Comparison of the Efficacy of Inhaled Versus Infused Milrinone in the Management of Persistent Pulmonary Hypertension in Infants in Resource-Limited Settings A Randomized Clinical Trial

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Research article

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Abstract

Background: Standard treatment of persistent pulmonary hypertension in neonates (PPHN) is inhaled nitric oxide (iNO), which is not available in Iran. Consequently, other drugs such as milrinone are prescribed. So far, no study has investigated the effect of inhaled milrinone on the management of PPHN.Our study was designed for better management of PPHN in the absence of iNO.

Methods: In this randomized clinical trial, neonates with PPHN admitted Neonatal intensive care unit of Hazrat Ali Asghar and Akbarabadi hospitals were treated with intravenous dopamine infusion and randomly divided into two groups receiving injectable and inhaled milrinone. Neonates were evaluated by Doppler echocardiography, clinical status, and oxygen demand. Patients were also evaluated for clinical symptoms and mortality during follow-up.

Results: A total of 31 infants with median age of 2 days (IQR: 4) were studied. There was a significant decrease in peak and mean pulmonary arterial pressure in both inhalation and infusion group following milrinone administration, with no statistical difference. (P=0.584 and 0.147, respectively). There was no significant difference among the frequency of tricuspid regurgitation and systolic blood pressure before and after treatment among two groups. Diastolic blood pressure was significantly lower in infusion group after treatment (P=0.020), however, the amount of decrease was not statistically significant among two groups (P=0.928). Overall, 83.9% achieved full recovery, of which 75% were among infusion groups while 93.3% were among inhalation group. (P=0.186)

Conclusion: Inhaled milrinone can have similar effects with injected milrinone as an adjunct in the management of PPHN. Also, the results indicate similar safety for both intravenous and inhaled prescriptions. .

Trial registration: IRCT code of this RCT trial is iIRCT20220130053890N1 and its Ethical verification code is IR.IUMS.FMD.REC.1400.493.

Background

The inability of the pulmonary circulation to carry out the processes of transferring the neonates to the ectopic environment leads to persistent pulmonary hypertension (PPHN), which results in increased pulmonary/systemic vascular resistance due to vasoconstriction, structural deformation of the pulmonary arteries, or intravascular obstruction. According to the etiology, PPHN is divided into two categories: primary (idiopathic), accounting for 10 to 20% of cases, and secondary. It indicates the absence of lung parenchymal disorder to explain the increase in pulmonary arterial pressure. If the cause of PPHN is lung parenchymal disorder like pneumonia it will called secondary [1]. PPHN is usually associated with systemic hypotension and decreased cardiac output due to increased right ventricular afterload and myocardial insufficiency [2, 3].

Management of neonates with PPHN includes maintenance therapy to maintain normal body temperature, serum electrolytes, intravascular volume, acid-base balance, analgesia, ventilation, and oxygenation[4]. Timely administration of inotropic and vasoactive drugs can increase cardiac output, maintain adequate blood pressure, and improve oxygen delivery [4]. The standard routine treatment for PPHN in reference books is inhaled nitric oxide (iNO) [5, 6], which unfortunately is not available in Iran; Therefore, other treatments are used in different medical centers, depending on the condition of the neonate and the decision of the treating physician. Available treatments in Iran include oral sildenafil, dobutamine, furosemide, and other inotropes and diuretics. In the absence of iNO, all medical centers in the country are forced to manage PPHN by a combination of available treatments including systemic blood pressure boosters, pulmonary arterial blood pressure reducers, supplemental oxygen, and intermittent mechanical ventilation.

Milrinone is a phosphodiesterase III inhibitor that has been shown to reduce filling pressure and reduce systemic and pulmonary arterial pressure by a mechanism of vasodilation and is among the drugs used in the absence of iNO [7]. Milrinone is part of Iran's Pharmacopoeia and is produced in the country by different pharmaceutical companies with the same quality and effectiveness and approved by the Food and Drug Administration. This drug is administered through intravenous infusion, and its indications for neonatal administration include acute management of low cardiac output following any underlying cause, including septic shock and PPHN [8]. This drug is also a pulmonary vasodilator and therefore can be used as adjunctive therapy along with iNO to

improve management of PPHN. Recent studies have used inhaled milrinone for the management of pulmonary artery hypertension after heart surgery in children with congenital heart disease [9]. Studies in adults have also used inhaled milrinone to reduce pulmonary hypertension after heart surgery [10–13] and to reduce pulmonary hypertension due to mitral valve stenosis [14].

