The Use of Milrinone in Neonates with Persistent Pulmonary Hypertension of the Newborn: A Randomised Controlled Trial Pilot Study

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Ethical review	Approved WMO
Status	Will not start
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON48755

Source
ToetsingOnline

Brief title
MINT 1 Study

Condition

- Other condition
- Heart failures
- Neonatal respiratory disorders

Synonym
Persistent pulmonary hypertension of the neonate;

Health condition

Persisterende pulmonale hypertensie van de pasgeborene

Research involving
Human

Sponsors and support

Primary sponsor: RCSI Clinical Research Centre, Royal College of Surgeons in Ireland
Source(s) of monetary or material Support: Onderzoeksbudget afdeling neonatologie Radboudumc

Intervention

Keyword: Milrinone, Neonate, Nitric Oxide, PPHN

Outcome measures

Primary outcome

The primary outcome of this study is the time on iNO in hours and the time on invasive ventilation.

Secondary outcome

The incidence of the use of other inotropes; critically low LV and RV function and output measured by echocardiography and a non-invasive cardiac output monitor (NICOM); the rate of adverse effects associated with milrinone including the incidence of hypotension; and the pre-discharge outcomes in the two groups.

We will collect the following demographic characteristics and relevant short-term secondary outcomes: duration of hospital stay; time to extubation; duration of oxygen therapy, and survival.
Details of cardiorespiratory stability (blood pressure, heart rate, oxygen saturation), ventilation support (FiO2, mean airway pressure (MAP), oxygenation index [MAP × F FiO2/PaO2]), efficacy of oxygenation [PaO2], plasma lactate, pH,

PCO2, HCO3-, Base excess; and relevant co- treatments (i.e., sedation, analgesics, muscle relaxants, inotropes, fluid administration) at the following time points:
1) Prior to treatment; 2) Following the loading dose; 3) 12 hours after initiation of therapy; 4) 24 hours after initiation of therapy; 5) Two hours after discontinuation of therapy

Monitoring of blood parameters will be carried out as follows during the study period and 24 hours after drug discontinuation:
* Daily full blood count (including platelets):
* Daily electrolytes, Urea and Creatinine:
* Daily liver function tests (ALT, AST, GGT):
* Twelve hourly blood gas analysis:

Echocardiography will be performed according to the following schedule: a timing window of ± 3 hours will be applied. 1) Prior to the Commencement of Study Drug: Diagnose PPHN and rule out CHD; 2) 12 hours following the administration of Study Drug; 3) 24 hours following the administration of the study drug; 4) 8 hours following the discontinuation of the study drug.

Non-invasive Cardiac output Monitoring (NICOM) will be commenced prior to the commencement of the study drug and continued until the last echocardiogram, 8 hours after the discontinuation of the study medication.

Cranial ultrasound will performed prior to treatment commencement and after the

discontinuation of the infusion.

Study description

Background summary

Persistent pulmonary hypertension of the newborn is common and leads to a major burden of neonatal illness, carries a significant mortality, need for ECMO, and adverse neurodevelopmental outcome. There is poor appreciation of the physiologic determinants of PPHN and predictors of iNO (nitric oxide inhalation) response at presentation; up to 40% of infants do not respond to iNO treatment. The increasing cost of iNO may preclude its use in both the developed and developing countries. The use of milrinone in infants with PPHN as an adjunct to iNO is worth further exploration with preliminary evidence suggesting an improvement in both oxygenation and myocardial performance in this group of infants. It*s inotropic, lusitropic and pulmonary vasodilator properties make it an ideal agent to use in this setting and may improve response to therapy and reduce mortality associated with the disease.

Study objective

The objective of this study is to analyse the hypothesis 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 and * 2000 grams with a clinical and echocardiography diagnosis of PPHN.

Study design

This is a multicentre, randomized, double-blind, two arm pilot study, with a balanced (1:1) allocation that will be carried out in level III neonatal intensive care units in Ireland and The Netherlands

Intervention

Infants in the intervention arm will receive an intravenous loading dose of milrinone lactate injection (10 mg/10 mL) at a dose of 50*g/kg administered over 60 minutes followed by a maintenance infusion, beginning at 0.375*g/ kg/min to a maximum 0.750*g/ kg/min. The duration of therapy is until discontinuation of iNO or a maximum of 35 hours in adherence with the SmPC recommendation. A 10 mL/ kg bolus of normal saline will be administered with the milrinone bolus over the same 1 hour period. Dose increase will be

performed in response to parameters reflecting oxygenation.

Infants in the control arm will receive 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 will accompany the placebo infusion, as per the intervention arm. Following the loading protocol, a saline infusion running at a rate similar to the milrinone infusion will be commenced for a maximum period of 35 hours or until discontinuation of iNO if it occurs sooner. The saline infusion will be titrated up in increments similar to the milrinone infusion.

Study burden and risks

The patients in this study are admitted to the neonatal intensive care unit, given their critical condition. The administration of milrinone in adjunct to nitric oxide inhalation is a strategy that is already in use on this department outside this trial.
Cardiac output will non-invasively be monitored using a thoracic bioreactance technology (NICOM, Cheetah Medical), which needs the application of 4 sensors on the newborn. These electrodes will not interfere with regular monitoring and nursing. This type of cardiac output monitoring is already in use on our department.
Echocardiography and echoencephalography is already part of standard neonatal intensive care in these patients with PPHN and will not have influence on the condition of the newborn.
The necessary monitoring of blood parameters is in accordance with the standard protocol of the NICU, so no extra blood is withdrawn solely for the purpose of this study.
Given the fact that these patients will have both an arterial and a central venous catheter, there will be no need for extra blood punctures.

All patients in this study are managed according current (inter)national guidelines and protocols.
A risk classification has been performed according the "NFU document 'Kwaliteitsborging mensgebonden onderzoek 2.0' ", that resulted in a neglectable risk associated with participation with this study.

The study is group related because persistent pulmonary hypertension is a condition that specifically concerns newborn infants without any known variability related to sex or ethnicity.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

1) Gestational age *34 weeks and birth weight *2000 grams
2) * 10 postnatal days of life and within 4 days of admission
3) Echocardiographic diagnosis of PPHN
4) Absence of significant congenital heart defect excluding a small atrial septal defect or ventricular septal defect (measuring< 3mm)
5) Oxygenation index of * 10

Exclusion criteria

1) Lethal congenital anomalies or obvious syndrome
2) Bleeding diathesis (abnormal coagulation screen/platelet <100,000/ mm3)
3) The presence of Intraventricular haemorrhage.
4) 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 of at least 10 *g/ kg/min)
5) Hypoxic-ischemic encephalopathy undergoing therapeutic hypothermia

6) Evidence of renal impairment (Creatinine > 100micromol/l)
7) Severe Hypovolaemia: Heart rate > 180, capillary refill > 5 seconds, urine output < 0.5ml/kg/hour, in addition to diastolic hypotension mentioned above.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	15
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Corotrope
Generic name:	Milrinone
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	09-09-2019
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Approved WMO

Date:	07-10-2019
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2014-002988-16-NL
ISRCTN	ISRCTN12949496
CCMO	NL64885.091.18