The Use of Milrinone in Neonates with Persistent Pulmonary Hypertension of the Newborn - A Randomised Controlled Trial Pilot Study (MINT 1)

Afif EL-Khuffash[1,2]; Patrick J McNamara[3]; Colm Breatnach[1]; Neidin Bussmann[1]; Aisling Smith[1]; Oliver Feeney[4]; Elizabeth Tully[4]; Joanna Griffin[4]; Willem P de Boode[5]; Brian Cleary[6,7]; Orla Franklin[8]; Eugene Dempsey [9,10].

[1]Department of Neonatology, The Rotunda Hospital, Dublin, Ireland.
[2]Department of Paediatrics, Royal College of Surgeons in Ireland.
[3]Division of Neonatology, Stead Family Department of Pediatrics, Iowa City, IA, USA.
[4]Department of Clinical Research, The Rotunda Hospital, Dublin, Ireland.
[5]Department of Neonatology, Radboud University Medical Center, Nijmegen, The Netherlands.
[6]Department of Pharmacy, The Rotunda Hospital, Dublin, Ireland.
[7]School of Pharmacy, Royal College of Surgeons in Ireland.
[8]Department of Paediatric Cardiology, Our Lady's Children's Hospital Crumlin, Dublin, Ireland.
[9]INFANT Centre, University College Cork, Ireland.
[10]Department of Paediatrics and Child Health, University College Cork, Ireland.

Short Title: Milrinone and pulmonary hypertension in neonates

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Abstract

Objective: This randomised control trial (RCT) was developed to assess the impact of milrinone administration on time spent on nitric oxide (iNO) in infants with acute pulmonary hypertension (aPH). We hypothesize that intravenous milrinone used in conjunction with iNO results in the reduction in the time on iNO therapy and the time spent on invasive ventilation in infants ≥ 34 weeks gestation a diagnosis of aPH. We aimed to assess the practicality of instituting the protocol and contributing to a sample size calculation for a definitive multicentre study.

Design: This was a multicentre, randomized, double-blind, two arm pilot study, with a balanced (1:1) allocation.

Setting: Three tertiary neonatal intensive care units across Europe

Participants: Infants with a gestation ≥ 34 weeks and a birth weight ≥ 2000 grams with a clinical and echocardiography diagnosis of aPH, an oxygenation index of ≤ 10, and commenced on iNO within the first 10 days following birth were eligible.

Intervention: Participants were assigned to either a milrinone infusion (intervention) or a saline infusion (placebo) in conjunction with iNO.

Primary Outcome: Time on iNO, feasibility of conducting the protocol.

Results: The trial was terminated early after 4 years of enrollment due to poor recruitment into the trial. A total of nine infants were included in the trial: 4 were allocated to the intervention arm. The groups were well matched for baseline variables. No differences were seen in any of the primary or secondary outcomes.

Conclusion: Conducting an interventional trial in the setting of pulmonary hypertension in infants is not feasible using our current approach. The apparent fall in the incidence of severe pulmonary hypertension, and the difficulty in approaching parents during a critical treatment window have led to very slow recruitment. Future trials in this area should be better designed to improve recruitment as this topic remains a much understudied area in the neonatal field.

Introduction

Acute pulmonary hypertension (aPH), formerly referred to as persistent pulmonary hypertension of the newborn (PPHN), occurs in 0.5 to 7 per 1000 live births and results in a mortality ranging between 4% to 33% (1, 2). The aetiology is multifactorial and current therapy is limited to inhaled nitric oxide (iNO) or extra corporeal membrane oxygenation (ECMO) (3, 4). The widespread use of iNO has resulted in a reduction of the use of ECMO, however, morality and long-term morbidity remains unchanged. The rate of poor response to iNO in this population remains relatively high with up 40% either failing to, or show a partial response (4, 5). In addition, iNO use does not provide support to myocardial performance which is often compromised in the presence of aPH. Due to these challenges, there is a real need to evaluate novel approaches to the management of aPH.

Milrinone is a selective phosphodiesterase 3 (PDE3) inhibitor with pharmacological effects including relaxation of vascular smooth muscle, enhanced myocardial contractility (inotropy) and improved myocardial relaxation (lusitropy) (6, 7). Milrinone may also exhibit synergistic effects with iNO in lowering PVR (8, 9). Its use in the setting of aPH in neonates is limited to case series demonstrating an improvement in oxygenation when used in infants with aPH failing to respond to iNO (10, 11). A recent Cochrane review illustrated the lack of randomised controlled trials (RCTs) comparing the use of milrinone versus placebo or as an adjunct to iNO compared with iNO alone in the setting of aPH and recommended limiting the use of Milrinone in aPH to the research setting (12). It is important to systematically investigate the efficacy of milrinone in the setting of aPH prior to widespread dissemination of this treatment.

In this pilot RCT, we hypothesize that intravenous milrinone used in conjunction with iNO results in the reduction in the time on iNO therapy and the time spent on invasive ventilation in infants ≥ 34 weeks gestation a diagnosis of aPH. We aim to assess the practicality of instituting the protocol and contributing to a sample size calculation for a definitive multicentre study.

