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ORIGINAL ARTICLE

Efficacy of Milrinone plus Sildenafil in the treatment of neonates with persistent pulmonary hypertension: A single center, randomized controlled trial.

Muhammad Awais Roomi[1], Abdur Rehman Malik[2], Rana Tashfeen Arshad[3], Muhammad Zahid[4], Muhammad Sohail Arshad[5]

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ABSTRACT… Objective: To compare the outcomes of milrinone plus sildenafil versus sildenafil alone in the treatment of persistent pulmonary hypertension (PPH) in neonates. **Study Design:** Randomized Controlled Trial. **Setting:** Department of Neonatology, The Children's Hospital and Institute of Child Health, Multan, Pakistan. **Period:** December 2023 to May 2024. **Methods:** A total of 42 neonates, diagnosed to have PPH were enrolled. Neonates were randomized to either oral sildenafil monotherapy (n=21) or oral sildenafil and intravenous (IV) milrinone (n=21). Primary outcome was decrease in pulmonary artery systolic pressure (PASP). Secondary outcomes were improvement in oxygen saturation, duration of hospitalization, treatment related side effects, and mortality. **Results:** In a total of 42 neonates, 25 (59.5%) were boys. The mean age at the time of enrollment was 9.63±3.51 days. The mean PASP at the time of enrollment was 55.73±7.91 mmHg. PASP was statistically similar at baseline (p=0.5512), and day-3 (p=0.2163). At day-7, PASP was significantly reduced in sildenafil plus milrinone group was reported in comparison sildenafil group (37.62±8.04 mmHg vs. 42.92±8.25 mmHg, p=0.0413). SPO2, mortality, and post-treatment complications were statistically similar among neonates of both study groups. The duration of hospitalization was significantly less among neonates of sildenafil plus milrinone group vs. sildenafil group (13.58±2.93 days vs. 16.82±4.24 days, p=0.0063). **Conclusion:** Combined oral sildenafil and IV milrinone was more efficacious than sildenafil alone in reducing pulmonary arterial pressure.

Key words: Milrinone, Mortality, Oxygen Saturation, Pulmonary Hypertension, Sildenafil.

INTRODUCTION

Persistent pulmonary hypertension (PPH) in neonates is a life-threatening condition marked by abnormally elevated pulmonary vascular resistance (PVR). The lungs receive inadequate blood flow, leading to impaired oxygen exchange and significant hypoxemia.[1] In neonates, this compromised oxygenation can rapidly lead to critical respiratory distress and organ dysfunction. PPH is often a challenging condition to manage in the neonatal period, requiring prompt and effective interventions to reduce pulmonary pressure and improve oxygen delivery to the body. PPH affects around 1.8 in 1000 live-births but among per-term newborns, its incidence surges around 5.4 per 1000.[2,3]

The most common cause of PPH in neonates is the abnormal constriction of pulmonary blood vessels, often triggered by underlying lung parenchymal diseases. Conditions such as "meconium aspiration syndrome (MAS)", neonatal "respiratory distress syndrome (RDS)", and neonatal pneumonia frequently lead to this vasoconstriction, resulting in increased PVR.[4] PPH can arise from structural changes within the pulmonary vasculature, as seen in idiopathic "persistent pulmonary hypertension of the newborn (PPHN)", where the vessels undergo pathological remodeling. Another significant cause is pulmonary vascular underdevelopment, which occurs in cases like congenital diaphragmatic hernia (CDH), where abnormal lung development impairs the pulmonary circulation.[5] Each of these conditions contributes to the disrupted pulmonary blood flow and severe

1. FCPS (Pediatric Medicine), Clinical Fellow Neonatology, The Children's Hospital and Institute of Child Health, Multan, Pakistan.
2. FCPS (Neonatology), FCPS (Pediatric Medicine), Assistant Professor Neonatology, The Children's Hospital and Institute of Child Health, Multan, Pakistan.
3. FCPS (Pediatric Medicine), Clinical Fellow Neonatology, The Children's Hospital and Institute of Child Health, Multan, Pakistan.
4. FCPS (Pediatric Medicine), Clinical Fellow Neonatology, The Children's Hospital and Institute of Child Health, Multan, Pakistan.
5. FCPS (Pediatric Cardiology), FCPS (Pediatric Medicine), Professor Pediatric Cardiology, The Children's Hospital and Institute of Child Health, Multan, Pakistan.

