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Effectiveness of Bosentan VS Sildenafil for the Treatment of Persistent Pulmonary Hypertension of the Newborn

Dr. Galiba Tasnim[1*], Dr. Wahida Khanam[2], Dr. Shahana Begum[3], Dr. Umme Saima Hossain[4], Dr. Tanjina Sharifa[5], Dr. Md. Moshiur Rahman Mia[6], Dr. Rubiya Parvin[5], Dr. Md. Mozibur Rahman[7]

[1]EMO, 250 bedded General Hospital, Pabna, Bangladesh
[2]Professor & Head Department of Paediatrics, ICMH, Matuail, Dhaka, Bangladesh
[3]Assistant Professor, Department of Paediatrics, Shaheed Monsur Ali medical college, Dhaka, Bangladesh
[4]Registrar, Department of Paediatrics, ICMH, Matuail, Dhaka, Bangladesh
[5]Assistant Professor, Department of Paediatrics, ICMH, Matuail, Dhaka, Bangladesh
[6]Registrar, Department of Gastroenterology, Shaheed Suhrawardy Medical College & Hospital, Dhaka, Bangladesh
[7]Associate Professor, Department of Paediatrics, ICMH, Matuail, Dhaka, Bangladesh

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***Corresponding author:** Dr. Galiba Tasnim
EMO, 250 bedded General Hospital, Pabna, Bangladesh

Abstract **Original Research Article**

Background: Persistent pulmonary hypertension of the newborn (PPHN) is a serious disease among newborns. Pulmonary vasodilators such as Sildenafil, Bosentan and Milrinone are important treatment modalities to treat persistent pulmonary hypertension of the newborn, especially in resource limited centers where inhaled nitric oxide is not available. ***Objective:*** To assess and compare the effectiveness of Bosentan and Sildenafil in persistent pulmonary hypertension of the newborn. ***Method:*** This randomized controlled trial was done in the NICU, ICMH, Matuail, Dhaka during July 2017 to July 2019. Following echocardiographic diagnosis, a total of 76 patients were randomly assigned into group A and group B (by lottery). Bosentan was given to group A (1mg/kg/body wt) 12 hourly for 7 days and Sildenafil was given to group B (2mg/kg/body wt.) 8 hourly for 7 days via oro-gastric tube/orally. Then heart rate, respiratory rate, cyanotic changes, SPO_2 was recorded every day for 7 days and finally on the 8th day echocardiographic findings were obtained. Effects of two groups were compared. ***Results:*** The age of presentation of persistent pulmonary hypertension of newborn was $\leq$ 24 hours and male newborns were predominant in both groups. Almost 100 % newborns had cyanosis, tachypnea and $SPO_2 \leq 80\%$ on admission. After intervention for 7 days in both groups no newborn had cyanosis or tachypnea. The mean pulmonary artery systolic pressure (PASP) on echocardiography before and after intervention was found (53.16 ± 9.263 and 35.55 ± 6.41) mm of Hg in group A. The mean PASP on echocardiography before and after intervention was found (53.24 ±11.012 and 35.45 ± 7.43) mm of Hg respectively in group B. In both groups the mean PASP was decreased significantly after intervention. But while comparing the PASP between two groups, there was no significant ($p>0.05$) difference. The mean length of stay in hospital was 13.05 ± 2.96 days for group A and 13.34 ± 2.86 days for group B. The mean length of stay in hospital was also statistically not significant ($p>0.05$) between two groups. ***Conclusion*:** Regarding the effectiveness of Bosentan and Sildenafil for the treatment of persistent pulmonary hypertension of the newborn in NICU of tertiary care hospital in Bangladesh, the present study did not observe significant difference between the two treatment groups. However multicentred study with large sample was recommended.

Keywords: Pulmonary hypertension, bosentan, sildenafil.

INTRODUCTION

Persistent pulmonary hypertension of the newborn (PPHN) is a diseases characterized by marked pulmonary hypertension resulting from elevated pulmonary vascular resistance and altered pulmonary vasoreactivity leading to right to left extra pulmonary shunting of blood across the foramen ovale and ductus arteriosus, if it is present [1, 2]. This disease was previously referred to as persistent fetal circulation (PFC) [2]. Persistent pulmonary hypertension of the new born (PPHN) results from failure of the normal fetal to neonatal circulatory transition [3, 4].

