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Closing patent ductus arteriosus in preterm babies by using a risk-based score

Submission date 01/07/2016	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 26/07/2016	**Overall study status** Completed	
Last Edited 18/08/2023	**Condition category** Circulatory System	

Plain English summary of protocol

Background and study aims

A patent ductus arteriosus (PDA) is a blood vessel connecting the two major vessels leaving the heart: the aorta and the pulmonary artery. While the baby is in the womb, it works as a lung bypass, sending blood away from the lungs to the rest of the body. In babies born at full term this connection usually closes in the first few days. In most babies born less than 29 weeks gestation the PDA can remain open for a long time. If this occurs, the PDA actually sends blood towards the lungs and away from the rest of the body (in a way opposite to that in the womb). This could cause the lungs to receive extra fluid and become water-logged. A PDA can be diagnosed in preterm babies using an ultrasound test of the heart called an echocardiogram.
Premature babies can have some problems relating to early birth. These include a condition called chronic lung disease (CLD). This is a condition affecting the growth of the lungs. This condition can result in your baby needing oxygen for a long period of time during his/her stay in the hospital and sometime even for a few months after discharge from the hospital. Babies who are premature who also have a large PDA have a higher chance of having CLD. But we are not sure if a PDA causes CLD or whether the two conditions happen together in a premature baby.
A PDA can be closed in a preterm baby over the first 48 hours of age using a medication called Ibuprofen. This is the same medication that you may have used for headaches (Nurofen). Ibuprofen has been used to close PDAs in preterm babies for many years and has been shown to be a safe way of closing the PDAs without needing surgery. However, using ibuprofen to close PDAs in all premature babies does not reduce the chance of them developing CLD. As a result, many hospitals that care for preterm babies do not close the PDA in preterm infants in the first few days of age. Those hospitals watch the open PDA and wait for it to either close naturally by its own during the baby's hospital stay (the most common outcome) or refer the baby for closure by a specialist heart surgeon (a rare outcome). Both approaches to PDA treatment (either using ibuprofen to close it early or waiting for the PDA to close on its own) are accepted ways to care for your baby as there is no difference to the chance of developing CLD in either way of management.
We however think that certain babies with a larger PDA and low heart function may actually benefit from closing their PDA using ibuprofen in the first 48 hours. We have developed a way of accurately predicting which baby with a PDA will go on to develop CLD using echocardiography. We would like to see if closing the PDA early in this situation results in a lower chance of developing CLD.

Who can participate?
Babies aged less than 29 weeks with a PDA

What does the study involve?
An echocardiogram scan (an ultrasound scan of the baby's heart) is performed during the second day of age. If the baby has a large PDA and low heart function then they are randomly allocated to one of two groups. One group receives ibuprofen to try and close the PDA. The other group receives a small dose of a saline solution (a liquid commonly given to preterm babies that looks the same as ibuprofen) and the PDA is monitored and left to close naturally (the standard of care). The treatment duration is three days (one dose every day for three days). This is repeated a second time if the baby's PDA remains open after the first treatment course. The baby undergoes close monitoring with regular echocardiograms: one after each treatment course, one before discharge at 36 weeks of age, and one follow up scan at 3 months of age performed by a cardiologist (heart specialist). The three-month scan is done in Temple Street Children's University Hospital. The baby is also checked to see if they have CLD before discharge. This is done by checking if he/she still needs oxygen at 36 weeks of age.

