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Comparison of the Efficacy of Milrinone Injection versus Milrinone Plus Oral Sildenafil in Newborns with Pulmonary Arterial Hypertension

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Abstract

Background: pulmonary hypertension is a serious problem in newborns, which is associated with increased pulmonary vascular resistance, leading to right-to-left extrapulmonary shunt and impaired lung oxygenation and severe hypoxemia in the neonatal period. The purpose of this study was to evaluate the effect of oral Sildenafil with intravenous Milrinone on the treatment of pulmonary hypertension in newborns.

Methods: The statistical population of this study consisted of all term and late preterm neonates admitted to NICU wards of Afzalipour Hospital in Kerman. A total of 80 neonates were included and divided into the intervention group (intravenous Milrinone with oral Sildenafil), and control group (intravenous Milrinone alone). The related criteria for increasing pulmonary artery pressure, including mean pulmonary artery pressure (mean PAP), Tricuspid valve regurgitation (TR), pulmonary artery diameter (PAD) and right ventricular systolic function by measuring TAPSE (Tricuspid annular presystolic excursion) were assessed by echocardiography in the first 24 hours after birth and 72 hours after the intervention in all patients. Data analysis was done through SPSS24 software.

Results: The mechanical ventilation time in the group treated with oral Sildenafil (2.5 days) was significantly ($p < 0.0001$) shorter than that in the control group (10.5 days). Also, the hospital stay in NICU in the intervention group (11.3 days) was significantly ($p < 0.0001$) shorter than that in the control group (20.2 days). Pulmonary artery pressure showed a significant decrease in the intervention group 72 hours after adding Sildenafil compared to the control group. The mean difference of TR gradient was significantly ($P<0.0001$) higher in the intervention group (59) than in the control group (22). The mean PAP difference was also significantly ($P= 0.005$) higher in the intervention group (47.7 mmHg) compared to the control group (33.3 mmHg). Besides the TAPSE difference was significantly ($P = 0.009$) lower in the intervention group (33.7) than in the control group (47.2). There was no significant difference in the PAD (Pulmonary artery diameter) between the two groups ($P = 0.312$). Also, there was no significant difference in mortality rate between the intervention group (3.7%) and control group (5%).

Conclusion: The results of our study showed that the addition of oral Sildenafil to intravenous Milrinone was associated with better therapeutic outcomes in the treatment of neonatal pulmonary hypertension. Conducting similar studies is necessary for the final proof of this issue.

Introduction

Pulmonary hypertension is a serious problem in the neonatal period, which is associated with increased pulmonary vascular resistance, leading to right-to-left extrapulmonary shunt and impaired lung oxygenation resulting in severe hypoxemia in the neonatal period (1). The most common cause of pulmonary hypertension is abnormal constriction of the pulmonary vasculature in response to pulmonary parenchymal diseases such as meconium aspiration syndrome (MAS), neonatal respiratory distress syndrome (RDS), and pneumonia, remodeling of the pulmonary vascular substrate in idiopathic persistent pulmonary hypertension (PPHN) and pulmonary vascular hypoplasia in congenital diaphragmatic hernia (CDH) (1). Inhaled nitric oxide (iNO) is the first-line treatment in neonatal pulmonary hypertension. Pulmonary vasodilators such as Sildenafil, Bosentan, and Milrinone are used in the centers that inhaled nitric oxide is not available (2). On the other hand, according to Kelly LE *et al*. paper in Cochrane Library, although iNO with mechanical ventilation is the main therapy for pulmonary hypertension, inhaled nitric oxide treatment fails in 30% of cases (3). Sildenafil is a 5-phosphodiesterase inhibitor that is used in the treatment of pulmonary hypertension, improves right ventricular function and reduces vascular smooth muscle contraction (4). Sildenafil therapy in neonatal pulmonary hypertension is safe and does not cause certain complications (5). In Limjico *et al*. study, using high and low doses of Sildenafil led to a significant decrease in mean PAP (6). Qasim *et al*. have investigated the use of oral Sildenafil in neonates with BPD and pulmonary hypertension and the effect of Sildenafil on NT-proBNP. According to them, Sildenafil reduced NT-proBNP but had no effect on the respiratory score. (7)

In Jiang *et al*. study, Sildenafil was administered to CDH patients with secondary pulmonary hypertension and it reduced the hospital stay in NICU, but had no effect on mortality rate (8).