Methods

Study Setting

This was a multicentre, randomized, double-blind, two arm pilot study, with a balanced (1:1) allocation that was carried out in the level III neonatal intensive care units in 2 centres in Ireland: The Rotunda Hospital Dublin and Cork University Maternity Hospital, and one centre in the Netherlands: Radboudumc Amalia Children's Hospital, Nijmegen. A detailed study protocol including detailed methodology was published previously (13). This study received ethical approval from the Clinical Research Ethics Committee, University College Cork, Ireland [Ref: ECM 5 (4) 03/03/15 & ECM 3 (bbbb) 09/05/17]. This study obtained Health Product Regulatory Authority Approval [CT Number: CT 900/557/1, Case Number 2190463].

Eligibility and Exclusions

All infants with a gestation ≥ 34 weeks and a birth weight ≥ 2000 grams with a clinical diagnosis of aPH, an oxygenation index of ≤ 10, and commenced on iNO within the first 10 days following birth were eligible. The process of iNO initiation in aPH was standardised in the NICUs and is detailed elsewhere (13). In addition; the infants needed to fulfil the following echocardiography criteria of aPH: Absence of significant congenital heart defect excluding a small atrial septal defect or ventricular septal defect (measuring less than 3mm) and the presence of any of the following: 1) A tricuspid regurgitant jet with a pressure gradient ≥ $^2/_3$ systemic systolic blood pressure; 2) Intra-ventricular septum flattening or bowing into the left ventricular cavity; 3) Patent ductus arteriosus bidirectional shunting or predominant right to left shunting; 4) A pulmonary artery acceleration time < 40 milliseconds.

The following infants were excluded: Lethal congenital anomalies or obvious syndrome; Bleeding diathesis (abnormal coagulation screen/platelet <100,000/ mm^3); The presence of

Intraventricular haemorrhage; Diastolic Hypotension (defined as a diastolic blood pressure less than the 3rd centile for any given gestation) unresponsive to medical treatment (≥30 mL/kg fluid bolus and ≥ 2 inotropes); Hypoxic-ischemic encephalopathy undergoing therapeutic hypothermia; Evidence of renal impairment (Creatinine > 100micromol/l); Severe Hypovolaemia: Heart rate > 180, capillary refill > 5 seconds, urine output < 0.5ml/kg/hour, in addition to diastolic hypotension mentioned above.

Study Intervention

Infants in the intervention arm received an intravenous loading dose of milrinone at a dose of 50µg/kg administered over 60 minutes followed by a maintenance infusion, beginning at 0.375µg/ kg/min to a maximum 0.750µg/ kg/min. the treatment continued until the discontinuation of iNO or a maximum of 35 hours in adherence with the summary of product characteristics (SmPC) recommendation. A 10 mL/ kg bolus of normal saline was administered with the milrinone bolus over the same 1 hour period. Infants in the control arm received an intravenous loading dose of placebo (normal saline) at a rate equivalent to the infusion rate of the milrinone bolus, administered over 60 minutes. A bolus of normal saline of 10 ml/kg also accompanied the placebo infusion, as per the intervention arm.

Randomisation, Concealment and Blinding

A computer-generated central randomisation scheme was used to assign the infants to the two arms in a 1:1 ratio. Both formulations are clear and colourless. Once a patient was recruited and randomised to either Milrinone or Placebo, the trial pharmacist was not involved in recruitment, allocation, and data collection prepared the trial drug or placebo and issued the syringe for infusion to the trial investigator team for administration. The trial participants and their

families, the care providers, the data collectors, the echocardiographers, the primary outcome assessors, and the data analysts were all blinded to the allocation.

Haemodynamic Monitoring

Continuous measurements of left ventricular output (LVO) and systemic vascular resistance (SVR) using bioreactance were facilitated by the NICOM system (Cheetah Medical, USA). Those were obtained at bassline, 6, 12 and 24 hours after milrinone administration. Detailed description of the technique, reproducibility and validation in the neonatal population is published by our group elsewhere (14-16).

The functional protocol for the echocardiography assessment was adapted from the recent American Society of Echocardiography Guideline on neonatal echocardiography (17, 18). All infants were assessed once established on iNO and in a quiet state using the Vivid E95 or the Vivid S6 (GE Medical, Milwaukee, WI, USA) and a 10 Mhz transducer. Congenital heart disease was ruled out on the first assessment. Offline analysis of all echocardiograms was performed at a dedicated workstation (EchoPAC version 202, GE Medical Systems) by a single operator (AF) who was blinded to the allocations of the infants. Detailed methods for image acquisition and analysis techniques have been published elsewhere (19-25). An assessment of pulmonary haemodynamics was performed via measurement of pulmonary artery acceleration time (PAAT), RV ejection time (RVET); PAAT to RVET ratio (PAATi) and LV eccentricity index. The PAAT is inversely correlated to pulmonary vascular resistance (PVR) and has been validated against right heart catheter-derived measurements in infants and children (22). The LV eccentricity index (LV EI) indicates the degree of interventricular septal flattening and associated elevation of RV pressures. Parameters of myocardial function including right ventricular output (RVO), LV global and RV free wall deformation measurements using speckle tracking echocardiography were recorded.

