Original article

Comparison of Milrinone with Sildenafil for the Treatment of Persistent Pulmonary Hypertension of the Newborn

Imtiaz Ahmed, Motia Javaid, Tanveer Ahmed, Imran Baloch, Nisar Khan Sajid, Abdul Razzaq Mughal

ABSTRACT

Objective: To compare outcomes of milrinone with sildenafil for management of persistent pulmonary hypertension in neonates at Aziz Fatimah tertiary care hospital, Faisalabad.

Methodology: An experiment study was conducted in Pediatrics Unit of Aziz Fatima Hospital Faisalabad from October 2022 to September 2023. Total 160 infants of persistent pulmonary hypertension were included through non probability consecutive sampling. Group 1 infants (n = 80) received a loading dose of milrinone intravenously administered over a 60-minute period at a dose of 50 µg/kg. Group 2 infants (n = 80) received sildenafil (2mg/kg/dose TDS). The medication was continued until ex-tubation. The primary outcome variables were the mortality of neonates and their stay duration at hospital. The secondary outcomes were duration of invasive ventilation, hypotension, inotropes support, post treatment oxygenation index, post treatment echocardiographic parameters.

Results: Out of 160, 92(57.5%) were male and 68(42.5%) were females. 111(69.4%) of the total, were full- term babies, whereas 49(30.6%) patients were pre term. Mortality was observed in 7 (8.8%) patients in milrinone group and 17 (21.2%) patients in sildenafil group with p-value = 0.027. The milrinone group exhibited a shorter duration of hospital stay compared to the sildenafil group, with respective averages of 14.22±3.75 days and 17.72±5.7 days, yielding a p-value of 0.0001.

Conclusion: Milrinone has been proven to be a promising therapeutic choice for persistent pulmonary hypertension in neonates, and it is effective in doing so in low resource settings.

KEYWORDS: Persistent Pulmonary Hypertension, Milrinone, Sildenafil, Mortality, Newborn.

INTRODUCTION

Persistent pulmonary hypertension (PPHN) is categorized by increased pulmonary vascular resistance, causing blood to shift from the right to the left side of the heart through open circulatory pathways like the ductus arteriosus and foramen ovale. This diversion results in inadequate perfusion of the lungs. According to estimates, there are 1.9 cases of PPHN for every 1000 live births. About 0.34–6.8 PPHN instances are detected for every 1000 live births, and 10–20% of these cases result in mortality.[1] PPHN puts newborns at risk for serious side effects such as asphyxia, neurological consequences, chronic lung disease and even demise.[2]

Alterations in the structure and function of the pulmonary arteries provide the basis of the pathophysiology of PPHN.[3] Pulmonary vasoconstriction, pulmonary muscular structural remodeling, intravascular blockage and lung hypoplasia can all lead to an increased pulmonary vascular

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resistance. It could have a secondary cause, such as congenital diaphragmatic hernia, infection, or meconium aspiration syndrome.[4] PPHN risk factors include preterm birth and Caesarean section as opposed to natural delivery. Prenatal exposure to selective serotonin reuptake inhibitors (SSRIs) used to treat maternal depression has been associated with PPHN.[5] Exposure to smoke during pregnancy is another recognized risk factor. PPHN is linked to the use of non-steroidal anti-inflammatory medications (NSAIDs), particularly ibuprofen, naproxen and aspirin during pregnancy.[6]

Although inhaled nitric oxide (iNO) is thought to be the cornerstone of treatment, approximately 40% of patients may not respond to it completely, in which case extracorporeal membrane oxygenation (ECMO) may be necessary.[7] To guarantee better results, it is crucial to use the treatment modalities that are currently available. Recently, phosphor-diesterase (PDE) inhibitors have been investigated as potential PPHN therapeutics. Sildenafil is the PDE5 inhibitor for PPHN that has been studied the most.[8] Sildenafil increases pulmonary vasodilation by triggering cyclic guanosine monophosphate (cGMP)-dependent protein kinase and obstructing calcium influx via the L-type calcium channel in vascular smooth muscle cells. Sildenafil may have an impact on the enzymes cystathionine γ-lyase (CSE) and cystathionine-β-synthase, which may then regulate the production of hydrogen sulfide (H2S) and the proliferation of pulmonary arterial smooth muscle cells. To sum up sildenafil helps the respiratory system (higher oxygen index) and the circulatory system (higher peripheral blood volume) both of which lead to an immediate improvement in ventilation perfusion.[9]