In Hussain AS *et al*. study on neonates with pulmonary hypertension, which was treated with oxygen 100% after using oral Sildenafil, oxygen requirement was reduced to 40% (9).

In a review study conducted by Nakwan *et al*., the treatment of pulmonary hypertension in resource limited countries, where nitric oxide is not available, the use of oral sildenafil has been introduced as the first line treatment followed by other pulmonary vasodilators such as Bosentan and magnesium sulfate (10). In a study on Sildenafil pharmacokinetics by Rafati *et al*., oral Sildenafil had no side effects in the treatment of neonatal pulmonary hypertension and has been suggested as a safe and inexpensive drug in the treatment of neonatal pulmonary hypertension (11).

According to Lakshminrusimha *et al*., iNO does not have a significant effect in neonates with secondary PPHN due to CDH and BPD. But, pulmonary vasodilators such as Sildenafil and Milrinone cause significant improvement in this population. Their study also showed that: 1. Sildenafil can be used as an adjunctive therapy in iNO-resistant PPHN or to switch a patient from iNo to Sildenafil. 2. Sildenafil can be used when iNO is not available or it is contraindicated. 3. It

can be used to treat PPHN in neonates with CDH and BPD developing PAH (12)

Milrinon is used as a routine treatment in resource limited countries where iNO is not available or is very expensive and ambient, but Due to the availability and cost effectiveness of Sildenafil and the absence of side effects, in the event of being effective in the treatment of neonatal pulmonary hypertension, it may be a good alternative for those with no access to iNO.

The effects of Sildenafil in the treatment of adults and children with pulmonary hypertension have been established, but there is no study about Sildenafil role in neonatal pulmonary hypertension. Moreover, neonatal pulmonary hypertension is very common and the pathophysiology of this disease in neonates (the failure of the pulmonary vascular resistance to normally decrease) is different from the pathophysiology in adults and children. Therefore, this study was aimed to investigate the effect of oral Sildenafil plus Milrinone injection in the treatment of neonatal pulmonary hypertension.

Method

This clinical trial study was aimed to investigate the effect of oral Sildenafil plus intravenous Milrinone on neonatal pulmonary hypertension in NICU wards of Afzalipour hospital in Kerman. The statistical population of this study was all neonates (younger than 28 days), as well as term and late preterm neonates (between 35-40 weeks of gestational age) with high pulmonary arterial pressure according to echocardiography who were admitted to NICU wards of Afzalipour Hospital, Kerman, Iran from March 2018 to March 2019.

The inclusion criteria were gestational age between 35 and 40 weeks, high mean pulmonary arterial pressure assessed by echocardiography and appropriate parental informed consents. Exclusion criteria were the presence of congenital anomalies or structural congenital heart disease at the time of birth and parental refusal to consent for this research.

In order to determine initial outcome, hemodynamic parameters such as blood pressure, FiO_2 and SpO_2 were measured at the beginning of the treatment and then in the post-treatment 24, 48 and 72hours. Echocardiography parameters such as mean PAP, TR gradient, pulmonary artery diameter and TAPSE were determined in the first 24 hours and then 72 hours after the starting of the treatment.

To determine secondary outcome, hospital stay time, duration of mechanical ventilation and mortality rate prior to discharge from hospital were assessed.

According to the previous studies that have evaluated the therapeutic effect of adding oral Sildenafil to the current treatment regimen (3, 5, 7), the total sample size was considered 80 subjects for this clinical trial (13, 14). Therefore, the minimization method was used to have two equal groups in term of study size, which is a non-random method of allocating participants to groups and in many similar studies, this method is a good alternative to classified randomization.

Minimization was performed using "minim" software. Since, in this study, drug interventions were important, so we applied the double-blind method. The parents were blinded about the type of treatment and the pulmonary pressure of neonates was assessed by someone outside the research team.