Outcome Assessment

In this pilot feasibility RCT, we aimed to assess our ability to recruit and retain infants, assess parental acceptability and adherence to the administration of the intervention, determine the feasibility of randomization, identification of optimal recruitment methods, and estimate an effect size that can be used to power a definitive trial. The primary clinical outcome of this study is the time on iNO in hours and the time on invasive ventilation and oxygen supplementation. We also collected secondary outcomes including duration of hospital stay, the rate of hypotension and the use of adjuvant inotropes, need for ECMO and mortality.

Sample Size and Statistical Analysis

This study was conducted to determine the feasibility of patient recruitment, instituting the study protocol, randomising and blinding allocation, collecting outcome data and contribute to determine the sample size necessary for a definitive multicentre trial. A sample of 10 infants per arm (a total of 20 infants) were planned for recruitment over a 4-year period. The trial was terminated by the data safety and monitoring board (DSMB) following 4 years of enrollment due to poor recruitment into the trial. A total of nine infants were included in the trial.

Continuous variables were presented as means (standard deviation) or median [inter-quartile range] as appropriate. Dichotomous variables were presented as proportions and summarised in contingency tables. All enrolled infants were grouped and presented on an intention-to-treat basis, including infants that have not continued treatment for any reason. We also performed a secondary presentation of data based on the receipt of milrinone in order to examine the potential haemodynamic impact of the medication. No statistical analysis was conducted due to the smaller number of infants in each group. Data were presented descriptively. We will use SPSS (version 25) to perform the statistical analysis.

Results

Between April 2016 and April 2020, thirty patients from 3 centres were screened for eligibility with a total of 9 infants included in the study (**Figure 1**). Four infants were randomised to milrinone (of which three received the drug), and five were randomised to placebo. The infant randomized to milrinone without receiving the drug deteriorated shortly following randomisation and required referral to the ECMO service. There was no difference in the baseline demographics in the two groups but the pre-enrolment OI appeared higher in intervention group (**Table 1**). All infants were in receipt of 20 parts per million of iNO at the time of enrolment.

There were no obvious differences in the time on iNO, duration of ventilation or duration of oxygen administration between the two groups (**Table 2**). The distribution of adverse events including hypotension, use of inotropes, need for ECMO, or death appeared similar between the two groups. However, when infants were compared based on the receipt of milrinone (n=3) compared with no milrinone (n=6), infants in receipt of milrinone had less ventilation days, less days on oxygen, and lower post treatment OI. Two of the infants not in receipt of milrinone were referred for ECMO (**Table 3**). Dopamine was the predominant additional inotrope used in this cohort.

There were no differences in the NICOM measured LVO or SVR between the two groups throughout the study period (**Figure 2A**). However infants who received milrinone demonstrated higher LVO and lower SVR and mean BP by 24 hours of milrinone administration (**Figure 2B**). Baseline measures of PVR including PAATi, LV EI and PDA systolic velocity appeared similar between the groups (**Figure 3A**). Infants in receipt of milrinone demonstrated an improvement in the surrogate markers of PVR including a higher PAATi, a lower LV EI, and a left to right flow pattern during systole across the PDA (**Figure 3B**). Baseline RVO was lower in the intervention group compared with controls with no differences in the baseline values of RV and LV longitudinal

strain (**Figure 4A**). Infants in receipt of milrinone appear dot have improved RVO, RV strain and LV strain by 24 hours following administration (**Figure 4B**).

Discussion

Despite recent advances in the management of aPH in late preterm and term infants, the risk of mortality and adverse neurological sequelae remains high. LV and RV function is often compromised secondary to increased RV afterload and reduced LV preload mediated by the higher PVR and resultant reduction in pulmonary venous return (26). The effects of a pressure-loaded, dilated right heart include a shift in the interventricular septum and compression of the left ventricle, both resulting in decreased LV filling and hence cardiac LV output (LVO). This has prompted the neonatal community to institute additional therapies. However, there is no consensus on the choice of therapeutic interventions in addition to iNO. Unfortunately, following four years of recruitment in three neonatal centres, the study was terminated due to futility following the enrolment of only nine infants, all of whom came from one centre (The Rotunda Hospital, Dublin, Ireland). Our ability to draw any robust conclusions is therefore limited. This study suffered from an increasingly evident pattern of the huge challenges that come with the early enrolment of critically ill, or haemodynamically unstable infant into an interventional trial involving a vasoactive agent. Recent studies including an RCT of hydrocortisone for neonatal hypotension, the HIP trial of Dopamine for hypotension, and the Bosentan trial for aPH in newborn infants (FUTURE-4), all terminated early due to poor recruitment (27-29).