Persistent pulmonary hypertension of the newborn (PPHN) may be primary or secondary. Primary PPHN is usually associated with neonatal lung diseases. PPHN may secondarily associate with severe perinatal asphyxia, acidemia, septicaemia, pulmonary hypoplasia, congenital heart diseases and drugs [1, 5] . The incidence of PPHN is 2- 6/1000 live births [2].

The pathogenesis of persistent pulmonary hypertension of the newborn (PPHN) is the failure of systemic oxygenation because of marked pulmonary arterial hypertension secondary to an elevated pulmonary vascular resistance (PVR) or altered pulmonary vasoreactivity [6, 7].

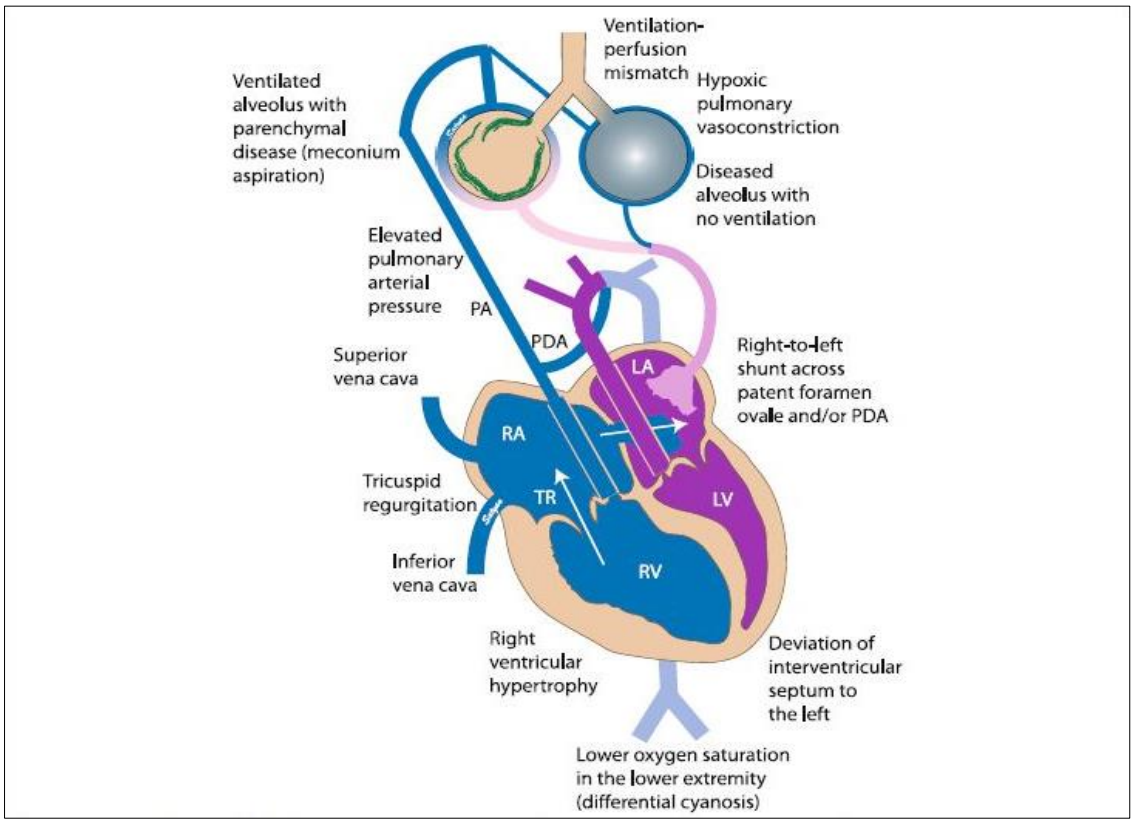

Figure: 1 Pathophysiology of PPHN

Parenchymal lung disease and ventilation-perfusion (V/Q) mismatch result in hypoxemia. Increased pulmonary vascular resistance results in reduced pulmonary blood flow and right to left shunt through PDA and/or PFO. Pulmonary hypertension is often associated with systemic hypotension with deviation of the interventricular septum to the left. PA – pulmonary artery; RV – right ventricle; LV – left ventricle; TR – tricuspid regurgitation; RA – right atrium; LA – left atrium; PDA – patent ductus arteriosus; PFO – patent foramen ovale.