The high expense of iNO makes it unavailable in developing nations, as does advanced ventilator assistance like extracorporeal membrane oxygenation (ECMO). This has forced a search for less expensive but effective medications that will allow newborns with PPHN to be stabilized [15].Furthermore, the rising cost and requirement for specialized delivery equipment make it a non-viable option in many developing countries, where both the incidence and mortality of PPHN are suspected to be higher. Clinical trials of alternative/adjunctive pulmonary vasodilator therapies have been conducted as a result of these considerations[16].

Since, until the date of our report, no studies have yet investigated the effect of adding injectable and inhaled milrinone to intravenous dopamine in the management of PPHN, the present study was designed to supplement previous studies and assist physicians in better management of this complication in neonates. It should be noted that milrinone is not a standard treatment for PPHN and is used only in the absence of iNO. Therefore, this study prescribes milrinone as an adjuvant drug added to intravenous dopamine in one of two models of intravenous injection or inhalation.

Method And Materials

In this randomized clinical trial study, neonates 1 to 28 days with PPHN hospitalized in the Neonatal intensive care unit of Hazrat Ali Asghar and Akbarabadi hospitals, affiliated by Iran University of Medical Sciences were included. Demographic information, underlying diseases, vital signs at baseline, and clinical examination findings were recorded in a checklist for each case. Diagnosis of PPHN was performed by color Doppler echocardiography using Bernoulli formula and neonates with pulmonary artery pressure greater than 40 mm Hg was considered as PPHN.

The exclusion criteria consisted of neonates with congenital heart disorders, diaphragmatic hernias, pulmonary abnormalities, as well as neonates who are candidates for major surgery to eliminate abnormalities. Expected side effects of this drug include increased heart rate, arrhythmias, systemic hypotension, and thrombocytopenia (a rare complication). Therefore, in case of hypotension (under the 10% quantile), arrhythmia, heart rate above 220 beats per minute, and thrombocytopenia, the neonate was excluded from the study, and supportive care measures were started.

We ensure quality and integrity of our research. We obtained informed consent from the parents of all infants participating in our study. We respect the confidentiality and anonymity of our research respondents. We guarantee that the infants participated in the study voluntarily and according to their parents' wishes. We also avid any harm to our participants. There is no conflict of interest in this study and we didn't get any financial support for this research. IRCT code of this RCT trial is iIRCT20220130053890N1 and its Ethical verification code is IR.IUMS.FMD.REC.1400.493.

All infants were treated with intravenous dopamine infusion at a dose of 5 macro/kg body weight per minute (injection time was 3 to 5 days, depending on the decision of the attending physician). The neonates were then divided into two groups through random allocation, receiving either infusion or inhaled milrinone. In the infusion group, 0.3 to 0.5 micrograms per kilogram body weight per minute of milrinone (Stragen UK Ltd Company) was administered as a continuous intravenous infusion and continued until the symptoms improve or appear (respiratory distress or increased oxygen demand). Patients in the inhaled milrinone group received 50 micrograms per kilogram bodyweight of inhaled milrinone (Stragen UK Ltd Company) for 10 minutes at a frequency of twice daily compared to the effectiveness of inhaled and injectable milrinone in the management of PPHN. During treatment, the infant was constantly monitored for heart rate and rhythm, intravascular pressure, urine output, peripheral perfusion, and intravenous injection site.

Neonates were evaluated by Doppler echocardiography at the start of the study and pulmonary artery systolic pressure was measured. Echocardiography was repeated for the first 24 hours for all infants, followed by echocardiography 24 hours after treatment or presenting signs of respiratory distress or increased need for oxygen. Echocardiographic examinations were performed by a pediatric echocardiologist, who was blinded to the treatment groups. M-mode, two-dimensional, and color Doppler echocardiography and Bernoulli formula were used to measure pulmonary artery pressure. Neonates were also evaluated for the

presence of tricuspid regurgitation (TR) and the presence or absence of this valvular insufficiency was reported in them with mild, moderate, and severe scales. Symptoms of respiratory distress and increased oxygen demand were assessed and recorded, and patients were evaluated for clinical symptoms and mortality during three months of follow-up.