The reasons for the poor recruitment are multifactorial. In our experience, the incidence of severe acute pulmonary hypertension not accompanying other important morbidities including neonatal encephalopathy or Down syndrome seems to be declining. In addition, the incidence of incomplete or failed response to iNO has fallen in our unit secondary to earlier recognition of aPH, and improvements in antenatal and early neonatal care. The mandated early recruitment of infants

with a condition that only manifests following delivery adds additional challenges. Approaching parents for consent shortly after discussing potentially devastating news about the health and wellbeing of their baby is a delicate process given the time sensitivity of the need for early enrolment.

Conducting the trial presented its own challenges. The requirement for echocardiography assessment prior to enrolment coupled with the small number of study investigators capable of performing the scans means that enrolment was limited to daytime working hours. In addition, the lack of 24-hour availability of pharmacy staff to prepare the study drug in a blinded fashion also curtailed enrolment. Finally, the COVID-19 pandemic led to further challenges in recruitment due the necessary diversion of staff and recourses.

We did observe some interesting difference in the haemodynamics in infants between the two groups especially when dividing the infants into those who received milrinone in conjunction with iNO compared to those who did not. Non-invasive cardiac output monitoring illustrated a higher LVO and a lower SVR by 24 hours in the 3 infants who received milrinone in conjunction with iNO. Their mean blood pressure was lower than those without milrinone but remained within a normal range. Similarly, surrogate markers of pulmonary vascular resistance including PAATi, LV EI and PDA systolic velocity all showed a favourable trend toward lower PVR following 24 hours of milrinone infusion. This was also accompanied by a rise in RVO, RV and LV strain. The rate of adverse effects in the two groups was similar with a high rate of hypotension and the use of inotropes likely reflecting the unstable nature of the condition rather than being a side effect of the medication. The low cardiac output state resulting from reduced LV preload can lead to a fall in blood pressure in infants with aPH necessitating the use of vasoactive inotropes such as dopamine and adrenaline. Animal data suggest that these inotropes raise systemic and pulmonary vascular resistance and may further contribute to RV compromise in the setting of aPH (30, 31).

Several studies have demonstrated the association of a low cardiac output in the setting of aPH with morbidity and mortality (32-34).

Cyclic nucleotide phosphodiesterases (PDE) are a family of enzymes that hydrolyse the phosphodiester bond in cAMP and cGMP thereby promoting pulmonary vascular constriction. PDE3 has a predominant hydrolysing effect on cAMP. The selective inhibition by milrinone of PDE3 lead to a rise in the levels of cAMP leading to relaxation of vascular smooth muscle, enhanced myocardial contractility (inotropy) and improved myocardial relaxation (lusitropy) (6, 7). In the newborn lamb, intravenous milrinone augments the action of prostaglandins (PGI_2) on pulmonary vasculature by significantly shortening the onset and prolonging the duration and degree of pulmonary vasodilation produced by PGI_2 (35, 36). The use of milrinone is established in neonates and children following cardiac surgery for the prevention of low cardiac output syndrome and the treatment of pulmonary hypertension (37, 38).

In conclusion, we demonstrated the conducting an interventional trial of a vasoactive agent in the setting of acute pulmonary hypertension in term infants is not feasible using our current approach. The apparent fall in the incidence of severe pulmonary hypertension, and the difficulty in approaching parents during a critical treatment window have led to very slow recruitment. Future trials in this area should be better designed to improve recruitment as this topic remains a much understudied area in the neonatal field.

