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ORIGINAL ARTICLE

Milrinone usage in a neonatal intensive care unit: Indications, side effects, and outcomes

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ABSTRACT

Objective: We aimed to evaluate the indications, side effects, and outcomes of milrinone infusion in neonates.

Material and Methods: Twenty-five neonates, who were admitted to the neonatal intensive care unit and received milrinone infusion between January 2015 and June 2019, were retrospectively evaluated.

Results: The mean birth weight and gestational age of the neonates were 2220±1020 g and 35±4 weeks, respectively. The indications for milrinone infusion included pulmonary hypertension (PH) (n=14, 56%), low cardiac output syndrome (LCOS) (n=10, 40%), and post-ligation syndrome (n=1, 4%). Hypotension was the most common clinical side effect (n=9, 36%), thrombocytopenia (n=7, 28%), and azotemia (n=5, 20%) which were the most common laboratory side effects. The mortality rate was higher among the neonates who had PH (n=12, 85.8%) compared to those who had LCOS (n=4, 40%). The mean vasoactive inotropic score was higher (79.5±74.48) in the neonates with LCOS who died compared to the ones who survived (45±29.6).

Conclusion: The most common indication for milrinone was PH, the most common clinical side effect was hypotension, and the most common laboratory side effect was thrombocytopenia. Close monitoring of blood pressure, thrombocyte count, and renal function tests should be performed in patients receiving milrinone. Milrinone was found to be more successful in treating LCOS compared to treating PH. The increased need for inotropic support while receiving milrinone was associated with high mortality.

Keywords: Low cardiac output syndrome, milrinone, post-ligation cardiac syndrome, pulmonary hypertension.

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INTRODUCTION

Milrinone is a selective phosphodiesterase III inhibitor, exerts vasodilator effect on pulmonary and systemic vessels, improves diastolic functions of the heart, and shows inotropic effect.[1–3] The use of milrinone in the neonatal period is controversial and has not yet been approved by the Food and Drug Administration, but its usage is increasing in neonatal intensive care units (NICU).[1–3] Indications for use of milrinone in the neonatal period include pulmonary hypertension (PH), post-ligation syndrome, and hypotension treatment in extremely premature neonates.[1–6] Although no sufficient evidence of the effectiveness of milrinone in preventing death or low cardiac output syndrome (LCOS) is shown in children undergoing surgery for congenital heart disease, milrinone is known to be the first choice drug to prevent and treat LCOS before open heart surgery for children.[7–9] In this study, we aimed to evaluate the indications, side effects, and outcomes of milrinone infusion in our NICU.

MATERIAL AND METHODS

This was a clinical, cross-sectional, and retrospective study. The neonates, who were admitted to a Maternity and Children's Training and Research Hospital NICU and received milrinone infusion between January 2015 and June 2019, were evaluated. The Local Ethics Committee approval was obtained for the study. Data were collected for the following variables: gender, type of birth, birth weight, gestational age, echocardiographic findings, indications for milrinone infusion, concomitant inotropic support (dopamine, dobutamine, adrenaline, and noradrenaline) and/or concomitant pulmonary vasodilator treatments (inhaled nitric oxide [iNO], intravenous iloprost, and inhaled iloprost), side effects, and duration and outcome of milrinone infusion. Side effects were classified as clinical or laboratory side effects as mentioned in the literature.[1] Clinical side effects included hypotension requiring inotropic support or increased need for inotropic support, tachycardia, arrhythmia, patent ductus arteriosus (PDA) requiring occlusion therapy, intraventricular hemorrhage, seizures, shivering, necrotizing enterocolitis, bowel perforation, diffuse intravascular coagulation, and rash. Laboratory side effects included hypokalemia, azotemia, elevated liver enzymes (more than two-fold the age-appropriate normal values), cholestasis, and thrombocytopenia. Side effects were recorded if they occurred while receiving milrinone infusion. Venous blood biochemical tests and complete blood count were evaluated daily in all neonates who were receiving milrinone. Treatment indications of milrinone infusion and concomitant treatments were compared between the neonates who died and who survived Outcomes of the neonates and concomitant treatments were assessed in terms of milrinone indications.