Data were entered into Statistical Package for Social Sciences (SPSS Inc., Chicago, Illinois, USA) version 21 software and subsequently analyzed. The normality of the distribution of data was initially checked with the Kolmogorov-Smirnov test. The collected data were summarized as means ± standard deviation (SD) or medians with interquartile ranges (IQR). For particular variables, the percentage of patients in each group was calculated. Unpaired Student's t-test, chi-square test, or Fisher's exact test were used to compare the characteristics of patients as appropriate. A P-value of less than 0.05 was considered as indicating statistical significance. Sample size estimation was performed based on a study by Abd Elbaser et al [17], and by considering an $\alpha = 0.05$ and $\beta = 0.2$, a sample size of 14 patients in each group was estimated.

Results

A total of 31 infants with a median age of 2 days (IQR: 4; range 1–20) which of them 21 (67.7%) were males. These subjects were randomly distributed among the inhalation and infusion groups. Figure 1 demonstrates the consort chart of our study.

There was no significant difference among the two groups regarding gender, weight, gestational age, mother underlying disease, and patent ductus arteriosus (PDA). However, the median age of the patients in the infusion group was lower than the inhalation group (P = 0.019). Table 1 demonstrates the clinical features of the patients in our study.

Table 1
Clinical features of infants with persistent pulmonary hypertension undergoing treatment with milrinone infusion or inhalation.

Variable		Total	Group; *N = 31*		P-value*
			Inhalation; *n = 15*	infusion; *n = 16*	
Age (days); median [IQR] (range)		2 [4] (1–20)	4 [5] (1–20)	1.5 [1] (1–15)	0.019
Gender; n (%)	Male	21 (67.7)	12 (80)	9 (56.3)	0.152
	Female	10 (32.3)	3 (20)	7 (43.8)	
Weight (gr); mean ± SD (range)		2691 ± 793 (950–4600)	2629 ± 861 (950–3730)	2753 ± 744 (1600–4600)	0.677
Gestational age (weeks); mean ± SD (range)		36.09 ± 3.41 (29–43)	35.67 ± 4.03 (29–43)	36.5 ± 2.78 (32–41)	0.506
Mother underlying disease		5	1	4	0.186
Patent Ductus Arteriosus		3.19 ± 1.39 (0–4.5)	3.16 ± 1.41 (0–4.5)	3.22 ± 1.41 (0–4.5)	0.919
Outcome	Recovery	26 (83.9)	14 (93.3)	12 (75)	0.186
	O_2 dependent	5 (16.1)	1 (6.7)	4 (25)	0.186
	Deceased	5 (16.1)	1 (6.7)	4 (25)	0.186

* Mann-Whitney, independent sample t-test or Fisher's exact test.

A total of two mothers had gestational diabetes and both of their infants were in the intravenous infusion group. Also, three mothers had gestational hypertension, of which two cases were in the intravenous infusion group (12.5%) and 1 case was in the inhalation group (6.7%). Another patient had hypothyroidism whose infant was in the intravenous infusion group. The frequency of each of the mentioned disorders was not significantly different between the two groups (P > 0.05). Also, the frequency of any underlying disorder in the mother was no significant difference between the two groups. (Four in the intravenous group and one in the inhalation group; P = 0.186)

The patients' features were also evaluated before and after intervention among the groups. There was a significant decrease in the peak and mean pulmonary arterial pressure in both the inhalation and infusion group following milrinone administration. However, the amount of decrease was not statistically different among the two groups. (P = 0.584 and 0.147, respectively). There was no significant difference among the frequency of TR, and also the systolic blood pressure before and after treatment among the two groups. The diastolic blood pressure was significantly lower in the infusion group after treatment (P = 0.020), however, the amount of decrease was not statistically significant among the two groups (P = 0.928). Table 2 demonstrates the clinical features of infants before and after infants with persistent pulmonary hypertension before and after treatment with infusion or inhalation of milrinone. [Table 2. Clinical features of infants before and after infants with persistent pulmonary hypertension before and after treatment with infusion or inhalation milrinone.

Table 2
Clinical features of infants before and after infants with persistent pulmonary hypertension before and after treatment with infusion or inhalation milrinone.