References

1. Lipkin PH, Davidson D, Spivak L, Straube R, Rhines J, Chang CT. Neurodevelopmental and medical outcomes of persistent pulmonary hypertension in term newborns treated with nitric oxide. J Pediatr. 2002;140(3):306-10.
2. Walsh-Sukys MC, Tyson JE, Wright LL, Bauer CR, Korones SB, Stevenson DK, et al. Persistent pulmonary hypertension of the newborn in the era before nitric oxide: practice variation and outcomes. Pediatrics. 2000;105(1 Pt 1):14-20.
3. Finer NN, Barrington KJ. Nitric oxide for respiratory failure in infants born at or near term. Cochrane Database Syst Rev. 2001(4):CD000399.
4. Inhaled nitric oxide in full-term and nearly full-term infants with hypoxic respiratory failure. N Engl J Med. 1997;336(9):597-604.
5. Goldman AP, Tasker RC, Haworth SG, Sigston PE, Macrae DJ. Four patterns of response to inhaled nitric oxide for persistent pulmonary hypertension of the newborn. Pediatrics. 1996;98(4 Pt 1):706-13.
6. Silver PJ, Harris AL, Canniff PC, Lepore RE, Bentley RG, Hamel LT, et al. Phosphodiesterase isozyme inhibition, activation of the cAMP system, and positive inotropy mediated by milrinone in isolated guinea pig cardiac muscle. J Cardiovasc Pharmacol. 1989;13(4):530-40.
7. LeJemtel TH, Scortichini D, Levitt B, Sonnenblick EH. Effects of phosphodiesterase inhibition on skeletal muscle vasculature. Am J Cardiol. 1989;63(2):27A-30A.
8. Deb B, Bradford K, Pearl RG. Additive effects of inhaled nitric oxide and intravenous milrinone in experimental pulmonary hypertension. Crit Care Med. 2000;28(3):795-9.
9. Khazin V, Kaufman Y, Zabeeda D, Medalion B, Sasson L, Schachner A, et al. Milrinone and nitric oxide: combined effect on pulmonary artery pressures after cardiopulmonary bypass in children. J Cardiothorac Vasc Anesth. 2004;18(2):156-9.
10. McNamara PJ, Laique F, Muang-In S, Whyte HE. Milrinone improves oxygenation in neonates with severe persistent pulmonary hypertension of the newborn. J Crit Care. 2006;21(2):217-22.
11. Bassler D, Choong K, McNamara P, Kirpalani H. Neonatal persistent pulmonary hypertension treated with milrinone: four case reports. Biol Neonate. 2006;89(1):1-5.
12. Bassler D, Kreutzer K, McNamara P, Kirpalani H. Milrinone for persistent pulmonary hypertension of the newborn. Cochrane Database Syst Rev. 2010(11):CD007802.
13. El-Khuffash A, McNamara PJ, Breatnach C, Bussmann N, Smith A, Feeney O, et al. The use of milrinone in neonates with persistent pulmonary hypertension of the newborn - a randomised controlled trial pilot study (MINT 1): study protocol and review of literature. Matern Health Neonatol Perinatol. 2018;4:24.
14. El-Khuffash A, McNamara PJ. Hemodynamic Assessment and Monitoring of Premature Infants. Clin Perinatol. 2017;44(2):377-93.
15. Weisz DE, Jain A, Ting J, McNamara PJ, El-Khuffash A. Non-invasive cardiac output monitoring in preterm infants undergoing patent ductus arteriosus ligation: a comparison with echocardiography. Neonatology. 2014;106(4):330-6.
16. Weisz DE, Jain A, McNamara PJ, El-Khuffash A. Non-invasive cardiac output monitoring in neonates using bioreactance: a comparison with echocardiography. Neonatology. 2012;102(1):61-7.
17. Mertens L, Seri I, Marek J, Arlettaz R, Barker P, McNamara P, et al. Targeted Neonatal Echocardiography in the Neonatal Intensive Care Unit: Practice Guidelines and Recommendations for Training Writing group of the American Society of Echocardiography (ASE) in collaboration

with the European Association of Echocardiography (EAE) and the Association for European Pediatric Cardiologists (AEPC). J Am Soc Echocardiogr. 2011;24(10):1057-78.
18. El-Khuffash AF, McNamara PJ. Neonatologist-performed functional echocardiography in the neonatal intensive care unit. Semin Fetal Neonatal Med. 2011;16(1):50-60.
19. El-Khuffash A, Schubert U, Levy PT, Nestaas E, de Boode WP, European Special Interest Group "Neonatologist Performed E. Deformation imaging and rotational mechanics in neonates: a guide to image acquisition, measurement, interpretation, and reference values. Pediatr Res. 2018;84(Suppl 1):30-45.
20. Nestaas E, Schubert U, de Boode WP, El-Khuffash A, European Special Interest Group "Neonatologist Performed E. Tissue Doppler velocity imaging and event timings in neonates: a guide to image acquisition, measurement, interpretation, and reference values. Pediatr Res. 2018;84(Suppl 1):18-29.
21. Jain A, Mohamed A, El-Khuffash A, Connelly KA, Dallaire F, Jankov RP, et al. A comprehensive echocardiographic protocol for assessing neonatal right ventricular dimensions and function in the transitional period: normative data and z scores. J Am Soc Echocardiogr. 2014;27(12):1293-304.
22. Levy PT, Patel MD, Groh G, Choudhry S, Murphy J, Holland MR, et al. Pulmonary Artery Acceleration Time Provides a Reliable Estimate of Invasive Pulmonary Hemodynamics in Children. J Am Soc Echocardiogr. 2016;29(11):1056-65.
23. Jain A, El-Khuffash AF, Kuipers BCW, Mohamed A, Connelly KA, McNamara PJ, et al. Left Ventricular Function in Healthy Term Neonates During the Transitional Period. J Pediatr. 2017;182:197-203 e2.
24. Levy PT, Patel MD, Choudhry S, Hamvas A, Singh GK. Evidence of Echocardiographic Markers of Pulmonary Vascular Disease in Asymptomatic Infants Born Preterm at One Year of Age. J Pediatr. 2018;197:48-56 e2.
25. van Laere D, van Overmeire B, Gupta S, El-Khuffash A, Savoia M, McNamara PJ, et al. Application of NPE in the assessment of a patent ductus arteriosus. Pediatr Res. 2018;84(Suppl 1):46-56.
26. Sehgal A, Athikarisamy SE, Adamopoulos M. Global myocardial function is compromised in infants with pulmonary hypertension. Acta Paediatr. 2012;101(4):410-3.
27. Dempsey EM, Barrington KJ, Marlow N, O'Donnell CPF, Miletin J, Naulaers G, et al. Hypotension in Preterm Infants (HIP) randomised trial. Archives of disease in childhood Fetal and neonatal edition. 2021;106(4):398-403.
28. Steinhorn RH, Fineman J, Kusic-Pajic A, Cornelisse P, Gehin M, Nowbakht P, et al. Bosentan as Adjunctive Therapy for Persistent Pulmonary Hypertension of the Newborn: Results of the Randomized Multicenter Placebo-Controlled Exploratory Trial. J Pediatr. 2016;177:90-6 e3.
29. Watterberg KL, Fernandez E, Walsh MC, Truog WE, Stoll BJ, Sokol GM, et al. Barriers to enrollment in a randomized controlled trial of hydrocortisone for cardiovascular insufficiency in term and late preterm newborn infants. J Perinatol. 2017;37(11):1220-3.
30. Jaillard S, Houfflin-Debarge V, Riou Y, Rakza T, Klosowski S, Lequien P, et al. Effects of catecholamines on the pulmonary circulation in the ovine fetus. Am J Physiol Regul Integr Comp Physiol. 2001;281(2):R607-R14.
31. Cheung PY, Barrington KJ. The effects of dopamine and epinephrine on hemodynamics and oxygen metabolism in hypoxic anesthetized piglets. Crit Care. 2001;5(3):158-66.
32. Evans N, Kluckow M, Currie A. Range of echocardiographic findings in term neonates with high oxygen requirements. Arch Dis Child Fetal Neonatal Ed. 1998;78(2):F105-F11.