Milrinone Dosing

Regardless of whether patients were receiving inotropic support or not, milrinone infusion was initiated at a dose of 0.5 mcg/kg/min after blood pressure was confirmed to be within the normal range according to gestational age. A loading dose of milrinone was not administered to minimize the risk of systemic hypotension.

Pulmonary Hypertension

PH was suspected in the presence of hypoxic respiratory failure despite optimal respiratory support and diagnosed by echocardiography. The neonates were diagnosed with PH if they had one or more of the following echocardiographic findings: Enlargement of the right heart chambers, left-sided deviation of the interventricular septum, tricuspid regurgitation and right-to-left or bidirectional shunting across patent foramen ovale, and PDA.[9] Systolic pulmonary artery pressure (SPAP) was determined by echocardiography. The pressure difference between the right ventricle and the right atrium was measured using the tricuspid regurgitation jet, and the right atrial pressure estimated was added to obtain the SPAP. Based on collapse of the inferior vena cava, the right atrial pressure estimated was assumed to be 5, 10, 15, or 20 mmHg.[10] In infants with PH, right and left ventricular function might be compromised due to increased right ventricular afterload and decreased left ventricular preload, and milrinone was effective in improving biventricular dysfunction.[11] In late preterm and term neonates, the primary treatment modality was iNO after a diagnosis of PH was made.[12] Inhaled iloprost and intravenous iloprost were initiated simultaneously for the treatment of iNO resistant cases. For neonates born before 34 weeks of gestation, intravenous iloprost and inhaled iloprost were used for the treatment of PH instead of iNO. Milrinone infusion was started in patients who were resistant to iNO, intravenous iloprost, and inhaled iloprost to both dilate pulmonary blood vessels and improve the ventricular functions in the neonates with PH.

Low Cardiac Output Syndrome

LCOS was defined as lactic acidosis (lactate >3 mmol/L or an increase of at least 2 mmol/L compared to the baseline value) and/or urine output <1 mL/kg/h in neonates with a cardiac index of <2.2 L/min/m^2 determined by Doppler echocardiography or the addition of a new vasoactive inotrope to the treatment to correct hypotension or a vasoactive inotropic score (VIS) above 15.[7,13] VIS was calculated as follows:

VIS=inotrope score (IS) + 10×milrinone dose (μg/kg/min) + 10,000×vasopressin dose (U/kg/min) + 100×norepinephrine dose (μg/kg/min); IS=dopamine dose (μg/kg/min) + dobutamine dose (μg/kg/min) + 100×epinephrine dose (μg/kg/min).[14]

As severe PH might also be a cause of LCOS, the neonates with both PH and LCOS were planned to be included only in the PH group.

Post-Ligation Cardiac Syndrome

Post-ligation cardiac syndrome is clinically characterized by systolic hypotension requiring inotropic therapy and/or oxygenation failure, usually occurring 8–12 h after PDA ligation.[15] Milrinone infusion was initiated after post-ligation cardiac syndrome was detected.

NICU Protocol for Management of Hypotension in Neonates

We used the Turkish Neonatal Society "Neonatal hemodynamics and management of hypotension in newborns" quideline to detect and manage hypotension.[16] Non-invasive blood pressure measurements were performed hourly using proper cuffs. In addition to blood pressure measurement, the decision to start inotropic therapy was made

Table 1: Demographic data, diagnoses, and concomitant treatments of the neonates who received milrinone infusion (n=25)

Demographic data	
Birth weight, g, mean±SD	2220±1020
Gestational age, week, mean±SD	35±4
Male, n (%)	12 (48)
Cesarean, n (%)	20 (80)
Treatment indications, n (%)	
Pulmonary hypertension	14 (56)
Low cardiac output syndrome	10 (40)
Post-ligation syndrome	1 (4)
Treatment duration, day, median (IQR)	3 (1–5)
Concomitant inotropic support, n (%)	
No inotrope	2 (8)
Single inotrope	4 (16)
Two inotropes	4 (16)
Three inotropes	7 (28)
Four inotropes	8 (32)
Concomitant pulmonary vasodilator support, n (%)	
Inhaled iloprost	3 (12)
Intravenous and inhaled iloprost	4 (16)
Inhaled nitric oxide, intravenous, and inhaled iloprost	8 (32)

IQR: Interquartile range; SD: Standard deviation.

considering clinical and echocardiographic findings, and inotropic agents were titrated hourly according to clinical and echocardiographic findings.[16] The treatment plans of the inotropes were made on a case-by-case basis. Dopamine, dobutamine, adrenaline, and noradrenaline were the preferred inotropes.