Variable		Inhalation; *n = 15*				Infusion; *n = 16*				P-value of before; after; and change
		Before	After	Change	P-value	Before	After	Change	P-value	
Peak pulmonary arterial pressure		49.73 ± 9.9	37.20 ± 10.4	-12.53 ± 5.5	< 0.001	61.53 ± 11.5	47.53 ± 9.9	-14.0 ± 8.7	< 0.001	**0.003**; **0.009**; 0.584
Mean pulmonary arterial pressure		32.40 ± 6.5	22.13 ± 7.6	-10.27 ± 4.3	< 0.001	35.93 ± 6.7	28.40 ± 7.2	-7.53 ± 5.7	< 0.001	0.130; **0.028**; 0.147
Tricuspid regurgitation	Mild	5 (33)	3 (20)	− 2	0.194	9 (56)	9 (56)	0	0.531	0.556; 0.162; 0.472
	Moderate	6 (40)	4 (27)	− 2		5 (31)	3 (19)	− 2		
	Severe	1 (7)	1 (7)	0		1 (6)	1 (6)	0		
Blood pressure	Systolic	74.80 ± 8.9	71.13 ± 5.4	-3.67 ± 6.2	0.077	71.69 ± 7	67.69 ± 9.1	-4 ± 9.9	0.128	0.288;0.216;0.911
	Diastolic	47.33 ± 9.3	40.94 ± 8.5	-1.67 ± 8	0.445	40.12 ± 13.5	38.06 ± 8.7	-2.07 ± 14	0.445	0.097; **0.020**; 0.928

P-values calculated based on Fisher's exact test or independent sample t-test.

Bold values indicator of significant association.

Overall, 26 out of 31 (83.9%) achieved full recovery, in which 12 (75%) were among the infusion groups while 14 (93.3%) were among the inhalation group. The five deceased patients all required oxygen therapy, in which the majority were among the infusion group (25%). However, there was no statistically significant difference among the two groups regarding the patient's outcome. (P = 0.186)

Discussion

The primary or idiopathic type of PPHN accounts for only 10 to 20% of all PPHN cases, while 80 to 90% of PPHN cases are secondary to an underlying disorder[(1)]. Many studies include both primary and secondary PPHN in their reports; while in our study, we included primary PPHN cases; Therefore, it can be stated that the present study had a more homogeneous statistical population eliminating the cofounding factor of etiology in the results. Also, secondary PPHN has a worse prognosis than primary PPHN. Also, there was no significant difference among our groups regarding sex, gestational age, and mothers' history of diabetes, which are all risk factors for PPHN[(18)]. Also, we performed serial echocardiography among our patients since studies have linked repeated echocardiographic findings to the prognosis of PPHN [(19)]. According to the results, inhaled milrinone can have similar effects with injected milrinone as an adjunct in the management of PPHN. Also, the results indicate similar safety for both intravenous and inhaled prescriptions.

Therapeutic effects of injectable milrinone as an adjuvant to other therapies (including iNO) have been reviewed and validated in previous studies. In a review article, Qasim et al[4] .reviewed six studies on the effect of injectable milrinone in the management of PPHN, in which all reported a positive effect of injectable milrinone in the treatment of PPHN. The dose of milrinone in three of the studies was 50 µg / kg bolus and then 0.33 µg / kg/min infusion, while in three studies without bolus and with an infusion rate of 0.99 – 0.33 µg / kg. Injectable milrinone in our study was administered as an intravenous infusion at a dose of 0.5 – 0.3 µg / kg/min. Furthermore, all of these studies examined term neonates, with a limited sample size of 4 to 17 neonates [20–23].

Although the standard treatment for PPHN in reference books includes iNO [5, 6], PPHN is resistant to iNO in some cases. Mat Bah et al. reported that iNO resistance worsens the prognosis of PPHN, especially if the PPHN is idiopathic (primary) [24]. Also, the management of primary PPHN is still a controversial issue that in many cases requires combination therapy with multiple drugs. Therefore, many studies are still evaluating the suitable drug combination to improve the management of primary PPHN, such as sildenafil [25], surfactant [26], and adenosine [27]. However, some studies have also reported a poorer prognosis by adding supplemental treatment, such as hydrocortisone [28].

Many previous studies have evaluated the efficacy of milrinone as an adjuvant treatment. El-Ghandour et al. [29] showed that the combination of oral sildenafil and intravenous milrinone did not increase the side effects and was more effective than monotherapy with any of the drugs. Also, previous studies have shown that injectable milrinone may improve prognosis in infants with iNO-resistant PPHN [24, 30]. Mat Bah et al reported a worse prognosis among iNO-resistant PPHN neonates, especially in the idiopathic type[24]. Also, Dillard et al. reported that infants who were non-respondent to iNO and received adjuvant milrinone had a better prognosis, better oxygenation, and less hemodynamic change [30]. However, in some cases, the addition of milrinone to iNO has shown no significant effect in improving treatment [31]. Finally, injectable milrinone, which demonstrated a satisfactory outcome in our study, can also be utilized as an adjuvant or alternative in PPHN management, especially in centers with limited access to iNO.