Correspondence Address:
Dr. Muhammad Awais Roomi
Department of Clinical Fellow Neonatology
The Children's Hospital and Institute of
Child Health, Multan, Pakistan.
drroomi73@gmail.com

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oxygenation difficulties characteristic of neonatal PPH.

Mortality ranges between 10-20% in PPH while there is high burden of ventilation, surfactant, "inhaled nitric oxide (iNO)", and "extracorporeal membrane oxygenation (ECMO)".[6] The literature demonstrates that around 30% infants do not improved despite nitric oxide administration. It has also been proposed that iNO displaces oxygen and binds to the hemoglobin forming methemoglobin, which can further reduce the oxygen carrying capacity of the blood.[7] ECMO is also not always available even in the developed regions so mortality may be even higher in resource limited settings.[8]

Sildenafil and milrinone are promising drugs for treating PPH in neonates. These can also be used as adjuncts to other PPHN treatment options. Oral sildenafil works by preventing the degradation of "cyclic guanosine monophosphate (cGMP)" through inhibition of phosphodiesterase 5, while milrinone prevents the degradation of cyclic adenosine monophosphate (cAMP) through inhibition of phosphodiesterase 3, thus decreasing pulmonary artery systolic pressure (PASP).[9,10] Rahman et al reported significantly less duration of hospitalization among neonates who were administered Milrinone plus Sildenafil in comparison to Sildenafil alone (11.4±2.1 days vs. 14.3±3.2 day, $p<0.001$). The same study found reported mortality rates of 2.9% and 11.8% in Sildenafil alone versus Milrinone plus Sildenafil and the difference was statistically insignificant.[10]

Not many studies are on view which have compared the outcomes of Milrinone plus Sildenafil versus any one of these alone. No local data exists in this regard. Neonates with PPH should be administered iNO and ECMO but these are not available in most resource constraint settings like ours. This study was conducted to compare the outcomes of Milrinone Plus Sildenafil versus Sildenafil alone in the treatment of PPH in neonates.

METHODS

This open labeled, randomized controlled trial was performed at the department of Neonatology, The Children's Hospital and institute of Child Health, Pakistan, from December 2023 to May 2024. Approval from "Institutional Ethical Committee" was obtained (letter number: ICH/2023/437, dated: 22/8/2023 on 18.06.21). Taking the mean duration of hospitalization among neonates with PPH to be 11.4±2.1 days and 14.3±3.2 day in Milrinone plus Sildenafil, and Sildenafil alone group, respectively,[10] with 99% confidence interval, 80% power, the sample size turned out to be 42 (21 in each group).

Inclusion criteria were neonates of either gender, aged between 1-28 days, birth weight above 2000 grams, diagnosed to have PPH (as per echocardiography). Exclusion criteria were neonates having congenital heart defects (CHDs), congenital diaphragmatic hernia, lung anomalies, or history of any surgical intervention. Neonates born below 28 weeks of gestation were also excluded. Echocardiography was performed by a pediatric cardiologist with over three years of post-fellowship experience, using a GE Vivid S5 ultrasound machine with a 7 MHz probe. M-mode, 2D, and color Doppler modes, along with pulsed and continuous waves, were utilized to evaluate pulmonary artery pressure using the modified Bernoulli equation: pulmonary artery systolic pressure (PASP) = tricuspid regurgitation gradient + right atrial pressure (RAP), $PASP = (Vmax^2 \times 4) + RAP$. Neonates with PPHN were defined as having PASP > 40 mmHg.[11]

Informed and written consents were sought from parents or guardians of all neonates studied. Neonates were randomized to either Group-A or Group-B. Group-A were given oral sildenafil as 2mg per kg per day, 6-hourly with incrementing of 0.5 mg per kg per dose and a target maintenance dose of 2 mg per kg per dose every 6 hourly by nasogastric tube. In Group-B, Milrinone was initiated at 0.5 ug per kg per minutes using intravenous infusion through syringe pump. In Group-B, Sildenafil was given in the same protocol mentioned for Group-A. Monitoring of SpO2 was done regularly and the neonates were gradually waned off from infusion milrinone at 72-hours following start of the treatment. Adverse effects

like hypotension, and bleeding manifestations were observed among both study groups. Primary outcome was decrease in pulmonary artery systolic pressure (PASP). Secondary outcomes were improvement in oxygen saturation, duration of hospitalization, treatment related side effects, and mortality.