Statistical Analysis

The Statistical Package for the Social Sciences version 21.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. The normality was assessed using descriptive statistics and Kolmogorov–Smirnov test. Categorical variables were expressed as frequency and percentage. Normally distributed continuous variables were expressed as mean±standard deviation (SD) and non-normally distributed variables were expressed as median (interquartile range [IQR] p25-p75). Chi-square test was performed for categorical variables. $P<0.05$ was considered statistically significant.

RESULTS

During the study period, 3798 neonates were admitted to NICU, and 25 (6.6/1000) of them received milrinone infusion. The mean birth weight and gestational age of the neonates were 2220±1020 g and 35±4 weeks, respectively. Of the neonates exposed to milrinone, 17 (68%) died before discharge. The indications for milrinone infusion included PH (n=14, 56%), LCOS (n=10, 40%), and post-ligation syndrome (n=1, 4%). The duration of milrinone infusion was 3 days (IQR 1–5). The demographic data, diagnoses, and concomitant treatments of the neonates, who received milrinone infusion, are presented in Table 1.

Table 2: Side effects of milrinone infusion (n=25)

Side effects	n	%
Hypotension	9	36
Tachycardia	3	12
Hemodynamically significant patent ductus arteriosus	2	8
Hypokalemia		
Potassium <3 mmol/L	1	4
Thrombocytopenia		
Platelet <100.000/mm^3	7	28
Azotemia		
Blood urea nitrogen >70 mg/dl and/or creatine >1.7 mg/dL	5	20

Side effects of milrinone infusion are shown in Table 2. The mean platelet count was found to be 52000/mm^3 (35000–65000) in the patients who had thrombocytopenia. After initiation of milrinone, the treatment was stopped in a period shorter than 24 h due to inotrope resistant hypotension in three patients and due to tachycardia in one patient.

The diagnoses and concomitant treatments of the neonates who died and who survived are presented in Table 3. The frequency of the neonates with PH who died was found to be significantly higher (n=12, 70%) compared to the ones who survived (n=2, 25%), while the frequency of the neonates with LCOS who survived was significantly higher (n=6, 75%) compared to the ones who died (n=4, 23.5%) (p=0.03; p=0.01, respectively). The mortality rate was higher among the neonates with PH (n=12, 85.8%) compared to those with LCOS (n=4, 40%). All eight neonates who needed four inotropes died. All eight neonates with PH who needed both iNO and intravenous and inhaled iloprost also died.

The underlying diagnoses, outcomes, and concomitant medications of the neonates with PH are presented in Table 4. Only one of three neonates (33%) diagnosed with primary PH and one of 11 neonates (9%) diagnosed with secondary PH survived. The etiology of secondary PH was as follows: Congenital diaphragmatic hernia, asphyxia, fetal anemia, critical congenital heart disease, and pulmonary hypoplasia.

Underlying diagnoses, outcomes and VIS of the neonates with LCOS are presented in Table 5. Two neonates with post-operative LCOS (100%), three neonates with pre-operative LCOS (60%), and one neonate with non-operative LCOS (33%) survived. The mean VIS of the neonates with LCOS who died was higher (79.5±74.48) compared to the ones who survived (45±29.6) (p value could not be calculated). One patient with congenital heart disease received short-term inhaled iloprost due to the clinical finding suggesting PH until PH was excluded by echocardiography.