Studies have shown that milrinone can also be given by inhalation and has similar effects to injectable milrinone[17, 32, 33]. However, none of these studies have been performed in infants with primary PPHN, which points to the novelty of our study compared to previous studies. In the present study, although the frequency of clinical improvement in the inhaled milrinone group was slightly higher than the injected milrinone group, this difference was not statistically significant. A study by Abd Elbaser et al. compared the effect of intravenous and inhaled milrinone in the management of pulmonary artery hypertension after heart surgery in children with congenital heart disease, which showed superior efficacy of inhaled milrinone in reducing pulmonary artery pressure and heart rate and increasing arterial blood pressure than injectable milrinone [17]. Patel et al. investigated the effect of inhaled milrinone in patients with mitral valve stenosis with pulmonary hypertension, which showed that administration of inhaled milrinone before and after heart surgery in these patients, although it is easier to administer than an injection, can improve right ventricular hemodynamics, right ventricular function and systemic hemodynamics [33]. Our study, like the previously mentioned reports, showed that inhaled milrinone could have a similar effect to injectable milrinone, however, inhaled milrinone was used as an adjuvant treatment in the management of early PPHN in our study. Neonatal hemodynamic parameters were not significantly different between the injected and inhaled milrinone groups, and even in cases such as clinical improvement, neonatal oxygen demand, and mortality, inhaled milrinone had a slightly better outcome (18%) than injectable milrinone. Although the two groups were not statistically significant, these findings are clinically noticeable.

The method of inhaled drug administration has become more and more considered today due to its ease of administration and direct effectiveness on pulmonary arteries. Several previous studies have examined the effect of inhaled administration of other drugs on the management of PPHN, such as magnesium sulfate [34] and iloprost [35], and reported this method as a safe treatment with low systemic side effects.

Among our study limitations is that we evaluated this clinical trial without using the gold standard therapy for severe PPHN (iNO and ECMO) as a comparator, and was designed to compare the effects of the milrinone. These findings, however, are critical for developing countries that do not have access to the gold standard therapy.

Conclusion

Considering the results of the present study and the similar effects of injectable and inhaled milrinone in PAP control, it can be concluded that inhaled milrinone can be prescribed as an injectable milrinone as an adjunct in the management of primary PPHN. Also, the results showed no significant change in neonatal hemodynamic parameters in both injectable and inhaled groups, which indicates similar safety to both injectable and inhaled. On the other hand, inhaled administration is an easier method than intravenous administration, especially in centers with limited facilities and in conditions of lack of access to iNO. Although the frequency of clinical improvement in inhaled milrinone group was slightly higher than injected milrinone group, this difference was not statistically significant. Furthermore, prioritizing inhaled milrinone, alleviates the need for obtaining a venous route, or transferring the neonate to a higher equipped center, and shortens the hospitalization duration compared to intravenous medication receiving neonates. All of these features result in a decrease in the patient load on the healthcare system and NICU centers. Since the present study is a pilot study with limited sample size, confirmation of the above results requires further studies in this field.

Abbreviations

IQR
Interquartile ranges
iNO
Inhaled Nitric Oxide
PDA
patent ductus arteriosus
PPHN
Persistent pulmonary hypertension of the newborn
SD
standard deviation
SPSS
Statistical Package for Social Sciences
TR
tricuspid regurgitation

Declarations

Ethics approval:

The current study was approved by the Ethics Committee of Iran University of Medical Sciences (Code: IR.IUMS.FMD.REC 1400.493) approved and conducted in compliance with local regulatory requirements and the Declaration of Helsinki. Confidentiality of patient information was guaranteed and protected and was also anonymized and de-identified before analysis. Informed consent forms were obtained from both the participants' parents (mother and father) or guardians regarding this study. The IRCT code of this study is iIRCT20220130053890N1.

Availability of data and materials:

All data regarding this study has been reported in the manuscript. Please contact the corresponding author if you are interested in any further information.

Competing interests:

The authors declare that they have no competing interests.

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Authors Contribution:

Choobdar F.A The main designer and the owner of the research project idea, Shahhoseini P collected the data, Vahedi X did the data analysis and interpretation, Khosravi N revised the article, Khalsei N drafted the article and Ghassemzadeh M wrote the paper and is the main corresponding author.