Statistical analysis was performed using "IBM-SPSS Statistics, version 26.0". Qualitative variables were shown as frequency and percentages. Mean and standard deviation were calculated for quantitative data. Independent sample test was used to compare numeric data between whereas chi-square test or fisher exact test were applied to compare categorical data. P value below 0.05 was labeled significant.

RESULTS

In a total of 42 neonates, 25 (59.5%) were boys, representing a boy to girl of 1.7:1. The mean age at the time of enrollment was 9.63±3.51 days. There were 27 (64.3%) neonates who were born at term. Birth weight was above 2500 grams among 21 (50.0%) neonates. Mode of delivery was cesarean section among 26 (61.9%) neonates. The mean PASP at the time of enrollment was 55.73±7.91 mmHg. Table-1 is showing comparison of baseline neonatal and maternal characteristics, and no statistically significant differences were observed (p>0.05).

Mechanical ventilation was required in a total of 7 (16.7%) neonates while no significant differences observed among neonates of both study groups (sildenafil group 19.0% [n=4] vs. sildenafil plus milrinone group 14.3% [n=3], p=0.6788). Continuous positive airway pressure (CPAP) was employed in 8 (38.1%) neonates in sildenafil group versus 6 (28.6%) in sildenafil plus milrinone group (p=0.5127). Inotropes were required among 6 (28.6%) neonates in sildenafil group versus 9 (42.9%) neonates in sildenafil plus milrinone group (p=0.3340).

In terms of primary outcome, PASP was statistically similar at baseline (p=0.5512), and day-3 (p=0.2163). At day-7, PASP was significantly reduced in sildenafil plus milrinone group was reported in comparison sildenafil group (37.62±8.04 mmHg vs. 42.92±8.25 mmHg, p=0.0413). In terms of secondary outcomes, SPO, mortality, and post-treatment complications were statistically similar among neonates of both study groups. Overall, the mean duration of hospitalization was noted to be 15.21±3.49 days. The duration of hospitalization was significantly less among neonates of sildenafil plus milrinone group vs. sildenafil group (13.58±2.93 days vs. 16.82±4.24 days, p=0.0063). Comparison of primary and secondary outcomes among neonates of both study groups are shown in Table-II.

DISCUSSION

Managing PPH among neonates can be challenging especially in resource limited settings like ours where iNO or ECMO are not available. Not many studies are on view analyzing the effectiveness of combination of sildenafil and milrinone in managing PPH. The findings of this study highlighted that combination of sildenafil plus milrinone resulted in significantly lower PASP at 7-days post-treatment (37.62±8.04 mmHg vs. 42.92±8.25 mmHg, p=0.0413), showing superiority of sildenafil plus milrinone over sildenafil alone in neonatal PPH. Our findings stand aligned with another study conducted by El-Ghandour et al from Egypt where they analyzing the effectiveness sildenafil plus milrinone in comparison of any of these alone. They found that PASP was significantly reduced in combination groups versus any of the single drugs (p=0.031).[12] A study analyzing the outcomes of PPH revealed that out of 11 infants who received sildenafil, 54.5% (n=6) of the infants responded initially. Three of those five non-responders were found to improve when sildenafil was further proceeded with a combination of milrinone exhibiting the effective of this combination in PPH.[13] Some others have demonstrated the efficacy of milrinone in lowering PVR as well as PASP among various age groups suffering with PPH.[14-16] Some others also reported that a combination of sildenafil and milrinone prevented PPH rebound rates among neonates.[17]

Characteristics		Sildenafil (n=21)	Sildenafil plus Milrinone (n=21)	P-Value
Gender	Boys	13 (61.9%)	12 (57.1%)	0.7532
	Girls	8 (38.1%)	9 (42.9%)	
Age (days)		9.42±3.57	9.94±3.25	0.6243
Gestational age (weeks)	28-36	8 (38.1%)	7 (33.3%)	0.7474
	≥37	13 (61.9%)	14 (66.7%)	
Birth weight (grams)	2000-2500	11 (52.4%)	10 (47.6%)	0.7576
	>2500	10 (47.6%)	11 (52.4%)	
Delivery mode	Cesarean section	14 (66.7%)	12 (57.1%)	0.5251
	Vaginal delivery	7 (33.3%)	9 (42.9%)	
Clinical Characteristics				
Respiratory rate (breaths/min)		65.29±8.24	61.48±7.19	0.7361
Heart rate (beats/min)		128.03±18.84	132.37±21.59	0.4916
Cyanosis		11 (52.4%)	9 (42.9%)	0.5366
SPO2 (%)		84.27±3.97	82.74±3.86	0.2128
Echocardiography bases PASP (mmHg)		54.94±8.25	56.39±7.36	0.5512
Maternal Characteristics				
Meconium stained liquor		3 (14.3%)	4 (19.0%)	0.6788
Gestational diabetes mellitus		3 (14.3%)	2 (9.5%)	0.6337
Hypertension		3 (14.3%)	5 (23.8%)	0.4319

