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Comparison of Efficacy between Sildenafil Alone and Sildenafil with Milrinone for Treatment of Persistent Pulmonary Hypertension of the Newborn

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Abstract **Original Research Article**

Introduction: In persistent pulmonary hypertension of the newborn (PPHN), some neonates do not response to single pulmonary vasodilator drug, so recently combination therapy is being tried to decrease pulmonary artery systolic pressure (PASP). The aim of the study was to compare the efficacy of oral sildenafil alone with combination of oral sildenafil and milrinone in neonates suffering from PPHN. ***Methods:*** This RCT study was conducted in Dhaka Shishu (Children) Hospital, from July 2018 to June 2020. Sixty eight (68) term and near term neonates aged <10 days (34 cases in each group) with moderate to severe PPHN were taken. Monotherapy with oral sildenafil was given in group-A and combined therapy with oral sildenafil and i/v milrinone in Group-B. Serial echocardiography was done at before starting the therapy, at 3 days and at 5 days of treatment. Data regarding baseline characteristics, clinical features, PASP, PO_2, Spo_2, hospital stay, mortality and others investigations were recorded and analyzed with SPSS version-26. ***Results:*** Post treatment PASP was significantly reduced in group A (sildenafil) and group-B (sildenafil plus milrinone) ($p<0.05$). But in combination group PASP was more reduced than monotherapy group ($p<0.05$). Within the group, the oxygen saturation and PO_2 significantly improved in both groups ($p<0.05$) but no significant difference was found in between two groups ($p>0.05$). Adrenaline infusion, hypotension and less hospital stay were significantly seen ($P<0.05$) in combination group. ***Conclusion*****:** Combined therapy with oral sildenafil and milrinone are more effective than monotherapy with oral sildenafil in reduction of PASP. Both therapies are effective in improvement of oxygenation.

Keywords: PPHN, Sildenafil, Milrinone.

INTRODUCTION

Persistent pulmonary hypertension of the newborn (PPHN) occurs in as many as 6.8 of 1000 live births. It is likely to be much more in developing countries, where little data is available [1]. Mortality is 10% to 20% with high-frequency ventilation, surfactant, inhaled nitric oxide (iNO), and extracorporeal membrane oxygenation (ECMO) but it is much higher when these therapies are not available [2].

Nitric oxide alone does not appear to be a solution to the problem. Upto 30% infants fail to improve despite nitric oxide [3]. The cost of its use is prohibitive. Also inhaled nitric oxide has the ability to displace oxygen and bind to hemoglobin forming methemoglobin, thereby further reducing the oxygen carrying capacity of blood. The availability ECMO, even in developed countries, is limited to few specialist centers and almost always involves transport of a very sick baby to the nearest available centre [1].

Sildenafil initially was used in newborn in absence of other modalities of treatment like iNO and ECMO in PPHN after its used in adult cardiac patients as well as in animal [4-7]. Both Sildenafil and milrinone are two most promising drugs to treat PPHN [8]. Also, they can be used as adjunct to other treatment modalities of PPHN [9]. Oral sildenafil acts by stopping cyclic guanosine monophosphate (cGMP) from degrading phosphodiesterase 5 and milrinone by cyclic adenosine monophosphate (cAMP) from degrading phosphodiesterase 3 thus decreasing the PASP [8,10].

Besides different studies supported that monotherapy with sildenafil or milrinone doesn't well response in many patients with PPHN [8, 10].

So, the aim of this study was to see the efficacy of monotherapy with oral sildenafil and combined therapy with oral sildenafil and i/v milrinone in management of PPHN.

MATERIALS AND METHODS

This randomized controlled trial study was conducted in SCABU (Special care baby unit), NICU (Neonatal intensive care unit and CICU (Coronary intensive care unit) of Dhaka Shishu Hospital (DSH), Dhaka, Bangladesh from July 2018 to June 2020.