The current treatment for PPHN involves conventional ventilation, extracorporeal membrane oxygenation, administration of oxygen, sedation and pulmonary vasodilators. Among pulmonary vasodilators (a) Inhaled nitric oxide (b) the phosphodiesterase 5 (PDE) inhibitor, sildenafil (c) Bosentan are important treatment modalities [8].

Inhaled nitric oxide (iNO) is a vasodilator substance which relaxes the vascular smooth muscle and causes pulmonary vasodilation. Inhaled nitric oxide and extracorporeal membrane oxygenation (ECMO) have been widely used as effective treatment modalities of PPHN in developed countries. Inhaled nitric oxide is very expensive and not all the newborn with PPHN respond to iNO.

Sildenafil is the phosphodiesterase-5 (PDE5) inhibitor. The phosphodiesterase-5 (PDE5) is enzyme, abundantly expressed in lung tissue and degrades cGMP. Sildenafil which is PDE5 inhibitor prolongs the half-life of cGMP which enhance the actions of both endogenous and exogenous nitric oxide and induce smooth muscle cell relaxation and pulmonary vasodilation [2]. Sildenafil has been used successfully in treating persistent pulmonary hypertension of newborn, pulmonary hypertension after cardiac surgery & rebound pulmonary hypertension after with-drawl of iNO. Studies have shown that oral sildenafil (dose range 1-2mg/kg body wt. every 6 h) improves oxygenation and reduces mortality in centers limited by non-availability of iNO and ECMO (Vargas-Origel, *et al.*, 2010).

OBJECTIVE

General Objective

To assess and compare the effectiveness of Bosentan and Sildenafil in persistent pulmonary hypertension of the newborn.

Specific Objectives

1. To identify effectiveness of Sildenafil and Bosentan for the treatment of PPHN in newborn.
2. To compare the effectiveness of Bosentan and Sildenafil on PPHN.
3. To compare the base line characteristics and hospital outcome between two groups.
4. To compare the adverse effects and laboratory parameters between two groups.

METHODOLOGY

Study Design: Randomized controlled trial.

Place of Study

The study was conducted at NICU, Institute of Child and Mother Health (ICMH), Matuail, Dhaka-1362.

Study Population

i) Term newborn (born at 37 0/7 to 41 6/7 weeks of gestational age).
ii) Late preterm newborn (born at 34 0/7 to 36 6/7 weeks of gestational age).

Inclusion Criteria

- Term newborn (born at 37 0/7 to 41 6/7 weeks of gestational age) and
- Late preterm newborn (born at 34 0/7 to 36 6/7 weeks of gestational age) newborn diagnosed as cases of PPHN by echocardiogram.
- (Echocardiogram had to show evidence of right-to-left shunt and estimated pulmonary artery pressures > 40 mmHg.)

Exclusion Criteria

- Cyanotic congenital heart disease.

Study Period: July 2017- July 2019.
Sample Size: Total sample size-76.

Study Procedure

All the consecutive term and late preterm newborns were admitted in NICU with the features of respiratory distress, cyanosis, reduced SPO_2, pre-ductal & post- ductal saturation difference > 10 %, suspected as cases of persistent pulmonary hypertension of the newborn (PPHN). The diagnosis was confirmed by echocardiogram & then cases of PPHN were enrolled. All the cases of PPHN were diagnosed by the skilled paediatric echocardiologist in NICU. For echocardiogram Vivid S 60 N machine and 12 C probes were used. After enrollment detail history taking and clinical examination was done and recorded by researcher. Consent was taken before starting the drug. Then by randomization two groups were selected such as group A and group B (by lottery).

Data Collection Instrument

A pre- tested, semi- structured questionnaire was used to collect data. Pre and post intervention findings were noted.

Statistical Analysis

SPSS Version 22 was used for data entry and analysis. Obtained information was presented in the form of tables and graphs. Descriptive statistics such as mean, standard deviation (SD), frequency, percentage were used. Test of significance (T test, chi square test) was done to see the significance of difference between the effects of two drugs.