Neonates with evidence of pulmonary hypertension at birth were identified by a pediatric cardiologist during the first 24 hours of birth and based on echocardiography using the Samsung UGEO HM70 Ultrasound. Then, patients were divided into the intervention and control groups. The control group received only intravenous Milrinone and the intervention group received low dose Sildenafil (3 mg /kg /day) divided into 3 doses plus infusion of Milrinone. For this, 50 milligrams of Sildenafil tablet was dissolved in 10 cc distilled water to obtain a solution with concentration of 5mg in 1cc. Then, the solution was given to neonates via a feeding tube with the size of 8 Fr. Immediately, 10 cc of distilled water was also given for ensuring that therapy solution was administered completely. Echocardiography was performed 72 hours after the intervention in both groups.

Echocardiography parameters that were checked were the pulmonary arterial pressure determined as mean pulmonary artery pressure by using the following formula:

$$\text{Mean PAP} = \frac{\text{PAP (Systolic)} + 2\ \text{PAP(Diastolic)}}{3}$$

and also the pulmonary artery diameter in para sternal short axis views in the diastolic phase, tricuspid regurgitation and right ventricular systolic pressure (RVSP) by using the formula of RVSP = TR pressure gradient + RA pressure to indirectly estimate the degree of pulmonary hypertension.

It is important to mention that pulmonary artery diameter has been used in numerous studies to obtain the severity of pulmonary hypertension by echocardiography (15), and in this study echocardiography was used both before and after the therapy. To evaluate the function of right ventricle, TAPSE by M-mode in apical 4 chamber view was obtained.

No side effects, such as hypotension, were observed. All newborns were also tested for ROP in the 28th day of life and no positive cases were reported.

This study was approved by the Research Ethics Committee (IR.KMU.AH.REC.1398.038) of Kerman University of Medical Sciences and obtained the IRCT code (IRCT20190731044393N1). Before data collection, providing a full explanation of how the research was conducted, and all participants provided written informed consent.

All neonates were evaluated by a checklist that collected demographic information including gestational age, Apgar score in the first and fifth minutes of birth, type of delivery, gender, birth weight, underlying disease, and echocardiographic criteria.

Statistical analysis

Frequency and percentage indices were used to describe the qualitative variables, and the quantitative variables were described using mean and standard deviation. A Mann–Whitney test was utilized for comparisons between the two groups. Data were analyzed through SPSS software (version 25, SPSS, Chicago, IL) and $P< 0.05$ was considered as statistically significant level.

Results

In this study, 80 term and late preterm neonates with pulmonary hypertension were studied. Forty of them were treated with oral Sildenafil in combination with intravenous Milrinone and 40 neonates were treated with intravenous Milrinone alone. The mean age of the mothers was 37.5 ± 1.99

years. The mean weight of the newborns was estimated to be 2666 g with a 95% confidence interval of 2530-2800 g.

Type of delivery was vaginal delivery in 29 newborns (36.3%) and cesarean section in 51 newborns (63.7%)that showed no significant difference in the two groups (p= 0.245). Also, the neonatal resuscitation status was similar in both groups (p = 0.07). The causes of admission in NICU were also investigated that were congenital diaphragm Hernia (CDH) in 4 neonates (5%), idiopathic persistent pulmonary hypertension (PPHN) in 2 neonates (2.5%), respiratory distress syndrome (RDS) in16 neonates (20%), hypoxic ischemic encephalopathy (HIE) in 37 neonates (46.3%), pneumonia in 5 neonates (6.3%) and meconium aspiration syndrome (MAS) in16 neonates (20%).