Milrinone is a selective phosphodiesterase III inhibitor that also has inotropic properties, enhances heart diastolic function and has a vasodilator effect on pulmonary and systemic vessels.[10] Neonatal physicians frequently need to implement additional therapies due to higher rate of neurological sequelae and mortality with recent advancements in PPHN management. The standard treatment PPHN for newborn is inhaled nitric oxide (iNO) and extracorporeal membrane oxygenation (ECMO), however in developing countries these established therapies are not widely available.[11] On the selection of therapeutic interventions beyond iNO, however, there is disagreement among the practitioners. Identifying practice variation is an essential first step in achieving better patient outcomes. Randomized control concerning safety and efficacy of milrinone and sildenafil drug was done by previous researchers in foreign countries, on the bases of these trials we aimed to compare the efficacy of milrinone and sildenafil in treating persistent pulmonary hypertension in newborns at Aziz Fatimah tertiary care hospital, Faisalabad.

METHODOLOGY

This study was carried out at the Aziz Fatima Hospital in department of Pediatrics in Faisalabad, Pakistan from October 2022 to September 2023. The Institutional Ethical Committee gave its approval for this this (ref. No: IEC/204-22). We did experimental study to compare outcomes of milrinone and sildenafil drugs, that are routinely used in our tertiary care hospital for the treating PPHN in infants. All study participants' parents or guardians were asked to sign a consent form to participate in study. They were assure to leave the study participation at any time, if they want sample size was calculated by using WHO sample size calculator for two proportions (one sided) using formula:

$$n = \frac{\left\{ z_{1-\alpha}\sqrt{2\bar{P}(1-\bar{P})} + z_{1-\beta}\sqrt{P_1(1-P_1) + P_2(1-P_2)} \right\}^2}{\left(P_1 - P_2\right)^2}$$

Where mortality in milrinone (P1) = 16.1%11 and mortality in sildenafil (P2) = 33%, 1 with a 5% level of significance and an 80% power of test. With 80 infants assigned to each group, the study's final sample size consisted of 160 participants. Non-probability consecutive sampling was the method used for sampling. The study included neonates diagnosed with Persistent pulmonary hypertension

(PPHN) who met specific criteria: an oxygenation index of at least 10, gestational age (GA) more than or equal to 34 weeks, and weight more than or equal to 2000 grams. PHHN diagnosis relied on specific echocardiographic criteria including: (i) a tricuspid regurgitant jet pressure gradient of at least two-thirds of the systemic systolic blood pressure (SBP); (ii) flattening or bowing of the intraventricular septum towards the left ventricular cavity; (iii) bidirectional shunting or predominant right-to-left shunting of the patent ductus arteriosus; and (iv) pulmonary artery acceleration time less than 40 milliseconds.

Infants who exhibited severe hypovolemia, bleeding diathesis, interventricular hemorrhage, hypoxic-ischemic encephalopathy undergoing therapeutic hypothermia, evidence of renal impairment, or lethal congenital anomalies or obvious syndromes were excluded from the study.

All of the patients were divided into two groups at random. The infants in group 1 (the intervention group) were given a loading dose of 50 µg/kg of milrinone intravenously over a 60-minute period. A maintenance infusion was kept at 0.375 µg/kg/min up to a maximum of 0.750 µg/kg/min. Ten milliliters per kilogram of normal saline bolus was given at the same hour as the milrinone bolus. Group 2 received three daily doses of sildenafil (2 mg/kg). Together with the sildenafil, a bolus of 10 ml/kg normal saline was also administered. The drug was kept up until the patient was extubated and then outcomes were observed and compared. Demographic and anthropometric data were recorded. The primary outcomes including mortality and duration of hospital stay. The secondary outcomes were duration of invasive ventilation, hypotension, inotropes support, post treatment oxygenation index, post treatment echocardiographic parameters (The criteria for PPHN diagnosis included a right-to-left or bidirectional shunt across the patent ductus arteriosus and pressure gradient across tricuspid valve).

SPSS V-16 was utilized as the data analysis tool. The means (standard deviation) were used for continuous variables, while frequency and percentages represented dichotomous variables. The independent sample t-test compared continuous variables, and the Chi-square test compared dichotomous variables. A P-value below 0.05 was deemed statistically significant.

RESULTS

160 infants with PPHN were included in the study and 80 infants were randomly allocated to group 1 (milrinone) and 80 patients in group 2(sildenafil). There were 160 patients total; 92(57.5%) were males and 68 (42.5%) were females. Vaginal delivery was noted in 46 (28.8%) and c-section was observed in 114 (71.2%) patients. 49 (30.6%) patients were pre term and MAS was the commonest associated condition recorded among 69 (43.1%) neonates. Mostly neonates 76 (47.5%) had severe PPHN. Baseline characteristics of neonates are mentioned in Table 1.