RESULTS

Table 1: Socio demographic variables of the studied newborns

Socio demographic variable	Group A (n = 38)	Group B (n = 38)	P value
	n (%)	n (%)	
Age in hours			
≤ 24	28 (73.7)	25 (65.8)	
>24	10 (26.3)	13 (34.2)	
Mean ±SD	36.71 ± 65.7	46.61 ± 72.8	[a]0.536[ns]
Sex			
Male	24 (63.2)	23 (60.5)	[b]0.813[ns]
Female	14 (36.8)	15 (39.5)	
Father's education			
Below primary	1 (2.6)	1(2.6)	
Primary	5 (13.2)	5 (13.2**)**	
Secondary	26 (68.4**)**	16 (42.1)	[b]0.691[ns]
Above secondary	6 (15.8)	16 (42.1)	
Mother's education			
Below primary	1 (2.6)	0 (0.0)	

Socio demographic variable	Group A (n = 38)	Group B (n = 38)	P value
	n (%)	n (%)	
Primary	5 (13.2)	2 (5.3)	
Secondary	26 (68.4)	22 (57.9)	[b]0.121[ns]
Above secondary	6 (15.8)	14 (36.8)	
Father's occupation			
Farmer	1 (2.6)	2 (5.3)	
Service	10 (26.3)	9 (23.7)	
Self - employed	7 (18.4)	8 (21.1)	
Business	18 (47.4)	16 (42.1)	[b]0.766[ns]
Day labour	1 (2.6)	0 (0.0)	
Others	1 (2.6)	3 (7.9)	
Mother's occupation			
House wife	31 (81.6)	29 (76.3)	
Service	6 (15.8)	6 (15.8)	[b]0.201[ns]
Self - employed	1 (2.6)	3 (7.9)	
Monthly income Category (taka)			
<10000	0 (0.0)	6 (15.8)	
10000 – 20000	25 (65.8)	14 (36.8)	[b]0.007[s]
>20000	13 (34.2)	18 (47.4)	

[a]p value reached from unpaired t-test, [b]p value reached from Chi-square test
Group A= Intervention Bosentan, Group B= Intervention Sildenafil

Table 1 showed socio demographic variable of the studied newborns, it was observed that 73.7 % newborns in group A and 65.8 % newborns in group B belonged to age ≤24 hours. In both groups male newborns were predominant. In each group most of the newborns father's and mother's education level was secondary. Most of the newborns father's occupation was business and mother's occupation was housewife in each group. 65.8 % newborns in Group A and 36.8 % newborns in Group B were in monthly income category 10000-20000 taka. The difference of monthly income was statistically significant ($p<0.05$) between two groups.

Table 2: Antenatal, perinatal history of the studied newborns

Perinatal history	Group A (n=38)	Group B (n=38)	P value
	n (%)	n (%)	
Gestational age (weeks)			
34 to 36 completed weeks	6 (15.8)	10 (26.3)	
37-41 completed weeks	32 (84.20)	28 (73.7)	[a]0.682[ns]
Mean ±SD	37.76 ± 1.19	37.63 ± 1.56	
Prolonged rupture of membrane			
Yes	2 (5.3)	3 (7.9)	[b]0.644[ns]
No	36 (94.7)	35 (92.1)	
Prolonged labour			
Yes	1 (2.6)	3 (7.9)	[b]0.304[ns]
No	37 (97.4)	35 (92.1)	
Febrile illness in the mother within 2 weeks prior to delivery			
Yes	3 (7.9)	3 (7.9)	[b]1.0[ns]
No	35 (92.1)	35 (92.1)	
Vaginal examination			
Yes	2 (5.3)	1 (2.6)	[b]0.556[ns]
No	36 (94.7)	37 (97.4)	
Mode of delivery			
Vaginal delivery	17 (44.7)	16 (42.1)	[b]0.817[ns]
Cesarean section	21 (55.3)	22 (57.9)	

s=significant, ns=not significant, [a]p value reached from unpaired t-test, [b]p value reached from Chi-square test

Table 2 showed antenatal, perinatal history of the studied newborns, it was observed that most of the newborns born at 37-41 weeks of gestational age. Few numbers of newborns perinatal histories was prolonged

rupture of membrane and prolonged labour. 7.9 % of newborns perinatal history was febrile illness in the mother within 2 weeks prior to delivery in each group. Cesarean section common than Vaginal delivery in both groups but p value was not significant (p>0.05) between two groups.