Table-I. Comparison of baseline characteristics (N=42)

Outcomes			Sildenafil (n=21)	Sildenafil plus Milrinone (n=21)	P-Value
Primary	PASP (mmHg)	Baseline	54.94±8.25	56.39±7.36	0.5512
		Day-3	49.74±9.41	46.18±8.95	0.2163
		Day-7	42.92±8.25	37.62±8.04	0.0413
Secondary	SPO2 (%)	Baseline	84.27±3.97	82.74±3.86	0.2128
		Day-3	90.73±3.24	90.32±3.65	0.7023
		Day-7	93.82±3.20	93.98±3.49	0.8787
	Duration of hospitalization (days)		16.82±4.24	13.58±2.93	0.0063
	Hypotension		2 (9.5%)	6 (28.6%)	0.1160
	Mortality		2 (9.5%)	3 (14.3%)	0.6337

Table-II. Comparison of outcomes (N=42)

Post-treatment hypotension was found among 28.6% neonates who were given sildenafil and milrinone in comparison to 9.5% neonates in sildenafil alone, but the difference was statistically insignificant (p=0.1160). Contrary to our findings, a study done by Rahman et al from Bangladesh showed that post-treatment hypotension in was observed in 5.9% of patients in sildenafil versus 32.4% in sildenafil plus milrinone group (p<0.05).[10] A study by McNamara et al found that infants treated with milrinone experienced less hypotension compared to those in the iNO group.[18] Some other studies reported no significant changes in systolic or diastolic blood pressure.[19,20]

The present study revealed that sildenafil and milrinone neonates experience significantly less duration of hospitalization in comparison to sildenafil alone. These findings stand aligned with the published literature endorsing the superiority of sildenafil and milrinone combination versus mono therapy.[10,12] El-Khuffash et al asserted that milrinone enhances the quality of life by lowering the chances of needing ECMO, shortening the duration of mechanical ventilation, and providing both short-term and long-term benefits.[21]

Milrinone and sildenafil are both potent pulmonary vasodilators that exert their effects through distinct mechanisms of action.[22] When

used together, these drugs have a synergistic effect, enhancing pulmonary vasodilation while simultaneously improving cardiac contractility.[23] Importantly, this enhanced hemodynamic profile results in significant improvements in pulmonary blood flow and right ventricular function, without causing an increase in systemic vasodilation or compromising systemic blood pressure.[24] This balance makes the combined therapy particularly valuable in managing conditions such as pulmonary hypertension or right ventricular dysfunction, where targeted pulmonary vasodilation and improved cardiac output are critical[25], but systemic hypotension must be avoided.

The present study had some inherent limitations. Single center study site and a relatively small sample size limits the generalizability of this research. Nevertheless, the present study presents the first local experience from Pakistan comparing the combination of sildenafil and milrinone versus sildenafil alone which should pave way for further research in evaluating effectiveness of contemporary treatment options in neonatal PPH.

CONCLUSION

Although, sildenafil alone or in combination with milrinone was found to be effective in persistent pulmonary hypertension among neonates but combined oral sildenafil and intravenous milrinone was more efficacious than sildenafil alone in reducing pulmonary arterial pressure.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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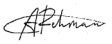
AUTHORSHIP AND CONTRIBUTION DECLARATION

No.	Author(s) Full Name	Contribution to the paper	Author(s) Signature
1	Muhammad Awais Roomi	Data collection, Drafting, Responsible for data's integrity, Approval for publication.	
2	Abdur Rehman Malik	Conception, Design, Critical revisions, Proof reading, Approval for publication.	
3	Rana Tashfeen Arshad	Data collection, Drafting, Responsible for data's integrity, Approval for publication.	
4	Muhammad Zahid	Data collection, Drafting, Responsible for data's integrity, Approval for publication.	
5	Muhammad Sohail Arshad	Conception, Design, Proof reading, Critical revisions, Approval for publication.