The admitted neonates suffering from PPHN were included in this study. The inclusion criteria were: (1) Term or late preterm (≥35 weeks gestation) and moderate to severe pulmonary hypertension confirmed by echocardiography. (2) Birth weight >2000gms. (3) Age: <10 days. The exclusion criteria were: (1) Newborn with congenital malformation except ASD, small VSD and PDA. (2) Sepsis. (3) Any bleeding manifestation. A written informed consent was obtained from parents or legal guardian. An ethical clearance was taken from the ethical review committee of Bangladesh Institute of Child Health (BICH), DSH.

Neonates in this study were randomly enrolled by inclusions and exclusions criteria, and were allocated either in sildenafil treatment group (group-A) or sildenafil plus milrinone group (group-B) by simple randomization with concealed sealed envelope technique. Only cardiologist was blinded to treatment given. Thirty-four cases (34) were in group-A and thirty-four cases (34) were in group-B.

A detailed history of each case was taken regarding age, sex, birth history, maternal history, respiratory distress and cyanosis etc.

Physical examinations were done to find out the temperature, heart rate, murmur, respiratory rate, blood pressure (NIBP) (Model: CLE0100 ACS medical), capillary refill time and oxygen saturation by pulse oxymeter (Model: CLE0100 ACS medical).

Blood was collected mainly for septic screening and blood gas analysis. CBC, RBS, serum electrolytes, CRP, ABG (Model: RAPID point 500e), blood culture and sensitivity were tested at the DSH laboratory. Chest x-ray was performed in neonates with stable vitals or those with need of minimum oxygen support in radiology department and in those with vitals unstable portable x-ray was done. Besides sildenafil and milrinone, Others treatment were given in all cases of both groups with conventional hospital protocol including i/v fluid, nutrition and oxygen supplementation etc.

In sildenafil treatment group (group-A) oral sildenafil was given at 2mg /kg/day 6 hourly with increments of 0.5 mg/kg/dose and a target maintenance dose of 2 mg/kg/dose every 6 hourly by nasogastric tube (Tablet Vigorex 25 mg, Batch No.- OL 00436. Manufacturing and expiry date- March, 2018 and October, 2020 respectively, manufactured by Square Pharmaceuticals Limited, Bangladesh). The solution for sildenafil was prepared by crushing a 25 mg tablet of sildenafil in 25 ml of distilled water to achieve a concentration of 1 mg/ml. Complications of sildenafil were monitored as regards the development of hypotension, bleeding, vomiting and skin rash.

In sildenafil plus milrinone group, sildenafil was given as mentioned. Milrinone was started at 0.5 µg/kg/min via i/v infusion by syringe pump (Injection Milicor 10ml, Batch No.- IMLRA 2902. Manufacturing and expiry date- April, 2018 and October, 2020 respectively, manufactured by Samarth Life Sciences Pvt Limited, India). SpO_2 was monitored regularly. The patient was gradually weaned off from infusion milrinone at 72 hours after initiation of treatment. Side effects were observed in the patients such as, hypotension and bleeding manifestation. All patients were discharged after clinical improvement.

Echocardiography was also done as soon as possible if any case developed progressive respiratory distress and/or increased oxygen requirements.

The diagnosis of PPHN was confirmed by 2D color echocardiography, which was performed by designated pediatric cardiologist. Echocardiography (Model no.GE Vivid E9) was performed in neonates with stable vitals or those with need of minimum oxygen support in ECHO lab and in those with vitals unstable portable echocardiography (Model no. GE Vivid Q) was done. To evaluate pulmonary artery pressure using the modified Bernoulli equation: Pulmonary artery systolic pressure (PASP) = Tricuspid regurgitation gradient + right atrial pressure (RAP). RAP was 10 mm of Hg.

STATISTICAL ANALYSIS

The primary outcome variable was PASP and secondary outcome variables were improvement of oxygen saturation, blood gases and duration of hospital stay, complications of either line of therapy and mortality.

All the data were entered into a personal computer and thoroughly checked for any possible errors and analyzed by Statistical Package for Social Science (SPSS 26.0 IBM Corporation, New York, USA). Data were expressed as numbers and percentages

for categorical variables or as means and range for quantitative variables**.** To compare categorical variables between groups, the chi-square ($\chi 2$) test and Fisher exact test was used. Paired and unpaired t- test was used for continuous variables. For all statistical test p value < 0.05 was considered as statistically significant.