Table 3: Clinical features of the studied newborns

Clinical features	Group (n=38)	Group B (n=38)	P value
	n (%)	n (%)	
Cyanosis			
Present	38 (100.0)	36 (94.7)	[a]0.152[ns]
Absent	0 (0.0)	2 (5.3)	
Grunting			
Present	7 (18.4)	13 (34.2)	[a]0.118[ns]
Absent	31 (81.6)	25 (65.8)	
Nasal flaring			
Present	4 (10.5)	8 (21.1)	[a]0.208[ns]
Absent	34 (89.5)	30 (78.9)	
Heart rate (bpm)			
<160	8 (21.1)	7 (18.4)	[a]0.773[ns]
160-180	30 (78.9)	31 (81.6)	
Tachypnea (>60 breath/min)			
Present	37 (97.4)	38 (100.0)	[a]0.314[ns]
Absent	1 (2.6)	0 (0.0)	
Spo2			
≤ 80%	20 (52.6)	15 (39.5)	[b]0.201[ns]
>80%	18 (47.4)	23 (60.5)	
Mean ±SD	79.66 ± 4.55	81.03 ± 4.69	
Capillary refill time (>3 sec)			
Present	9 (23.7)	6 (15.8)	[a]0.387[ns]
Absent	29 (76.3)	32 (84.2)	
Murmur			
Present	17 (44.7)	19 (50.0)	[a]0.646[ns]
Absent	21 (55.3)	19 (50.0)	

ns=not significant, [a]p value reached from Chi-square test [b]p value reached from unpaired t-test

Table 3 showed clinical features of the studied newborns, it was observed that most of the newborns in group A and also in group B had cyanosis. Small number of newborns had grunting and nasal flaring. 78.9 % newborns in group A and 81.6% newborns in group B heart rate were in between 160-180 bpm. 97.4 % newborns in group A and 100 % newborns in group B had tachypnea. 52.6 % newborns in group A and 39.6% newborns in group B had $SPO_2 \leq 80\%$. Some newborns had murmur and capillary refill time >3 sec.

Table 4: Clinical parameters within one week of intervention between two groups

Follow up	Day 1		Day 7	
	Group A (n = 38)	Group B (n = 38)	Group A (n = 38)	Group B (n = 38)
	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD
Heart rate(beat/min)	163.8 ± 7.05	164.55 ± 5.5	151.16 ± 5.3	151.53 ± 5.7
P value	0.644[ns]		0.774[ns]	
Respiratory rate (breath/min)	71 ± 4.7	70.47 ± 5.5	53.03 ± 4.5	52.34 ± 5.04
P value	0.657[ns]		0.537[ns]	
SPO_2 (%)	87.45 ±2.8	86.79 ± 2.6	95.97 ± 1.8	96.13 ± 1.6
P value	0.299[ns]		0.696[ns]	
Cyanosis	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Present	35 (92.1)	36 (94.7)	0 (0.0)	0 (0.0)
Absent	3 (7.9)	2 (5.3)	38 (100.0)	38 (100)
P value	0.649[ns]			

ns=not significant, p value reached from unpaired t-test

Table 4 showing after intervention of 7 days the mean heart rate, respiratory rate, SPO_2 were improved compare to day 1 in both group A and group B. But these values were not significant (p>0.05) between two groups. After intervention of 7 days no newborn had cyanosis in both groups.

Table 5: Hematological parameters before & after intervention between two groups

	Group A (n=38)		Group B (n=38)		P value
	Mean	±SD	Mean	±SD	
TC-WBC (mm^3)					
Before intervention	17230 ± 6347.1		15809 ± 6654.0		0.344^{ns}
After intervention	15066 ± 3848.9		14881 ± 4025.2		0.838^{ns}
Hb% (gm/dl)					
Before intervention	17.58 ± 1.49		17.43 ± 1.78		0.677^{ns}
After intervention	17.59 ± 1.46		17.52 ± 2.07		0.859^{ns}
Platelet (mm^3)					
Before intervention	278928 ± 80246		253397 ± 86697		0.187^{ns}
After intervention	252002 ± 67238		242439 ± 65668		0.532^{ns}
Serum creatinine (mg/dl)					
Before intervention	0.52 ± 0.19		0.52 ± 0.15		0.898^{ns}
After intervention	0.53 ± 0.13		0.55 ± 0.15		0.587^{ns}
SGPT(U/L)					
Before intervention	36.89 ± 5.81		35.97 ± 5.60		0.484^{ns}
After intervention	38.32 ± 6.16		37.34 ± 9.55		0.599^{ns}

ns=not significant, p value reached from unpaired t-test

Table 5 showing the mean Tc-WBC, Hb%, platelet count, serum creatinine level before and after intervention almost similar in group A and group B. P value was not statistically significant between two groups. Mean SGPT after intervention became mild elevated in both groups but p value was not statistically significant (>0.05) between two groups.

