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Using milrinone in babies with high blood pressure in the lungs soon after birth

Submission date 24/06/2015	**Recruitment status** Stopped	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data [_] Record updated in last year
Registration date 07/07/2015	**Overall study status** Stopped	
Last Edited 18/11/2022	**Condition category** Circulatory System	

Plain English summary of protocol

Background and study aims

During pregnancy, when babies are in the womb the blood vessels in the baby's lungs are constricted as the placenta is responsible for the delivery of oxygen to your baby. After birth, those blood vessels in the lungs begin to relax and allow more blood to flow through them as the lungs take over the delivery of oxygen. Persistent Pulmonary Hypertension of the Newborn (PPHN for short) is a condition that can occur in babies at or close to term. In this condition, blood vessels in the lung do not relax normally like they should after the baby is born. As a result, the baby can become very sick and need a lot of oxygen and artificial ventilation with a tube and a breathing machine. This condition can be very serious and some babies can unfortunately die from it. There are many causes for this condition but the treatment is generally the same. The treatment for PPHN is to use a gas called nitric oxide that is delivered through the ventilator. Nitric oxide works by relaxing those tight blood vessels in the lungs to allow more blood to flow through the lungs to get oxygen from the air. Nitric oxide works well most of the time but in some babies, it is not enough. A new medicine has shown promise in some studies in helping nitric oxide relax the blood vessels and support the heart. We are conducting a study to look at whether milrinone can help babies with PPHN by reducing the time the baby spends on a ventilator.

Who can participate?

Babies born at or after 34 weeks of gestation, weighing at least 2000 grams and admitted to the neonatal intensive care unit diagnosed with PPHN.

What does the study involve?

The babies are randomly assigned to one of two groups. Those in group 1 receive milrinone on top of nitric oxide. Those in group 2 receive normal care currently given to babies with PPHN which includes nitric oxide. We want to see whether giving babies milrinone in addition to nitric oxide results in shortening the time babies needs nitric oxide and the time the baby spends on a breathing machine. We will also examine the baby's heart using an ultrasound machine to examine the effect of milrinone on the heart.

What are the possible benefits and risks of participating?

Not provided at time of registration.

Where is the study run from?
At the level III neonatal intensive care units in the Rotunda Hospital Dublin and Cork University Maternity Hospital.

When is the study starting and how long is it expected to run for?
November 2015 to February 2020

Who is funding the study?
Health Research Board (Ireland)

Who is the main contact?
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Public

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Additional identifiers

EudraCT/CTIS number
2014-002988-16

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
MINT-2014-01

Study information

Scientific Title
The use of milrinone in neonates with persistent pulmonary hypertension of the newborn: a randomised controlled trial pilot study

Acronym
MINT

Study objectives
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 and ≥ 2000 grams with a clinical and echocardiography diagnosis of PPHN.

The purpose of this pilot study is to assess the feasibility of performing the trial and to obtain preliminary data to calculate a sample size for a definitive multi-centre trial of milrinone therapy in PPHN. We aim to recruit a total of 30 infants with PPHN (15 receiving milrinone and 15 receiving placebo) over a one year period. We will also aim to seek additional funding under the EU 2020 scheme in order to facilitate the running of the multicentre RCT in Europe and North America.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Clinical Research Ethics Committee, University College Cork, Ireland, ref: ECM 5 (4) 03/03/15

Study design
Multicentre randomized double-blind two-arm pilot study

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet

Not available in web format, please use contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Persistent pulmonary hypertension of the newborn (PPHN)

Interventions
1. Intervention:
Infants in the intervention arm will receive an intravenous loading dose of milrinone lactate injection (10 mg/10 mL) 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 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. A loading dose was chosen to ensure the rapid attainment of therapeutic blood concentrations. The slow rate of administration was chosen to minimize the risk of infusion-related adverse effects, such as hy¬potension. This dosing regimen was established following the recent pharmacokinetic study performed by our group and described above. Dose incrementation will be performed in response to the need for oxygen (FiO2) to maintain adequate pre-ductal saturations (95% or greater). Dose incrementation will be carried out every 2 hours following the bolus if the fall in FiO2 needed to maintain an adequate saturation is less than 20%. Dose escalation will be carried out as described below (Section 2.1.5). For example if two hours after administration, the FiO2 of an infant falls from 60% to 45% (< 20%) to maintain a saturation of 95% or greater, the rate of infusion will be increased based on the table below. This escalation will continue every two hours until a reduction of FiO2 of 20% or greater is achieved down to 40% FiO2. The maximum dose will be 0.750 µg/ kg/min.

2. Control:
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.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Milrinone

Primary outcome measure
Time on iNO therapy and the time spent on invasive ventilation

Secondary outcome measures
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.

Overall study start date
01/11/2015

Completion date
01/02/2020

Reason abandoned (if study stopped)
Participant recruitment issue

Eligibility

Key inclusion criteria
All infants with a gestation ≥ 34 weeks and a birth weight ≥ 2000 grams admitted to the neonatal intensive care unit with a clinical diagnosis of PPHN, and commenced on iNO will be deemed potentially eligible for this study. The process of iNO initiation in PPHN on clinical grounds is standardised in the NICUs. In addition, the infants must satisfy the following criteria:
1. ≤ 10 postnatal days of life and within 24 hrs of admission
2. Echocardiography diagnosis of PPHN (see below)
3. Absence of significant congenital heart defect excluding a small atrial septal defect or ventricular septal defect (measuring less than 3mm)
4. Indwelling arterial line; oxygenation index ≥25 on at least two consecutive arterial blood gas samples at least 20 minutes apart

Participant type(s)
Patient

Age group
Neonate

Sex
Both

Target number of participants
20

Total final enrolment
9

Key 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 µg/ 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

Date of first enrolment
01/11/2015

Date of final enrolment
01/01/2020

Locations

Countries of recruitment
Ireland

Study participating centre
The Rotunda Hospital
Dublin
Ireland
-

Study participating centre
Cork University Hospital
Cork
Ireland
-

Sponsor information

Organisation
The Royal College of Surgeons in Ireland

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Sponsor type
University/education

Website
https://www.rcsi.ie/

ROR
https://ror.org/01hxy9878

Funder(s)

Funder type
Government

Funder Name
Health Research Board

Alternative Name(s)
HRB

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
Ireland

Results and Publications

Publication and dissemination plan

Intention to publish date

Individual participant data (IPD) sharing plan
Not provided at time of registration

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	03/12/2018		Yes	No
Results article		16/11/2022	18/11/2022	Yes	No