Sample size

$$n = \frac{2\sigma^2(Z_\alpha + Z_\beta)^2}{(\mu_1 - \mu_2)^2}$$

Here,
n = sample size
Z_α= z-value of SND at a Confidence level at 95% (p<0.05, standard value is 1.96)
Z_β= z-value of SND at a given power, if power 90%, Z_β = 1.28
$\boldsymbol{\sigma}$ = SD of control group (4.5)
μ_1 = expected control group mean (17.1)
μ_2= expected experimental group mean (20.6)
} Values are taken from Pieravian *et al*., 2013
n= 34

Therefore, 34 patients in each group.

RESULTS

Out of total 68 neonates, male was 23(67.6%) in group-A and 20 (58.8%) in group-B (p=0.451). Term neonates were 79.4% in group-A and 76.5% in group-B (p=0.770). The mean age was 6.5±2.0 days in group-A and 6.4±1.7 days in group-B (p=0.821). Mean weight was 2665.2±240.9 gms in group-A and 2581.1±181.5 gms in group-B (p=0.109). Regarding comparison of all others baseline variables, no significant differences were found in between two groups (p>0.05) (Table-I). In group-A 19(55.9%) cases had moderate and 15(44.1%) severe PASP. In group-B 16 (47.1%%) cases had moderate and 18(52.9%) severe PASP (P>0.05).

In group-A mean PASP was 53.3±8.7mm of Hg, 46.4±10.1mm of Hg, and 40.9±9.5 mm of Hg at diagnosis, at 72 hours and at 5 days after treatment respectively which was statistically significant (p<0.05) (Table-2). In group-B mean PASP was 55.3±9.8 mm of Hg, 44.1±8.5 mm of Hg, and 36.6±7.6 mm of Hg at diagnosis, at 72 hours and at 5 days after treatment respectively which was statistically significant (p<0.05) (Table-2).

In comparison between group-A and group-B mean PASP was not significant at diagnosis and after 72 hours of treatment. But, after 5 days of treatment mean PASP reduced in combination group (group-B) which was statistically significant (p<0.05) (Table-2).

The initial pulmonary artery systolic pressure is higher in group-B (sildenafil with milrinone) comparing to group-A (sildenafil). Gradually pressure decreased in both groups in relation to time. But more reduction of pulmonary artery systolic pressure noted in group-B rather than group-A within 5 days of treatment (Figure-1).

Within the group the oxygen saturation and PO_2 gradually improved in both groups which were statistically significant (p<0.05) but Comparison in between two groups oxygen saturation and PO_2 were not statistically significant (p>0.05) (Table-3,4).

Adrenaline infusion was predominant in group-B (50.0%) than group-A (23.5%), which was statistically significant (p<0.05) (Table-5). Hypotension was noted in group-A (5.9%) and in group-B (32.4%) which was statistically significant (p<0.05) (Table-5). Within 5 days of treatment 1 patient died due to aspiration pneumonia in group-A and 4 patients in group-B due to sepsis and pneumonia which was not statistically significant (p>0.05) (Table-6). Hospital stay in the combination group was found shorter than sildenafil group which was statistically significant (p<0.05) (Table-6).

Table-1: Demographic characteristics of the study patients and their maternal characteristics (N=68)