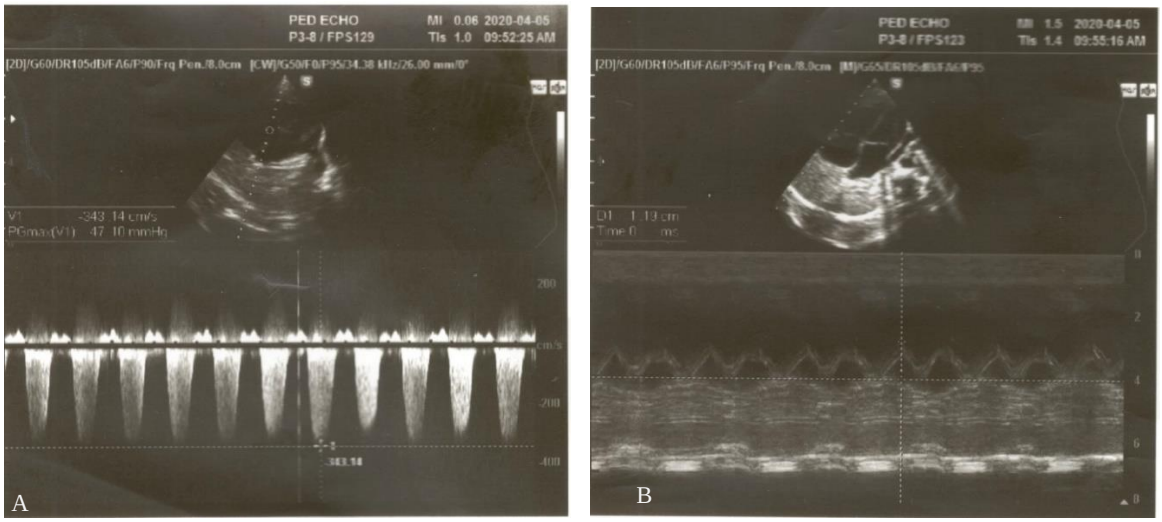

Figure 1. Neonatal echocardiography
A.TR Gradient, B.TAPSE

As it is seen in table 1, mechanical ventilation duration in the intervention group (2.5 days) was significantly (P< 0.0001) lower than that in the control group (10.5 days). Also, hospital stay in the NICU in the intervention group (11.3 days) was significantly (P< 0.0001) lower than that in the control group (20.2days).The difference of TR gradient was significantly (P < 0.0001) higher in the intervention group (59 mm Hg) than in the control group (22 mm Hg); that is, in the second echo after the treatment, the intervention group showed more decrease of TR (Fig 1.A). The mean difference of PAP between the first and second echo was also significantly higher in the intervention group (47.7 mmHg) than in the control group (33.3 mmHg) and showed a significant reduction in the intervention group (P = 0.005). The difference of TAPSE was also significantly lower in the intervention group (33.7) than the control group (47.2), which shows a higher increase in the intervention group (P= 0.009, Fig1.B). The PAD difference was not significant between groups. (P = 0.312, Fig 2).

Also, there was no significant difference in mortality in the intervention group 3 (3.7%) and control group 4 (5%).

Table 1. The comparison of pulmonary artery pressure variables in the two groups

Variable	Control Group (mean)	Intervention Group (mean)	P value
Duration of invasive mechanical ventilation (day)	10.5	2.5	<0.0001*
Duration of hospitalization in NICU (day)	20.2	11.3	<0.0001*
Mean difference of TR	22	59	<0.0001*
Mean difference of PAP	33.3	47.7	0.005*
Mean difference of TAPSE	47.2	33.7	0.009*
Mean difference of PAD	43.11	37.8	0.312

*P<0.05 Significant

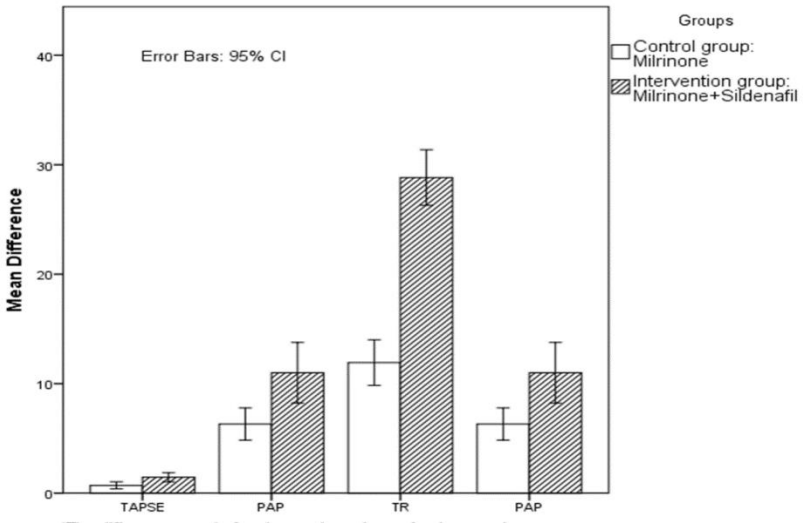

Figure 2. The mean difference of variables based on the first and second echocardiography in the intervention and control groups