33. Peterson AL, Deatsman S, Frommelt MA, Mussatto K, Frommelt PC. Correlation of echocardiographic markers and therapy in persistent pulmonary hypertension of the newborn. Pediatr Cardiol. 2009;30(2):160-5.
34. Musewe NN, Poppe D, Smallhorn JF, Hellman J, Whyte H, Smith B, et al. Doppler echocardiographic measurement of pulmonary artery pressure from ductal Doppler velocities in the newborn. J Am Coll Cardiol. 1990;15(2):446-56.
35. Kumar VH, Swartz DD, Rashid N, Lakshminrusimha S, Ma C, Ryan RM, et al. Prostacyclin and milrinone by aerosolization improve pulmonary hemodynamics in newborn lambs with experimental pulmonary hypertension. J Appl Physiol (1985). 2010;109(3):677-84.
36. Rashid N, Morin FC, III, Swartz DD, Ryan RM, Wynn KA, Wang H, et al. Effects of prostacyclin and milrinone on pulmonary hemodynamics in newborn lambs with persistent pulmonary hypertension induced by ductal ligation. Pediatr Res. 2006;60(5):624-9.
37. Hoffman TM, Wernovsky G, Atz AM, Kulik TJ, Nelson DP, Chang AC, et al. Efficacy and safety of milrinone in preventing low cardiac output syndrome in infants and children after corrective surgery for congenital heart disease. Circulation. 2003;107(7):996-1002.
38. Jain A, Sahni M, El-Khuffash A, Khadawardi E, Sehgal A, McNamara PJ. Use of targeted neonatal echocardiography to prevent postoperative cardiorespiratory instability after patent ductus arteriosus ligation. J Pediatr. 2012;160(4):584-9.

Table 1: Patient demographics in the two groups

	Milrinone n=4	**Placebo n=5**
Gestation (Weeks)	40.0 [38.9 – 41.6]	40.1 [38.0 – 41.1]
Birthweight (Kg)	3.4 [3.2 – 3.6]	3.9 [3.6 – 4.1]
Male	1 (25)	2 (40)
Vaginal Delivery	2 (50)	3 (60)
Five Minute Apgar Score	9 [8 – 10]	8 [4 – 10]
Surfactant Administration	2 (50)	1 (20)
Meconium Aspiration	1 (25)	2 (40)
RDS/TTN	1 (25)	1 (20)
Idiopathic	2 (50)	2 (40)
Pre Treatment OI	27 [17 – 44]	14 [11 – 19]

Values are presented as medians [Inter-Quartile Range] or count (percent). RDS: Respiratory Distress Syndrome; TTN: Transient tachypnoea of the newborn; OI: Oxygenation index.

Table 2: Outcomes in the two groups

	Intervention n=4	**Control n=5**
Time on iNO (Hours)	92 [42 – 161]	48 [28 – 118]
Ventilation Days	6 [3 – 24]	6 [4 – 12]
Oxygen Days	6 [1 – 13]	6 [3 – 19]
Hospital Days	16 [9 – 27]	21 [9 – 31]
Death	0	0
ECMO	1 (20)	1 (25)
Hypotension	3 (60)	3 (75)
Inotrope	3 (60)	3 (75)
Post Treatment OI	6 [3 – 24]	8 [4 – 27]

Values are presented as medians [Inter-Quartile Range] or count (percent). iNO: Inhaled nitric oxide; ECMO: extracorporeal membrane oxygenation; OI: oxygenation index.