Variables		Group A (n=34)	Group B (n=34)	p value
Age (days)		6.5±2.0	6.4±1.7	0.821
Gender				
Male		23(67.6%)	20(58.8%)	0.451
Female		11(32.4%)	14(41.2%)	
Gestational age				
< 37 weeks		7(20.6%)	8(23.5%)	0.770
> 37 weeks		27(79.4%)	26(76.5%)	
Mode of delivery				
NVD		19(55.9%)	22(64.7%)	0.457
LUCS		15(44.1%)	12(35.3%)	
Maternal characteristics				
Meconium stained liquor		7(20.6%)	11(32.3%)	0.271
GDM		6(17.7%)	7(20.6%)	0.757
Maternal hypertension		5(14.7%)	4(11.8%)	0.720
Clinical findings				
Weight (gm)		2665.2±240.9	2581.1±181.5	0.109
Respiratory rate (breaths/min)		62.7±12.5	57.2±12.6	0.078
Heart rate (b/min)		135.1±16.9	133.8±16.4	0.733
Chest retraction		24(70.1%)	22(64.7%)	0.604
Cyanosis		15(44.1%)	17(50.0%)	0.627
SPO_2 (RA) (%)		85.9±2.9	84.4±4.9	0.124
SPO_2 (LL) (%)		80.5±6.4	82.5±7.5	0.075
Investigation findings				
CBC	TLC (/cumm)	8488.8±3236.2	8286.2±3212.1	0.796
	N (%)	63.5±13.8	67.8±11.9	0.175
	L (%)	28.2±11.3	23.5±9.4	0.066
	Hct (%)	47.6±8.2	46.1±5.2	0.353
	Hb (gm/dl)	15.5±5.8	13.9±2.4	0.152
	Platelet Count (/cumm)	125217.7±25347.4	126505.9±30204.6	0.750
S.electrolytes	Na (mean± SD)	142.1±2.3	137±3.2	0.316
	K (mean± SD)	3.9±1.0	4.2±1.0	0.442
	RBS (mmol/L)	4.3±0.8	4.5±1.3	0.494
ABG	pH	7.3±0.1	7.2±0.1	0.337
	PCO_2	27.2±6.7	28.71±6.3	0.332
	PO_2	78.2±46.1	76.3±28.5	0.844
	HCO_3	13.6±2.9	15.4±4.9	0.078
Echocardiography	PASP (mm of Hg) (mean±SD)	53.32±8.7	55.33±9.8	0.372
	PDA	18(52.9%)	23(67.6%)	0.215
	ASD	26(76.4%)	28(82.3%)	0.548

Group A: Sildenafil, Group B: Sildenafil + Milrinone
RA=right arm; LL=Lower limb
Statistical analysis was done by unpaired t-test for quantitative variables and Chi-square test for qualitative variables
p-value <0.05 is the level significance

Table-2: Comparison of PASP in group and between groups (N=68)

Assessment		Group A (n=34)	Group B (n=34)	p-value
PASP (mm of Hg) (mean±SD)	At diagnosis	53.3±8.7	55.3±9.8	0.372
	At 72 hours	46.4±10.1 (0.004*¶)	44.1±8.5 (<0.001*¶)	0.230
	At 5 days	40.9±9.5 (<0.001*¶)	36.6±7.6 (<0.001*¶)	0.044*

Group A: Sildenafil, Group B: Sildenafil + Milrinone
Paired t- test was used to analyze data, *significant
p-value <0.05 is the level significance.
¶ comparison done with the value at diagnosis within the group

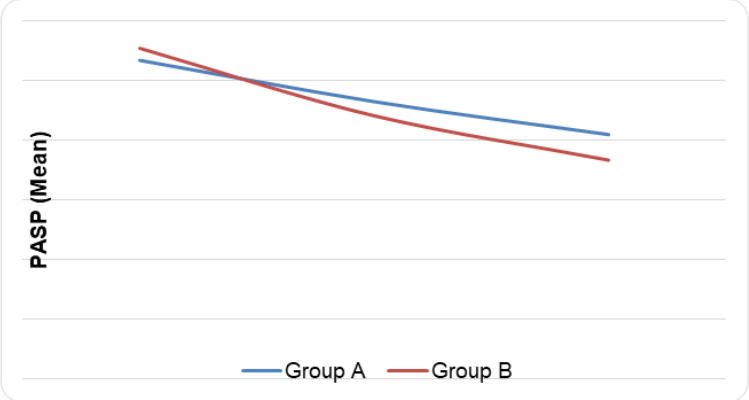

Figure-1: Graphical representation of pulmonary arterial systolic pressure (PASP) in mm of Hg in two groups from diagnosis to 5 days of treatment
(Group A: Sildenafil and Group B: Sildenafil + Milrinone)

Table- 3: Comparison of oxygen saturation in group and between groups (N=68)