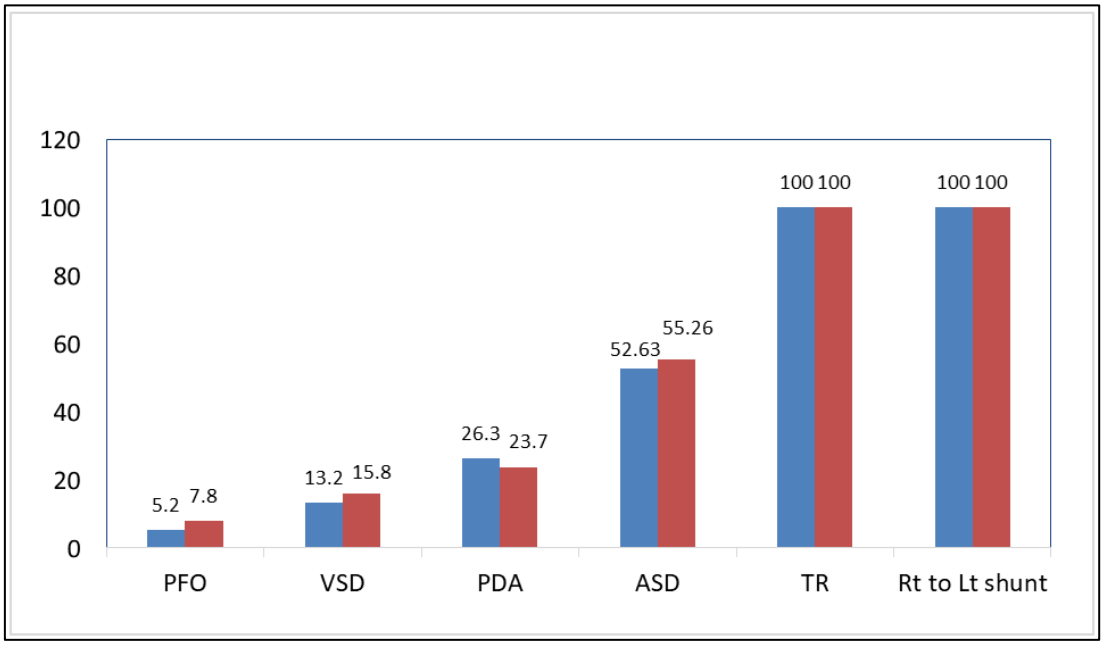

Figure 2: Bar diagram showing echocardiography findings associated with PPHN

It was observed that 5.2% newborns in group A and 7.8 % newborns in group B had patent Foramen Ovale (PFO). 13.2 % newborns in group A and 15.8 % newborns in group B had Ventricular Septal Defect (VSD). 26.3 % newborns in group A and 23.7 % newborns in group B had Patent Ductus Arteriosus (PDA). 52.63 % newborns in group A and 55.3 % in group B had Atrial Septal Defect (ASD). Most of the newborns had Tricuspid Regurgitation (TR) and Shunt in both groups.

DISCUSSION

Persistent pulmonary hypertension of the newborns (PPHN) is a diseases characterized by an increased pulmonary vascular resistance, right-to-left shunt and severe hypoxemia without evidence of congenital heart disease [9].

In this study, the socio demographic characteristics of the newborns revealed that most of the newborns belonged to age ≤24 hours and male gender predominant in both group A and group B. Almost similar male predominance was reported by Hernandez-Diaz *et al.,* 2007 [10]. In another prospective study, out of 32 newborns, 18 males were diagnosed as having persistent neonatal pulmonary hypertension [11].

In the study, most of the parents were educated up to secondary school levels in both groups. Most of the newborns father's occupation had business and mother's occupation had housewife in each group. 65.8 % newborns in group A and 36.8 % newborn have in group B family belonged to monthly income category Tk 10000-20000. The difference of monthly income was statistically significant ($p<0.05$) between two groups. Another study reported that socioeconomic status affects pulmonary hypertension disease severity at the time of first evaluation. However, in another study authors stated that socioeconomic factors play a minor role as risks for PPHN [12].