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Ethical Statement : We ensure quality and integrity of our research. We obtained informed consent from the parents of all infants participating in our study. We respect the confidentiality and anonymity of our research respondents. We guarantee that the infants participated in the study voluntarily and according to their parents' wishes. We also avid any harm to our participants. There is no conflict of interest in this study and we didn't get any financial support for this research. IRCT code of this RCT trial is iIRCT20220130053890N1 and its Ethical verification code is IR.IUMS.FMD.REC.1400.493.

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Figures

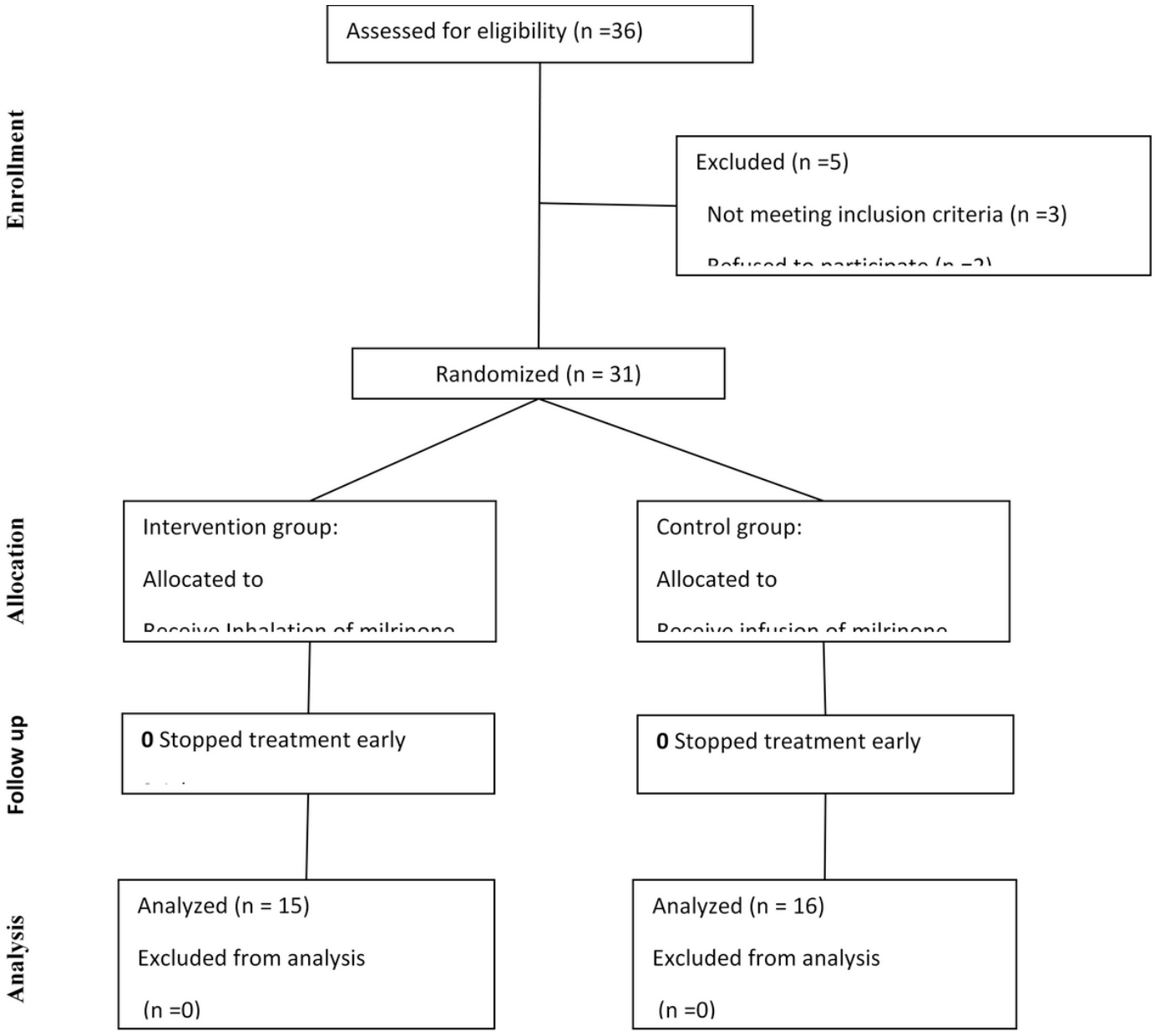

Figure 1

CONSORT Flow diagram of a Randomized Clinical Trial of inhalation vs. infusion of milrinone in Patients with PPHN