Assessment		**Group A (n=34)**	**Group B (n=34)**	**p-value**
SpO_2 (%) (Mean±SD)	At diagnosis	80.0±2.9	82.4±4.9	0.056
	At 72 hours	90.9±1.9 (<0.001*¶)	90.7±3.4 (<0.001*¶)	0.827
	At 5 days	92.8±2.2 (<0.001*¶)	93.7±2.1 (<0.001*¶)	0.068

Group A: Sildenafil , Group B: Sildenafil + Milrinone
Unpaired t- test was used to analyze data, *significant
p-value <0.05 is the level significance
¶ comparison done with the value at diagnosis within the group

Table-4: Comparison of improvement of PO_2 in group and between groups (N=68)

Assessment		**Group A (n=34)**	**Group B (n=34)**	**p-value**
PO_2 (mm of Hg) (Mean±SD)	At diagnosis	78.4±46.8	76.6±29.1	0.845
	At 72 hours	100.5±18.6 (0.013*¶)	88.8±35.3 (0.150¶)	0.076
	At 5 days	115.6±26.3 (0.0001*¶)	96.9±46.3 (0.033*¶)	0.052

Group A: Sildenafil, Group B: Sildenafil + Milrinone
Unpaired t- test was used to analyze data, *significant
p-value <0.05 is the level significance
¶ comparison done with the value at diagnosis within the group

Table-5: Treatment given in both groups (N=68)

Treatment	**Group A (n=34)**	**Group B (n=34)**	**p value**
Mechanical ventilation	6(17.6%)	8(23.5%)	0.549
CPAP	10(29.4%)	7(20.6%)	0.401
Inotropes			
Adrenaline	8(23.5%)	17(50.0%)	0.024*

Group A: Sildenafil, Group B: Sildenafil + Milrinone
Statistical analysis was done by Chi-square test

Table-6: **Comparison of outcome in both groups (N=68)**

Outcome	Group A (n=34)	Group B (n=34)	p-value
Hospital stay (Day)	14.3±3.2	11.4±2.1	<0.001*
Mortality	1(2.9%)	4(11.8%)	0.163
Complication			
Hypotension	2(5.9%)	11(32.4%)	0.005*
GI bleeding	7(20.6%)	5(14.7%)	0.525

Group A: Sildenafil, Group B: Sildenafil + Milrinone
Fisher exact test and Unpaired t-test used to analyze data, *significant
p-value <0.05 is the level significance

DISCUSSION

This study was carried out in NICU, SCABU and CICU of Dhaka Shishu (Children) Hospital, from July 2018 to June 2020. Out of total 68 neonates (34 cases in each group) with moderate to severe PPHN were included. In this study, in group-A 23(67.6%) and in group-B 20 (58.8%) infants were male. Though male patients were more than female, the difference was not statistically significant (p>0.05) between two groups. Rahman *et al*., Fatema *et al*., and Ghandour *et al*., observed similar findings [11-13].

Term neonates were 79.4% in group-A and 76.5% in group-B (p=0.770). The mean age was 6.5±2.0 days in group-A, and 6.4±1.7 days in group-B (p=0.821). In this study, majority patients belonged to less than 1 week of age, that was not statistically significant (p>0.05) in between two groups. Similar findings were stated in other study [14].

In current study, neonates presented with cyanosis in group-A (44.1%) and in group-B (50%). Hussain *et al*., stated that neonates with PPHN manifest with cyanosis and signs of respiratory distress, because of raised PVR and right to left shunting of blood [15].

Investigation findings, regarding CBC, CRP, RBS, serum electrolytes, ABG, blood C/S, CxR and echocardiography findings in between groups were not statistically significant (p>0.05). Regarding comparison of all others baseline variables, no significant differences were found in between two groups (p>0.05) like other studies [11, 14].

In group-A mean PASP gradually decreased with the treatment which was statistically significant (p<0.05). Also, in group-B mean PASP gradually decreased with the treatment which was statistically significant (p<0.05). In comparison between group-A and group-B mean PASP difference was not significant at diagnosis and after 72 hours of treatment. But, after 5 days of treatment mean PASP reduced in combination group (group-B) which was statistically significant (p<0.05).

