Survivorgroup (n=21)	Non survivorgroup (n=29)
	N (%)	N (%)	N (%)
Gestational age(weeks) <37 weeks (n%)	9 (18.0)	3 (14.2)	6 (20.6)
Birth weight (gm) <2500gm (n%)	18 (38.2)	6 (28.5)	12 (41.3)
Male n%	31 (62.0)	15 (71.4)	16 (55.1)
Out born n%	35 (70.0)	16 (76.1)	19 (65.5)
Aetiologies of PPHN*			
MAS	21 (42.0)	11 (52.3)	10 (34.4)
Birth asphyxia	8 (16.0)	3 (14.2)	5 (17.2)
RDS	5 (10.0)	2 (09.5)	3 (10.3)
TTNB	6 (12.0)	4 (19.0)	2 (06.8)
CDH	4 (08.0)	1 (04.7)	3 (10.3)
Sepsis	3 (06.0)	2 (09.5)	1 (03.4)
Cong. pneumonia	3 (06.0)	2 (09.5)	1 (03.4)

*multiple aetiologies.

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

Treatmentgiven	Totaln=50	Survivors	Non survivors
	N (%)	N (%)	N (%)
Mechanicalventilation	47 (94)	23 (48.9)	24 (51.0)
Sildenafil	32 (64)	14 (43.7)	18 (56.2)
Inotropes	47 (94)	23 (48.9)	24 (51.0)
Surfactant	07 (14)	04 (57.1)	03 (42.8)
Sedation	45 (90)	22 (48.8)	23 (51.1)
Milrinone	02 (04)	01 (50.0)	01 (50.0)

Discussion

Although recognized for decades, the persistant pulmonary hypertension is a leading cause for respiratory failure in the newborn. Little is known about the direct aetiology, physiopathology and preventive strategies of persistent pulmonary hypertension of the newborn (PPHN) and its treatment remains a major challenge for neonatologists.[7]In this current study, we evaluated the predisposing risk factors and their outcomes in neonates with persistent pulmonary hypertension. We made an attempt to note similarities and differences between current study and studies by others. Ours being a rural referral centre, out born babies 35 (70%) were more than the inborn babies. As observed in other studies PPHN is a disease of term and post term neonates in our study 41 (82%) babies belonged to this group as compared to pre term neonates 9 (18%).[17-18] Of the 50 babies in our study, majority were male (62%). Several previous studies found an increased incidence of PPHN in male, term and post term babies.[8,9] Regarding aetiology, MAS (42%) was the most common aetiology followed by birth asphyxia (16%) and TTNB (12%). Rest of the cases were due to RDS

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(10%), CDH (8%), sepsis and congenital pneumonia (6%). MAS has been repeatedly reported as the most common cause of PPHN.[10,11]In our study, ventilation, milrinone, combined use of pulmonary vasodilators and inotropes were all associated with increased mortality. These findings are similar to those noted by Sardar et al a study from eastern India.[10] Inhaled NO is the treatment of choice in PPHN. Use of other pulmonary vasodilators (sildenafil, milrinone etc) in the absence of iNO have inconsistent results. Major reason being that these pulmonary vasodilators lack selective effect of inhaled NO and thus leads to systemic adverse effects (hypotension) and worsen the PPHN further. In developed countries, iNO delivered through HFOV is associated with better survival and less need of ECMO.[11]Sildenafil is the first line pulmonary vasodilator in our NICU, in the absence of iNO. However, in cases of patients with left ventricular dysfunction, sildenafil is replaced with milrinone. Inotropes were used in hypotensive babies. Ventilation and sedation were also used. Use of multiple treatment modalities simultaneously implies sick babies who had less survival chance and thus associated with increased mortality. Although Cochrane meta-analysis by Kelly et al. noted decreased mortality in PPHN patients with sildenafil, the only intervention that was associated with better survival was use of surfactant, which can be explained by the better lung recruitment with surfactant and concomitant ventilation which improves the oxygenation.[12] Also the most common aetiologies in our NICU were MAS and TTNB, where surfactant has a role in management.[10,13]The mortality in our study was 58%. The mortality with PPHN ranges from 4% to 33%. However, mortality in developing countries is much higher, ranging from 25% to 48%.[6,12,19] Reported mortality in PPHN varies in different countries, such as 20.6% in Asian countries, 32% in Portugal, 4%-33% in the USA and 26.6% in Pakistan.[9,14,15,16] In our study increased risk of mortality was noticed in premature infants (6 infants out of 9) who all required mechanical ventilation and those with CDH.In spite of progress in understanding the pathophysiology and treatment of PPHN, prognosis remains poor in developing countries, mostly because of non-availability of newer treatment modalities, such as HFOV, inhaled NO or ECMO.Our study has few limitations, first because of retrospective nature, few essential data were lost. Second, is the small sample size of the study and lastly non- availability of iNO, HFOV and ECMO for quality care. On the other hand, strength of our study being that diagnosis of PPHN was confirmed in each and every casewith echocardiography and was not solely based on clinical assessment.

Conclusion

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

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