Table 3: Diagnoses and concomitant treatments of the neonates who died and who survived

	Died n=17 (68%)		Survived n=8 (32%)		p
	n	%	n	%	
Diagnoses					
Pulmonary hypertension	12	70.6	2	25	**0.03**
Low cardiac output syndrome	4	23.5	6	75	**0.01**
Post-ligation syndrome	1	5.9	–	–	–
Concomitant treatments					
No inotrope	1	5.9	1	12.5	0.56
Single inotrope	1	5.9	3	37.5	**0.04**
Two inotropes	2	11.8	2	25	0.39
Three inotropes	5	29.4	2	25	0.8
Four inotropes	8	47	–	–	–
Inhaled iloprost	1	5.9	2	25	0.16
Intravenous and inhaled iloprost	3	17.6	1	12.5	0.74
Inhaled nitric oxide, intravenous, and inhaled iloprost	8	47	–	–	–

Table 4: Underlying diagnoses, outcomes, and concomitant medications of the neonates with pulmonary hypertension (n=14)

	n	%	Survived		Dop		Dob		A		NA		iNO, int. and inhaled ilioprost		Int. and inhaled ilioprost	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%
Primary PH	3	21.4	1	33	3	100	1	33	1	33	1	33	2	66	1	33
CDH	2	14.3	–	–	1	50	1	50	1	50	1	50	1	50	1	50
Asphyxia	4	28.7	–	–	4	100	4	100	4	100	4	100	2	50	2	50
Fetal anemia	2	14.3	–	–	2	100	2	100	2	100	1	50	2	100	–	–
CCHD	2	14.3	1	50	2	100	2	100	2	100	–	–	1	50	–	–
Pulmonary hypoplasia	1	7	–	–	1	100	1	100	1	100	1	100	–	–	–	–

A: Adrenalin; CCHD: Critical congenital heart disease; CDH: Congenital diaphragmatic hernia; Dob: Dobutamin; Dop: Dopamin; iNO: Inhaled nitric oxide; NA: Noradrenalin; Int: Intravenous; PH: Pulmonary hypertension.

DISCUSSION

In our study, the frequency of the use of milrinone in NICU was higher compared to the frequencies reported in the literature (6.6/1000 vs. 4/1000).[1] In a study conducted by Samiee-Zafarghandy et al., [1] it was emphasized that the proportion of the infants exposed to milrinone increased from 0 in 1997 to 4/1000 infants in 2010. As our data were newer, we might have found the frequency of milrinone use to be higher and use of milrinone in NICUs might have been still increasing. In our study, the mortality rate (68%) was higher compared to the rates reported in the literature (8%).[1] The reason of the high mortality rate in our study might be that we evaluated the total mortality rate not just during the first course of milrinone infusion but during the hospital stay. Another reason of this high mortality rate might be that we started milrinone as a resque treatment in patients with PH, who accounted for 12 of 17 patients who died. In fact, none of the deaths could be directly attributed to milrinone infusion. We found that the most common indication for milrinone was PH, the most common clinical side effect was hypotension, and the most common laboratory side effect was thrombocytopenia in line with the existing literature.[1] Although we did

Table 5: Underlying diagnoses, outcomes and vasoactive inotropic scores of the neonates with low cardiac output syndrome (n=10)

	LCOS	Survived	VIS
Critical aortic stenosis	Post-operative	Yes	55
Hypoplastic left heart syndrome	Pre/post-operative	Yes	15
Atrial septal defect and tricuspid regurgitation	Pre-operative	Yes	45
Supraventricular tachycardia	Non-operative	Yes	45
Tricuspid and mitral regurgitation	Pre-operative	Yes	15
Atrial septal aneurysm, cardiac hypertrophy	Pre-operative	Yes	95
Dilated cardiomyopathy	Non-operative	No	15
Ventricular septal defect, pulmonary atresia	Pre-operative	No	145
Tetralogy of fallot and congenital diaphragmatic hernia	Pre-operative	No	143
Elevated lactate level, impaired capillary refill	Non-operative	No	15

LCOS: Low cardiac output syndrome; Op: Operative; VIS: Vasoactive inotropic score.

not administer a loading dose to minimize the risk for low blood pressure, hypotension requiring inotropic support or increasing the need for inotropic support was the most common side effect within the first 24 h after treatment initiation. It was observed that deep hypotension requiring four inotropic drugs resulted in 100% mortality.