Discussion

Examination of pulmonary arterial hypertension in neonates, which happens for various causes such as respiratory distress syndrome, meconium aspiration syndrome, neonatal diaphragmatic hernia, etc., can be performed by non-invasive echocardiography. Several parameters can be studied with this method. In this study, the severity of tricuspid valve regurgitation (TR), mean pulmonary artery pressure (Mean PAP), pulmonary artery diameter (PAD) and right ventricular systolic function by measuring TAPSE were investigated. The same parameters have been considered in previous studies. Decreased pulmonary vascular bed resistance following drug administration improves right ventricular systolic function, which is supported by an increase in TAPSE, and occurs following tricuspid valve regurgitation, reduction in mean pulmonary artery pressure, and eventually pulmonary artery diameter.

Studies comparing the therapeutic efficacy of the combination of Milrinone injection and oral Sildenafil with Milrinone injection alone in infants are limited. Kelly *et al.* paper in Cochrane library about the effects of Sildenafil in the treatment of neonatal hypertension shows a significant decrease

in mortality rate in neonates who were treated with sildenafil compared to placebo group. However, this study did not appreciate any significant differences in the Sildenafil group with groups that were administered other vasodilators such as Milrinone (3). Our study also did not show any significant difference in mortality rates between the intervention and control groups. Kelly et al, study also showed FiO_2 and PaO_2 improvement following using Sildenafil (3). Our study also showed FiO_2, PaO_2 improvement and decrease in the duration of mechanical ventilation after using Sildenafil.

In a study by Lobato et al., 24 adult pigs were anesthetized using isoflurane MAC1 and underwent the mechanically ventilated with FiO_2 = 100. Pulmonary blood flow was measured by perivascular probe ultrasonography. Pulmonary hypertension was induced using the continuous injection of thromboxane analog. Animals were randomly divided into the four groups (n=6): group 1. 50 mg Sildenafil, group 2. Intravenous Milrinone, group 3. Sildenafil followed by Milrinone, and group 4. Placebo injection. The results of this study showed that the mean of PAP was decreased by 37%(P <0.005) in the Sildenafil plus Milrinone group(16).

In a study conducted by Farah P *et al*, a total of 48 postoperative children with pulmonary hypertension in three equal groups (n = 16); Milrinone group received intravenous milrinone, Sildenafil group received oral sildenafil and the Combination group received both medications. Combination of two drugs reduced the risk of rebound pulmonary arterial hypertension after discontinuation of Milrinone (17).

In our study, too, pulmonary arterial hypertension was significantly reduced in the sildenafil plus milrinone group compared with the control group.

Therefore, according to the results of our study, Milrinone in combination with oral Sildenafil can reduce mechanical ventilation duration, duration of hospitalization in NICU, and decrease pulmonary artery pressure compared to intravenous Milrinone alone.

In resource limited countries where iNO is not available, due to the availability and cost effectiveness of Sildenafil and the absence of side effects, it can be a good alternative. The future clinical trial studies should be performed to improve the quality of evidence. Sildenafil can also be evaluated by placebo or iNO. Subsequent double-blind studies are needed to increase the evidence.

Conclusion

The results of our study showed that the combination of intravenous Milrinone and oral Sildenafil reduces mechanical ventilation duration, the hospital stay in NICU, and also, decreases TR gradient and pulmonary artery pressure compared to intravenous Milrinone alone. However, further studies are necessary in order to investigate the association between the consumption of Sildenafil and the treatment of Pulmonary Hypertension in neonates.