Table 3: Outcomes based on receipt of Milrinone

	Received Milrinone n=3	No Milrinone n=6
Time on iNO (Hours)	80 [55 – 91]	53 [40 – 179]
Ventilation Days	5 [4 – 6]	8 [4 – 15]
Oxygen Days	1 [1 – 8]	8 [3 – 15]
Hospital Days	15 [11 – 21]	13 [11 – 21]
Death	0	0
ECMO	0	2 (33)
Hypotension	2 (67)	4 (67)
Inotrope	2 (67)	4 (67)
Post Treatment OI	5 [4 – 5]	9 [5 – 25]

Values are presented as medians [Inter-Quartile Range] or count (percent]. iNO: Inhaled nitric oxide; ECMO: extracorporeal membrane oxygenation; OI: oxygenation index.

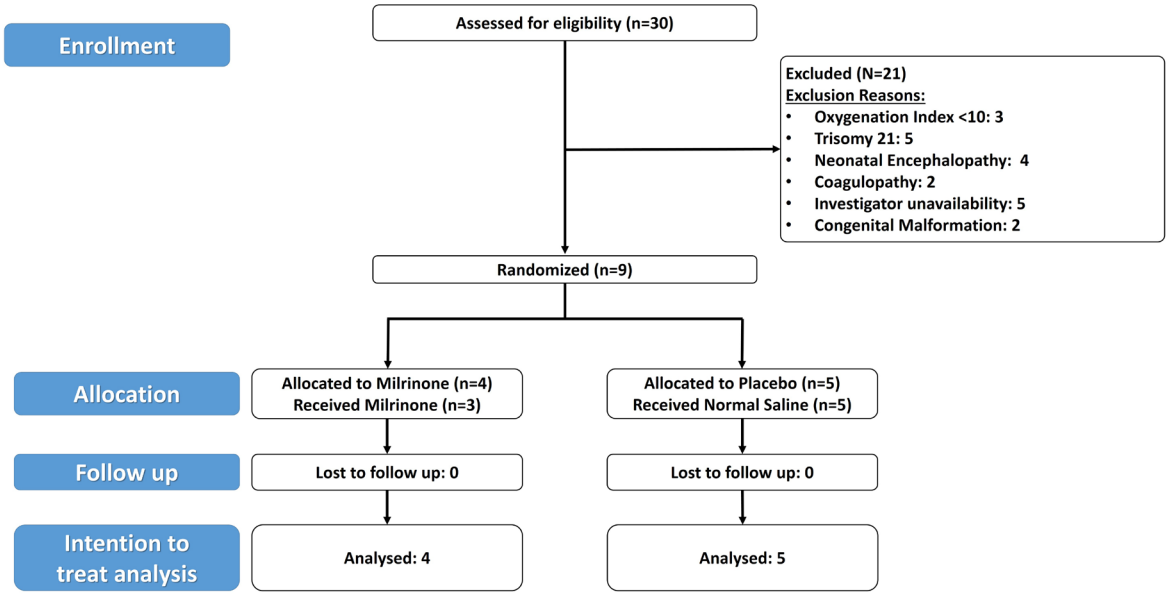

Figure 1: CONSORT Diagram.

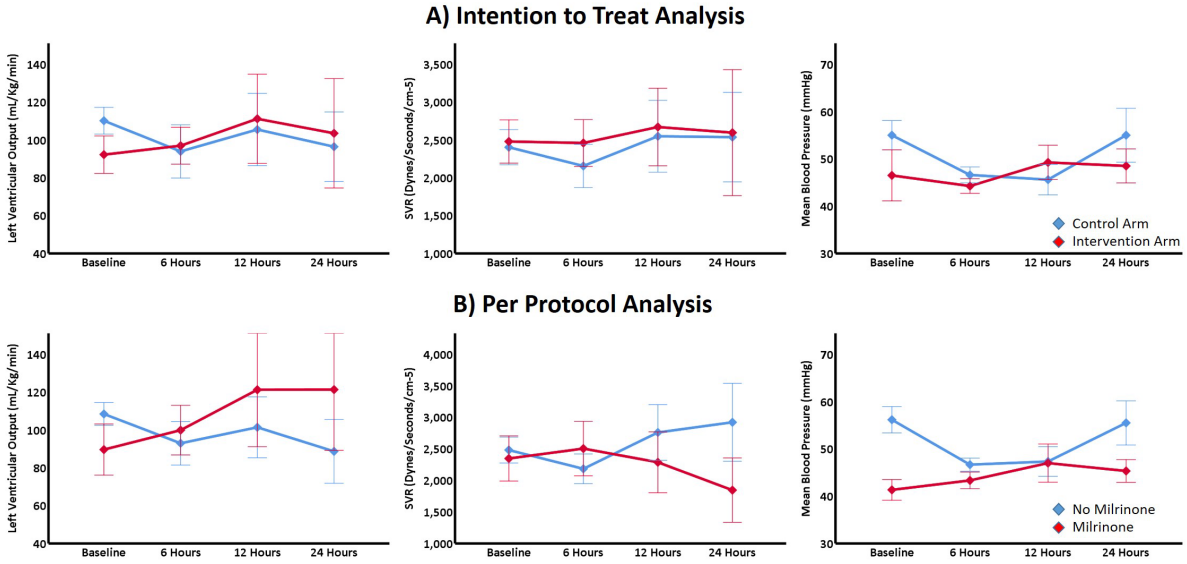

Figure 2: NICOM readings of left ventricular output, systemic vascular resistance, and mean blood pressure. Values are presented as means and one standard error.