What are the possible benefits and risks of participating?
Reducing the rate of CLD in preterm babies will have substantial short and long term benefits for the infants and their families. It would lead to less hospital stays, help with earlier nutrition and discharge, reduce lung-related problems in early childhood, and potentially improve neurodevelopmental outcome. Ibuprofen is commonly used to close a PDA in preterm babies. Compared to indomethacin (the medication we used before ibuprofen), ibuprofen has much lower side effects than indomethacin. Ibuprofen is as good as indomethacin in closing a PDA and currently appears to be the drug of choice. It is used across Europe and North America to close a PDA. Rarely, Ibuprofen may cause the baby to pass less urine as it can reduce the blood flow to the baby's kidneys. If this happens, ibuprofen treatment is stopped. This will lead to recovery of the kidneys. The functioning of the baby's kidneys is checked before and after treatment using a blood test. This blood test will be done routinely as part of intensive care and will not result in extra use of needles or blood. Ibuprofen may also cause the baby to have an upset stomach. This is extremely rare. The echocardiogram in this study is routine practice and no unpleasant effects are expected. More than 1000 babies have been monitored with this tool over the past 5 years and it has not resulted in any additional discomfort or complications. The echocardiogram is well-tolerated by babies and it is safe. If the baby doesn't bear the procedure for any reason, testing will stop immediately. If anything unusual or unexpected is found in the study, the cardiology team in the hospital will be notified immediately and their advice will be sought.

Where is the study run from?
Rotunda Hospital (Ireland)

When is the study starting and how long is it expected to run for?
July 2016 to July 2018

Who is funding the study?
Temple Street Foundation (Ireland)

Who is the main contact?
Dr Afif El-Khuffash

Contact information

Type(s)
Scientific

Contact name
Dr Afif El-Khuffash

Contact details
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The Rotunda Hospital
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Additional identifiers

Clinical Trials Information System (CTIS)
2015-004526-33

Protocol serial number
PDARCT1

Study information

Scientific Title
A randomised controlled trial of early targeted patent ductus arteriosus treatment using a risk-based severity score

Acronym
PDA

Study objectives
We hypothesise that:
1. in preterm infants less than 29 weeks gestation
2. at high risk of developing Chronic Lung Disease (CLD)/death (primary outcome) based on a PDAsc ≥ 5.0
3. obtained using echocardiography carried out between 36 and 48 hours of life
early treatment with ibuprofen compared with placebo will result in a reduction of CLD/death by 36 weeks post menstrual age (PMA). Infants with a PDAsc < 5 will not be enrolled in the study but will be followed up to discharge to confirm their low risk status.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Clinical Research Ethics committee of the Cork teaching hospitals, 25/04/2016, ref: EC09.2016

Study design
Single-centre randomized double-blind two-arm pilot study with a balanced (1:1) allocation

Primary study design

Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Patent ductus arteriosus, preterm infants

Interventions
We aim to identify infants at high risk of developing CLD/death by utilising the PDAsc, and randomise those infants to early treatment with Ibuprofen versus placebo.

Intervention arm
Infants in the intervention arm will receive intravenous Ibuprofen (5mg/1ml) at a dose of 10mg /kg (2ml/kg), followed by 2 doses of 5mg/kg (1ml/kg) 24 hours apart administered as a short infusion over 15 minutes. The patency of the ductus will be assessed 24 hours after the last ibuprofen dose using echocardiography. If the PDA remains open (PDA diameter > 1.5 mm), then a second course of ibuprofen will be given. No further doses of ibuprofen will be administered.

Control arm
Infants in the control group will receive an intravenous dose of placebo (normal saline) at a volume equivalent to that in the intervention group (2ml/kg 1st dose; 1ml/kg 2nd & 3rd doses). The patency of the ductus will be assessed 24 hours after the last placebo dose using echocardiography. If the PDA remains open (defined as any identifiable flow on colour Doppler), then a second course of placebo will be given.

Intervention Type
Drug

Phase
Phase III

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

Primary outcome(s)
Chronic lung disease, defined as the need for oxygen at 36 weeks corrected age, and/or death before discharge. This will be assessed prior to hospital discharge at 36 weeks corrected age.