Table 1: Baseline characteristics of the patients (n = 160)

Variables	Group		P-Value
	Milrinone (n = 80)	Sildenafil (n = 80)	
Age (days)	3.6±2.09	3.35±2.36	0.48
Gender			
Male Female	48 (60%) 32 (40%)	44 (55%) 36 (45%)	0.522
Birth weight (kg)	3.01±0.41	2.88±0.45	0.064
Gestational age			
Pre term Term	22 (27.5%) 58 (72.5%)	27 (33.8%) 53 (66.2%)	0.391
Mode of delivery			
Vaginal delivery C-section	25 (31.2%) 55 (68.8%)	21 (26.2%) 59 (73.8%)	0.485
APGAR score at 5 min	6.94±1.69	7.04±1.63	0.704
Comorbid condition			
MAS	33 (41.2%)	36 (45%)	0.936
RDS	30 (37.5%)	27 (33.8%)	
Pneumonia	11 (13.8%)	12 (15%)	
Idiopathic	6 (7.5%)	5 (6.2%)	
verity of PPHN	11 (13.8%)	11 (13.8%)	0.943
Mild Moderate	30 (37.5%)	32 (40%)	
Severe	39 (48.8%)	37 (46.2%)	
Pre-treatment oxygenation index	27.7±8.42	28.81±8.27	0.401

Pearson Chi- Square test with p value <0.05 as significant€

Milrinone group patients spent less time in the hospital and there is significant difference between milrinone and sildenafil (p value = 0.0001). Mortality was more common in sildenafil group than milrinone group (p value = 0.027). Treatment outcomes are mentioned in Table 2.

Table 2: Treatment outcomes among the study groups (n = 160)

Variables	Group		P-Value
	Milrinone (n = 80)	Sildenafil (n = 80)	
Mortality	7 (8.8%)	17 (21.2%)	0.027*
Hospital stay (days)	14.22±3.75	17.72±5.7	0.0001*
PDA shunting Left – right Bidirectional Right – left	67 (83.8%) 4 (5%) 9 (11.2%)	54 (67.5%) 4 (5%) 22 (27.5%)	0.033*
Pressure gradient across tricuspid valve Mild Moderate	62 (77.5%) 18 (22.5%)	49 (61.2%) 31 (38.8%)	0.026*
Inotropic Support	34 (42.5%)	47 (58.8%)	0.04*
Duration of ventilation (days)	10.6±3.75	13.84±5.61	0.0001*
Hypotension	34 (42.5%)	49 (61.2%)	0.018*
Post treatment oxygenation index	12.85±5.97	14.62±6.06	0.064

Pearson Chi- Square test with p value <0.05 as significant

DISCUSSION

Persistent pulmonary hypertension, of the newborn is responsible for a to higher mortality rates in both term and per-term infants and is regarded as a potentially fatal condition.[12-13] Acute pulmonary hypertension in term infants is challenging using our current approach.[14] Although inhaled nitric oxide (iNO) and extracorporeal membrane oxygenation is thought to be the standard treatment, However, in nearly half of late-preterm and term infants with persistent newborn pulmonary hypertension, the response to iNO is suboptimal, so alternative or adjuvant safe therapeutics needed to be explored for these cases or in developing countries lacking inhaled facilities for nitric oxide and extracorporeal membrane oxygenation.[7] This study aimed to assess the efficacy of milrinone versus sildenafil as available alternative therapeutics in treating PPHN. Milrinone causes vasodilation in the pulmonary and systemic artery beds in addition to its lusitrope function, which improves diastolic function[15] Milrinone may also exhibit synergistic effects with iNO in lowering pulmonary vascular resistance.[14]

The majority of newborns with PPHN in the current study (71.2%) were delivered by c-section. Previous studies discovered that cesarean sections, both elective and emergency were a common delivery method.[1,12-13] The current study's findings show that 47.5% of the newborns had severe PPHN, which support those of the earlier study.[1] Previous researches were evident that the meconium aspiration syndrome (MAS) and respiratory distress syndrome (RDS) are the predominant associated conditions among neonates diagnosed with persistent pulmonary hypertension (PPHN).[12,13] In current study we noticed MAS and RDS in 41.2% and 37.5% of the neonates on Milrinone, whereas we observed MAS and RDS in 45% and 33.8% patients respectively on Sidenafil therapy. no significant differences in terms of MAS and RDS were observed in both drugs groups.[12] As the previous study shows, MAS and RDS are believed to be the most common conditions associated with newborns presenting with PPHN.[13]

In Milrinone group patients spent less time in the hospital and there is significant difference between milrinone and sildenafil (p = 0.0001). Our results are in line with the imam et al, who reported significantly shorter he length of hospital stay in the milrinone group than that in the sildenafil group.16 This finding may reflect that milrinone induced its therapeutic effect rapidly as compared to sidenafill.

In current study mortality was significantly higher in sildenafil group than milrinone group, we observed, 8.8% and 21.2% neonatal mortality rates in the milrinone group and sildenafil respectively, which was significantly different. In contrast to our finding imam et al did not find significant differences in mortality between the milrinone or sildenafil groups (P > 0.05).[16] In comparison to our results El-Ghandour, et al study reported comparatively higher mortality rate in milrinone group in contrast to sidenafil had (30 verses25%)

death rate. However El-Ghandour ,et al reported reduced mortality with the use of dual-therapy with milrinone plus sidenafil compared with the monotherapy, as this study found improvement in 85% of patients on dual therapy and only 15% were deceased.[17] This aforementioned clinical trial suggested that combined use of both drugs demonstrated a beneficial synergistic effect with better outcomes and reduced mortality.[17] Concerning mortality rate after use of milrinone and sidenafil, conflicting results have been documented so future research works still to be need for validation of these results.

Current results concerning the duration of mechanical ventilation we notice that the patients on milrinone required mechanical ventilation for less duration (10.6±3.75 days) as compared to sildenafil (13.84±5.61 days), the difference was significant. These findings are not in agreement with Imam et al study who did not find any significant difference in both drugs in term of mechanical ventilation.[16]

Our research indicates that the milrinone group had a lower post-treatment oxygenation index than the sidenefil group. Khorana et al also found better oxygenation in their patients with the addition of pulmonary vasodilator milrinone along with standard treatment nitric oxide and mechanical ventilation in non-responders.[18] Contradictory findings are reported by El-Ghandour et al and colleagues that the oxygenation index statistically decreased among the sildenafil group and the dual therapy groups of their study, but the decrease was not statistically proven among the milrinone group of their study.[17]

The distribution of adverse events including hypotension, use of inotropes, was comparable between the two groups. Our results also reveals that less than half the Neonate patients (42%) on milrinone experienced hypotension whereas 61% of patients in sildenafil experienced hypotension Inotropic drugs to stabilize the hemodynamic were used only in 42.5% of patients in milrinone group, whereas more than half (58%) of the patient required inotropics drug after treatment with sildenafil. Current results are supported by imam study that also documented that Milrinone is superior to sildenafil in improving oxygenation without lowering blood pressure parameters.[16] Our results are also in line with El-Khuffash study that also found lesser number of patient experienced hypotension and required inotropic drugs as compared to their control group on Plecebo.[14] Previous RCT done by El-Ghandour reported no significant side effects with the use of dual-therapy with milrinone plus sidenafil; in terms of hypotension in any recipient patients with severe PPHN. El-Ghandour et al suggested that sildenafil combined with milrinone was more effective at normalizing pulmonary artery pressure and improving survival rates than treatment with either of the two drugs as monotherapy.

In current study, post-treatment echocardiography showed less bidirectional or right-left shunting. Previous pilot study on the milrinone demonstrated an improvement in right-left or bidirectional shunting.[7] On comparison of right ventricular function, we observed that 77% patient on milrinone has mild nature of pressure gradient across the tricuspid valve reflecting improvement in patient's condition, while patients in sidenafil group only 61% is in mild and 38% remain at moderate level at end of management. In Elghandour study found no significant difference concerning tricuspid regurgitation at the end of management, in milrinone, sidenafil or dual therapy groups of their Randomized control trial.

Although results of current study remain crucial for developing countries without access to the gold standard iNO and ECMO therapy for severe PPHN, additional clinical trials should be done to determine strategies for management and efficient treatment of persistent hypertension with stabilized hemodynamics for our pediatric patients.

CONCLUSION

It is indicated that milrinone is useful for the treatment of persistent pulmonary hypertension in

neonates in low resource settings where iNO is not available for treatment of PPHN. It can be applied to lower the length of hospital stay and mortality as well as to enhance echocardiographic parameters in patients. Milrinone successfully reduces the need for oxygen and hypotension rate.

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Tanveer Ahmad: Data collection, writing plus Data collection plus drafting manuscript and approved the manuscript.

Imran Baloch: Data collection, writing manuscript and revised and approved it.

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