Regarding perinatal history of the studied newborn, it was observed that the mean gestational age of newborn was 37.76 ± 1.19 weeks in group A and 37.63 ± 1.56 weeks in group B. In group A 5.3% newborns and in group B 7.9% newborns had perinatal history of prolonged rupture of membrane along with prolonged labour. 7.9 % of newborns perinatal history had febrile illness in the mother within 2 weeks prior to delivery in both groups. The difference was statistically not significant ($p>0.05$) between two groups. This observation is similar with the study done by Delaney C and Cornfield DN (2012). In that study they reported that there were certain perinatal factors such as prematurity, prolonged rupture of membrane, prolonged labour and cesarean section predisposed to persistent pulmonary hypertension of the newborn. Another study similar with current study showed that a wide variety of predisposing factors can lead to PPHN and is most common among full-term infants [10]. Although PPHN is traditionally considered a disease of term and late preterm infants, it is increasingly being diagnosed in extremely preterm infants [10]. In another study mentioned that preterm infants with fetal growth restriction and born after prolonged rupture of membranes are at higher risk for developing pulmonary hypertension [13].

It was observed in current study that 44.7% newborns in group A and 42.1% newborns in group B born by cesarean section. This result is similar with the study done by Winovitch *et al.,* (2011) [14]. They concluded that a high rate of PPHN followed elective cesarean delivery and suggested that physicians should consider this added morbidity when performing elective cesareans section (C/S). Moreover, Babooa *et al.,* (2017) reported that cesarean section (C/S) delivery results in limited endogenous pulmonary vasodilator synthesis and lower levels of protective anti-oxidants in the neonates [15].

In this study, it was observed that majority newborns had tachypnea. Similarly, Hermansen and Mahajan in 2015 stated that newborn respiratory distress presents a diagnostic and management challenge and newborns with respiratory distress commonly exhibit tachypnea with a respiratory rate of more than 60 respirations per minute. This is in accordance with other researchers [16].

Clinical features of the studied newborns showed that 100% newborns in group A and 94.7% newborns in group B had cyanosis. Similarly in another study showed that differential cyanosis (saturation in the lower limb is 5-10% lower than right upper limb) had observed in most of the cases of PPHN (Vinay *et al.*, 2015).

In this study, 18.4% newborns in group A and 34.2% newborns in group B had grunting and some newborns had nasal flaring. Similar findings were observed by other authors stated that in PPHN, respiratory distress recognized as one or more signs of increased work of breathing, such as tachypnea, nasal flaring, chest retractions or grunting [17].

In current study 44.7% newborns in group A and 50.0% newborns in group B had murmur. Similarly in another study, authors reported that cardiac examination may reveal prominent precordial impulse, single or narrowly split and accentuated second heart sound and/or a systolic murmur consistent with tricuspid valve regurgitation. Heart failure is usually not seen though hypotension is encountered [5]. In another study, authors showed that on cardiac auscultation there was increased intensity of the second heart sound due to pulmonary artery hypertension and systolic murmur of the tricuspid regurgitation [18].

In current study most of the newborns was improved in day 7 in both groups as evidenced by decrease in heart rate, respiratory rate, absence of cyanosis, improvement of SPO_2 by giving any of drugs. Baquero *et al.,* (2006) showed steady improvement in SPO_2 and Oxygenation index (OI) within 6 to 30 hours by treatment with Sildenafil in PPHN [19]. Duration of improvement was earlier in that study compared to current study. Maneenil *et al.,* (2018) found that Oxygen saturation and Oxygenation index (OI)

improved at 2 hours after treatment by Bosentan in PPHN [20].

Regarding hematological parameters such as the mean Tc-WBC, Hb%, platelet count, serum creatinine level before and after intervention almost similar in group A and group B. These parameters were not statistically significant (p>0.05) before and after intervention between two groups. Both drugs are metabolized in the liver and eliminated by biliary excreation. But in current study, before and after intervention mean SGPT almost similar in group A and also in group B. Mean SGPT was not statistically significant between two groups (p>0.05). Similar to this study, Maneenil *et al.*, (2018) found that liver enzymes (SGPT) did not elevate in any of the newborn [20]. The mean SGPT was 45 U/L. Moreover, there was no pulmonary hemorrhage or feeding intolerance in any of the patient. In current study no significant clinical or hematological adverse effect was found in either group.

CONCLUSION

This study showed almost similar results regarding the effectiveness of Bosentan and Sildenafil for the treatment of persistent pulmonary hypertension of the newborn. No significant adverse effect was observed either of the drugs during the treatment of PPHN.

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