References

1. Millman GC. Fanaroff and Martin's neonatal-perinatal medicine diseases of the fetus and infant. Arch Dis Child Fetal Neonatal Ed 2006; 91(6):F468.
2. Fatima N, Arshad S, Quddusi AI, Rehman A, Nadeem A, Iqbal I. Comparison of the efficacy of sildenafil alone versus sildenafil plus bosentan in newborns with persistent pulmonary hypertension. J Ayub Med Coll Abbottabad 2018; 30(3):333-6.
3. Kelly LE, Ohlsson A, Shah PS. Sildenafil for pulmonary hypertension in neonates. Cochrane Database Syst Rev 2017; 8(8):CD005494.
4. Simonca L, Tulloh R. Sildenafil in infants and children. Children (Basel) 2017; 4(7):60.
5. Baquero H, Soliz A, Neira F, Venegas ME, Sola A. Oral sildenafil in infants with persistent pulmonary hypertension of the newborn: a pilot randomized blinded study. Pediatrics 2006; 117(4):1077-83.
6. Limjoco J, Paquette L, Ramanathan R, Seri I, Friedlich P. Changes in mean arterial blood pressure during sildenafil use in neonates with meconium aspiration syndrome or sepsis. Am J Ther 2015; 22(2):125-31.
7. Qasim A, Dasgupta S, Aly AM, Jain SK. Sildenafil use in the treatment of bronchopulmonary dysplasia-associated pulmonary hypertension: a case series. AJP Rep 2018; 8(4):e219-22.
8. Jiang R, Wang L, Zhu CT, Yuan P, Pudasaini B, Zhao QH, et al. Comparative effectiveness of sildenafil for pulmonary hypertension due to left heart disease with HFrEF. Hypertens Res 2015; 38(12):829-39.
9. Hussain AS, Ali R, Ahmed S, Naz F, Haroon A. Oral sildenafil use in neonates with persistent pulmonary hypertension of newborn. J Ayub Med Coll Abbottabad 2017; 29(4):677-80.
10. Narongsak Nakwan, Suksham Jain, Kishore Kumar, Shigeharu Hosono, Majeda Hammoud, Yasser Yahia Elsayed, Shabina Ariff, Babar Hasan, Waqar Khowaja & Woei Bing Poon (2018): An Asian multicenter retrospective study on persistent pulmonary hypertension of the newborn: incidence, etiology, diagnosis, treatment and outcome, The Journal of MaternalFetal & Neonatal Medicine, DOI: 10.1080/14767058.2018.1536740
11. Rafati MR, Shiran MR, Badiee A, Rashidi Ghader F, Saeedi M. Determination of pharmacokinetics properties of sildenafil syrup in pediatric pulmonary hypertension. Journal of Mazandaran University of Medical Sciences 2013; 23(102):9-17. [In Persian].
12. Lakshminrusimha S, Konduri GG, Steinhorn RH. Considerations in the management of hypoxemic respiratory failure and persistent pulmonary hypertension in term and late preterm neonates. J Perinatol 2016; 36(Suppl 2):S12-9.
13. Noordzij M, Tripepi G, Dekker FW, Zoccali C, Tanck MW, Jager KJ. Sample size calculations: basic principles and common pitfalls. Nephrol Dial Transplant 2010; 25(5):1388-93.
14. Copay AG, Subach BR, Glassman SD, Polly DW Jr, Schuler TC. Understanding the minimum clinically important difference: a review of concepts and methods. Spine J 2007; 7(5):541-6.
15. Augustine DX, Coates-Bradshaw LD, Willis J, Harkness A, Ring L, Grapsa J, et al. Echocardiographic assessment of pulmonary hypertension: a guideline protocol from the British Society of Echocardiography. Echo Res Pract 2018; 5(3):G11-24.
16. Lobato EB, Beaver T, Muehlschlegel J, Kirby DS, Klodell C, Sidi A. Treatment with

phosphodiesterase inhibitors type III and V: milrinone and sildenafil is an effective

17. Farah P, Ahmad-Ali A, Hanane G, Abbas E. Additive effect of phosphodiesterase inhibitors in control of pulmonary hypertension after congenital cardiac surgery in children. Iran J Pediatr 2013; 23(1):19-26.