The initial pulmonary artery systolic pressure is higher in group-B (sildenafil with milrinone) comparing to group-A (sildenafil). Gradually pressure decreased in both groups in relation to time. But more reduction of pulmonary artery systolic pressure noted in group-B rather than group-A within 5 days of treatment.

Ghandour *et al*., found sildenafil decreased PASP more in later phage of treatment as monotherapy [11]. Probably sildenafil needs a longer treatment duration to induce a therapeutic effect. In case of milrinone as monotherapy PASP was decreased more in early phage of therapy. They also found combined effect of sildenafil and milrinone showed significant improvement in both early and late phase of therapy [11].

This findings of synergistic effect of sildenafil and milrinone was similar like our study. Peiravian *et al*., in their study claimed that addition of sildenafil with milrinone prevents rebound PPHN [16].

In group-A from the day of diagnosis to 5 days of treatment oxygen saturation improved which was statistically significant (p<0.05). Same finding was observed in group-B. Comparison in between two groups oxygen saturation was not statistically significant (p>0.05).

In group-A from the day of diagnosis to 5 days of treatment PO_2 improved which was statistically significant (p<0.05). Same finding was observed in group-B. Comparison in between two groups PO_2 was not statistically significant (p>0.05). Similar findings were observed by Mamun *et al*., Ghandour *et al*., They showed the oxygenation index decreased more both in sildenafil and combined group [11, 17].

In this study, hypotension was noted in group-A (5.9%) and in group-B (32.4%) which was statistically significant (p<0.05). However, in one study done by Mcnamara *et al*., infants received milrinone developed less hypotension in comparison with iNO group [18]. But other study no significant decrease in systolic or diastolic blood pressure was observed in any of their cases [11, 19-21]. Another complication was GI bleeding that observed in both groups but statistically was not significant. In this study whether hypotension was due to drug's effect or comorbidities, could not be differentiated.

In present study, all patients were on dopamine infusion (7.50-12.5 µg /kg /dose) initially. Some patients who did not maintain normal blood pressure, adrenaline infusion was administered instead of dopamine. Adrenaline infusion was predominant in group-B (50.0%) than group-A (23.5%), which was statistically significant ($p<0.05$).

In the study of El-Khuffash *et al*., stated that dopamine and/or adrenaline were used in continuous infusion for systemic hypotension as the most common co-morbidity accompanying PPHN. They mentioned that hypotension was treated with a bolus of saline (10 ml/kg) followed by dopamine at a dose of 5 µg/kg/min up to a maximum of 20 µg/kg/min or adrenaline at a dose of 0.5 µg/kg/min up to 2 µg/kg/min. Adrenaline was used as a second line agent [22].

During hospital stay 1(one) patient died due to aspiration pneumonia in group-A and 4 patients in group-B due to sepsis and pneumonia which was not statistically significant ($p>0.05$). Like this, another study also supported this finding [11].

Hospital stay in the combination group was found shorter than sildenafil group which was statistically significant ($p<0.05$). El-Khuffash *et al*., claimed that milrinone improves the quality of life by reducing the chance of undergoing ECMO, reducing the time on mechanical ventilation and thus provide short and long-term benefit [22].

Limitation of this study was (1) Echocardiographic findings were taken upto 5 days of hospital admission (2) Oxygenation index was not calculated (3) Causes of hypotension were not identified.

To the best of our knowledge, only few studies have assessed the combined effect of sildenafil and milrinone. However, more studies are required to demonstrate the beneficial effect of these drugs.

CONCLUSION

Combined therapy with oral sildenafil and intravenous milrinone is more effective than monotherapy with oral sildenafil in reduction of pulmonary arterial pressure in moderate to severe PPHN. Both therapies are effective in improvement of oxygenation. Combination of these drugs also reduces hospital stay of neonates with PPHN.

Author's Contribution Statement

Dr. Maksudur Rahman and Nondini Rahman Nupur conceptualized, gathered and analyzed the data. Prof, Dr. M. Monir Hossain supervised and reviewed the manuscript. Dr Abdullah Al Mamun analyzed the data and gave necessary inputs in designing the manuscript. All authors discussed the methodology, results and contributed to the final manuscript

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Conflict of Interest: Conflict of interest declared none.

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