In our study, milrinone was found to be more successful in treating LCOS compared to treating PH. We speculated that milrinone could be preferably used in the neonatal period for its inotropic effects on the heart rather than pulmonary vasodilator effect. Milrinone has been shown to improve oxygenation index and myocardial performance in the primary PH without leading to systemic hypotension in neonates with poor response to iNO.[4,17,18] Although there are many case series showing that milrinone is effective in the primary PH, its success in the secondary PH is controversial. In one study, milrinone was found to improve left ventricular systolic and diastolic functions and oxygenation index in the secondary PH.[19] On the other hand, the beneficial effect of milrinone could not be demonstrated in another study.[20] According to our findings, milrinone infusion seemed to be more effective for treating primary PH compared to treating secondary PH. The high mortality rate in neonates with PH might be caused by late addition of milrinone to the treatment of PH as a rescue treatment or by the fact that the underlying diagnoses of PH in our patients were intractable to respond milrinone. A randomized controlled study investigating the effects of milrinone infusion on the duration of iNO use, myocardial function, and invasive ventilation duration in neonates >34 gestational weeks and >2000 g, is still going on.[21]

Studies evaluating the efficacy and safety of milrinone in LCOS included mainly pediatric patients undergoing cardiac surgery. Although the efficacy and safety of milrinone to prevent and treat LCOS among neonates, infants, and children are still uncertain, it is being widely used in this group of patients.[7–9,22,23] We could not find any literature evaluating efficacy and safety of milrinone for non-operative neonatal LCOS. In our study, it was remarkable that the rate of survival was higher in post-operative LCOS (2/2; 100%), compared to pre-operative (3/5; 60%) and non-operative LCOS (1/3; 33%). We also found that high VIS was associated with mortality among neonates with LCOS. The higher need for concomitant inotropic support could be considered to reflect worse clinical status and therefore, poor prognosis for LCOS. The underlying diagnoses of LCOS in our patients were not homogenous to make a conclusion to use milrinone for a specific group of patients, but it could be concluded that milrinone was effective for neonates with LCOS by way of inotropic properties.

Milrinone was shown to reduce the incidence of respiratory failure and the need for inotropes and improve the recovery of the left ventricular systolic function after surgical PDA closure,[24–26] though this findings were not proved by subsequent studies.[27,28] In our study, one patient, who was clinically diagnosed with post-ligation cardiac syndrome and received milrinone postoperatively, was lost on the 5th day of milrinone infusion.

Study Limitations

Our study has some methodological limitations. The most important limitations of our study included its retrospective design and small sample size. Second, the heterogeneous patient group did not allow us to make clear conclusions about the efficacy of milrinone for certain indications. Third, it was difficult to come up with a single treatment algorithm for neither inotrope treatment nor milrinone. Since the included patients were those with the worst clinical condition and had limited time to wait to be kept alive, we did not hesitate to aggressively initiate inotropes to achieve normotension before starting milrinone infusion. Finally, we could not determine whether the high mortality rate was a result of milrinone infusion as we took the whole in-hospital mortality into account to assess the mortality rate.

CONCLUSION

Although uncertainties regarding the efficacy and safety of the use of milrinone in the neonatal period continue, it can be a useful drug in selected patient groups, considering its mechanism of action. We confirmed that close monitoring of blood pressure, thrombocyte count, and blood biochemical values, especially renal function tests, should be performed in patients receiving milrinone. We also found that milrinone was more successful in treating LCOS than treating PH, more effective for the primary PH than secondary PH, and it

was also remarkable that the rate of survival was higher in post-operative LCOS compared to pre-operative and non-operative LCOS. Whatever the underlying etiologies are, neonatal PH and LCOS are both hard-to-treat conditions, and the most suitable treatment for these conditions should be decided on a case-by-case basis until evidence-based treatment protocols are achieved.

Statement

Ethics Committee Approval: The Zeynep Kamil Maternity and Children's Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 20.01.2021, number: 24).

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