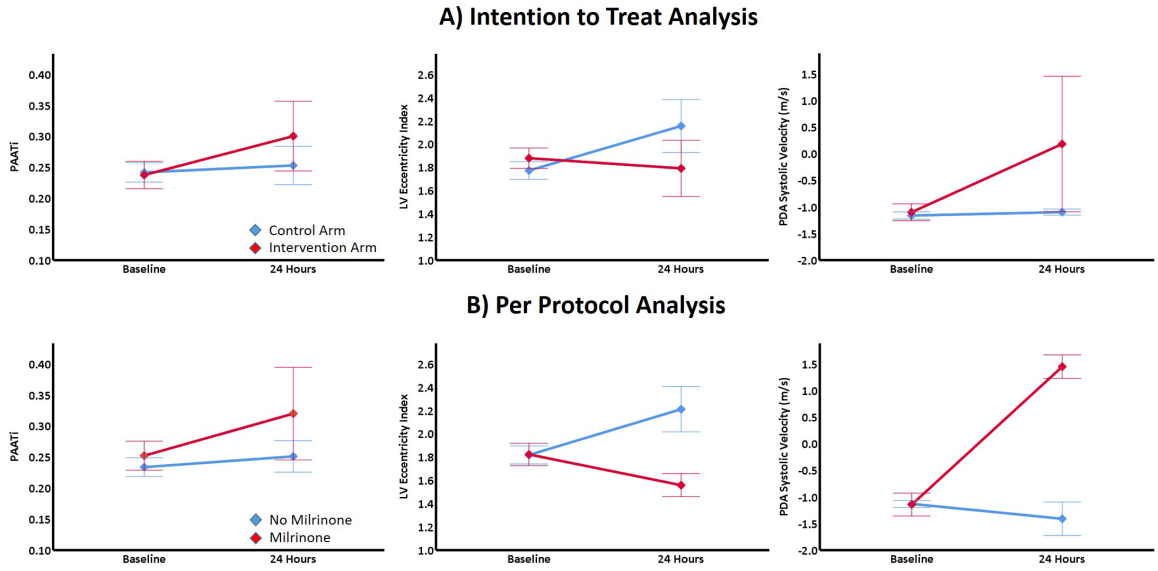

Figure 3: Surrogate markers of pulmonary vascular resistance. Values are presented as means and one standard error.

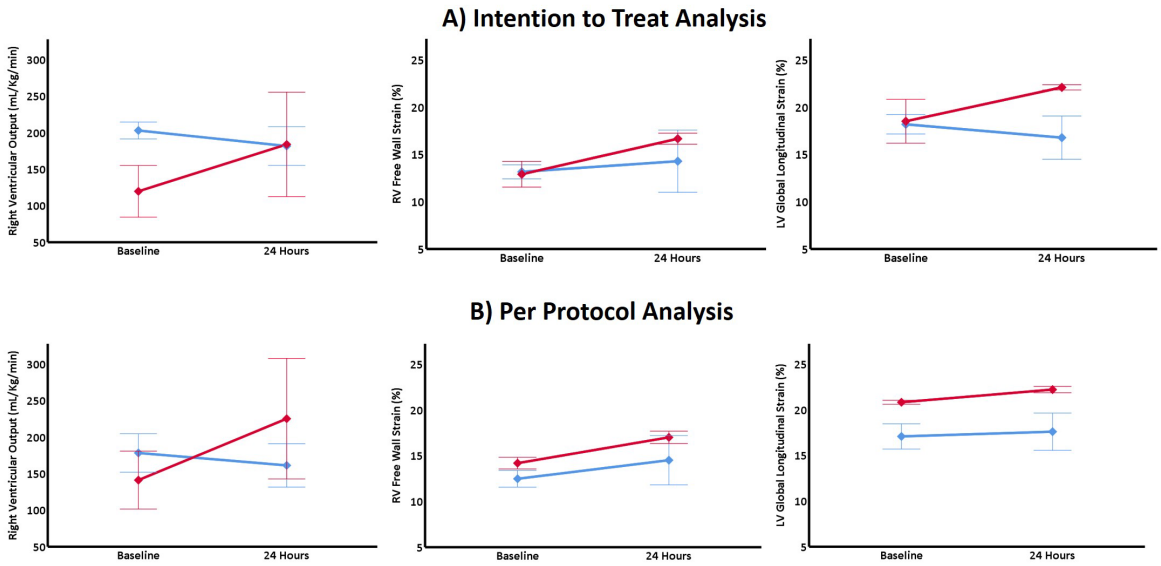

Figure 4: LV and RV function. Values are presented as means and one standard error.