Key secondary outcome(s))
1. Culture proven sepsis (Yes/No)
2. Number of inotropes used (numeric)
3. Duration of inotrope used in Days (numeric)
4. Pulmonary haemorrhage (Yes/No)
5. Frusemide use (Yes/No)
6. Red cell, fresh frozen plasma and platelet transfusion (Yes/No and number)
7. Frusemide day of life (numeric)
8. Days on total parenteral nutrition (numeric)
9. Time to full feeds (120ml/kg/day of enteral feeds) (numeric)
10. Postnatal steroids administration (Yes/No)
11. PDA treatment beyond day 14 of age (including PDA ligation)

12. Necrotizing enterocolitis (Yes/No)
13. Intraventricular haemorrhage (Yes/No)
14. Days on invasive ventilation (numeric)
15. Number of extubation failures (numeric)
16. Days on continuous positive airway pressure (CPAP) (numeric)
17. Days supplemental oxygen (numeric)
18. Hospital days (numeric)
19. Treated retinopathy of prematurity (Yes/No)
20. Final cranial ultrasound (at 34 weeks corrected): (Normal/IVH/PVL)

The following safety evaluations will be performed during ibuprofen administration:
1. Urine output (daily)
2. Blood pressure (daily)
3. Heart rate (daily)
4. Feeding intolerance (daily)
5. Gastrointestinal haemorrhage (daily)
6. Full blood count for platelet and neutrophil assessment (after three doses)
7. Renal function including sodium and creatinine (after three doses)

0-48 hours: antenatal history, birth demographics, clinical assessment cardiorespiratory characteristics, laboratory tests, and head ultrasound.
36-48 hours: dispensing of study medications, concomitant medications and echocardiogram.
48-120 hours: laboratory tests, concomitant medications, echocardiogram, head ultrasound, adverse event assessments, medication compliance check.
120-168 hours: laboratory tests, concomitant medications, echocardiogram, head ultrasound, adverse event assessments, medication compliance check.
36 weeks: echocardiogram, outcome measures.
3 months: cardiorespiratory characteristics, echocardiogram.

Completion date
01/08/2020

Eligibility

Key inclusion criteria
All infants aged less than 29 weeks admitted to the NICU with a PDA identified on echocardiography between 36 and 48 hours of life will be eligible for inclusion. A comprehensive assessment of PDA significance will be performed using echocardiography to derive a PDA risk score based using a mathematical formula:
(Gestation in weeks × -1.304) + (PDA diameter in mm × 0.781) + (Left ventricular output in ml/kg /min × 0.008) + (maximum PDA velocity in m/s × -1.065) + (LV a` wave in cm/s × -0.470) + 41, where 41 is the constant of the formula

Infants with a risk score ≥ 5.0 are deemed to be at high risk of developing CLD/death and will be randomised to either arm.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Neonate

Upper age limit
29 weeks

Sex
All

Total final enrolment
60

Key exclusion criteria
1. Lack of consent or study investigators to carry out echocardiogram examination
2. Lethal congenital abnormality or obvious syndrome
3. Pulmonary hypoplasia
4. Known or suspected NEC
5. Thrombocytopenia: platelet count < 100/mm2
6. Impaired renal function creatinine > 100 µmol/L; and/or oliguria < 1ml/kg/hour
7. Culture positive sepsis
8. Congenital heart disease other than a PDA or a patent foramen ovale
9. Active bleeding including grade 3 or higher IVH or gastrointestinal haemorrhage

Date of first enrolment
01/09/2016

Date of final enrolment
01/01/2020

Locations

Countries of recruitment
Ireland

Study participating centre
Rotunda Hospital
Parnell Square
Dublin
Ireland
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Sponsor information

Organisation
Royal College of Surgeons in Ireland

ROR
https://ror.org/01hxy9878

Funder(s)

Funder type
Charity

Funder Name
Temple Street Foundation (Ireland)

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are not expected to be made available as this will be against GDPR.

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/02/2021	20/10/2020	Yes	No
Protocol article	RCT protocol	25/11/2020	21/09/2021	Yes	No
Other publications	cohort study	01/02/2021	16/12/2020	Yes	No
Other publications		18/05/2022	18/08/2023	Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes