

Does selective early treatment of patent ductus arteriosus in extreme preterm infants reduce the complications and improve their long-term outcome?

Submission date 13/08/2010	Recruitment status No longer recruiting	<input checked="" type="checkbox"/> Prospectively registered <input checked="" type="checkbox"/> Protocol
Registration date 15/09/2010	Overall study status Completed	<input checked="" type="checkbox"/> Statistical analysis plan <input checked="" type="checkbox"/> Results
Last Edited 15/07/2024	Condition category Neonatal Diseases	<input type="checkbox"/> Individual participant data

Plain English summary of protocol

<https://www.npeu.ox.ac.uk/baby-oscar>

Study website

<https://www.npeu.ox.ac.uk/baby-oscar>

Contact information

Type(s)

Scientific

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Additional identifiers

EudraCT/CTIS number

2013-005336-23

IRAS number

ClinicalTrials.gov number

Nil known

Secondary identifying numbers

Nil known

Study information

Scientific Title

Outcome after Selective early Closure of patent ductus ARteriosus (PDA) in extreme preterm infants: a randomised controlled trial

Acronym

Baby-OSCAR

Study objectives

Current hypothesis as of 03/08/2023:

To determine if the selective treatment of echocardiographically confirmed large PDAs in extremely preterm babies with ibuprofen within 72 hours of birth reduces the incidence of death or bronchopulmonary dysplasia (BPD) at 36 weeks postmenstrual age.

Previous hypothesis as of 10/04/2014:

To determine if the selective treatment of confirmed large PDAs in extremely preterm babies with ibuprofen within 72 hours of birth reduces the incidence of death or bronchopulmonary dysplasia (BPD) at 36 weeks postmenstrual age.

Previous hypothesis:

Early echocardiographic screening and targeted treatment of a PDA that fails to constrict spontaneously (LARGE PDA) will result in reduced incidence of death/chronic lung disease at 36 weeks and eventually less death/neurodevelopmental disability at 2 years corrected age.

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Ethics approval required

Old ethics approval format

Ethics approval(s)

Approved 23/05/2014, Health Research Authority NRES Committee East Midlands - Nottingham 2 (Royal Standard Place Nottingham NG1 6FS, Nottingham, NG1 6FS, United Kingdom; +44 (0) 115 8839425; NRESCommittee.EastMidlands-Nottingham2@nhs.net), ref: 14/EM/0172

Study design

Multicentre randomized placebo-controlled trial

Primary study design

Interventional

Secondary study design

Randomised controlled trial

Study setting(s)

Hospital

Study type(s)

Treatment

Participant information sheet

<https://www.npeu.ox.ac.uk/assets/downloads/baby-oscar/Baby-OSCAR%20PIL%20ENGLAND%20v7.0%20-%2010-Jul-2018.pdf>

Health condition(s) or problem(s) studied

Patent Ductus Arteriosus (PDA)

Interventions

Current interventions as of 10/04/2014:

This trial is intending to treat infants in the same window as the prophylaxis trials using ibuprofen with recommended doses as per study protocol. Patients will be randomised (1:1 ratio) to receive study medications or placebo, intravenously. Study medication will be provided as a clear sterile preservative-free solution for intravenous injection. An initial dose of 10 mg/kg will be followed by two doses of 5 mg/kg at 24 and 48 hours apart. The solution of ibuprofen is provided at a concentration of 10 mg/ml in a 5 ml single-use vial, thus 1 ml/kg, followed by two administrations of 0.5 ml/kg, will be required.

Previous interventions:

This trial is intending to treat infants in the same window as the prophylaxis trials using ibuprofen with recommended doses as per study protocol. Patients will be randomised (1:1 ratio) to receive study medications or placebo, intravenously.

Intervention Type

Drug

Pharmaceutical study type(s)

Not Applicable

Phase

Not Applicable

Drug/device/biological/vaccine name(s)

Ibuprofen

Primary outcome measure

Current primary outcome measures as of 03/08/2023:

The primary outcome is defined as a composite outcome of death by 36 weeks postmenstrual age or moderate or severe BPD at 36 weeks post-menstrual age.

Severity-Based Diagnostic Criteria for BPD is defined as:

Therapy with oxygen $>21\%$ and/or respiratory support for ≥ 28 days and the following:

Mild BPD: Baby is breathing room air

Moderate BPD: Baby is in $22\text{--}29\%$ oxygen, or $0.01\text{--}1.0$ L/min

Severe BPD: $\text{FiO}_2 \geq 0.3$, or low flow oxygen ≥ 1.1 L/min, or the baby is receiving any respiratory support (ventilation, CPAP, or high flow oxygen therapy) to achieve saturations of $\geq 91\%$

The need for oxygen is subjective and hence oxygen dependency is confirmed using an 'oxygen reduction test'. This is based on the threshold at which the baby is able to maintain oxygen saturations $\geq 91\%$ whilst breathing in air or at a given minimum FiO_2 . Babies unable to achieve this are considered to be oxygen-dependent. This test only applies to those babies whose oxygen requirements are <0.3 , or low flow oxygen <1.1 L/min, and who have not received any additional respiratory support in the previous 24h. Babies outside of this are not tested, but data on their oxygen requirements will be collected.

Previous primary outcome measures as of 10/04/2014:

The primary outcome is defined as a composite outcome of death or BPD at 36 weeks post-menstrual age. BPD is defined as the need for respiratory support and/or oxygen for 28 days or more and at 36 weeks post-menstrual age. The need for oxygen is subjective and hence oxygen dependency will be confirmed using an oxygen reduction test. This is based on whether the baby is able to maintain oxygen saturations over 90% for 1 hour whilst breathing air. Babies unable to achieve this will be considered to be oxygen dependant.

Previous primary outcome measures:

Death or severe neuro-developmental disability at 2 years corrected age.

The Bayley's scale of infant development III will be used to assess outcomes.

Secondary outcome measures

Current secondary outcome measures as of 03/08/2023:

Short-term outcomes:

1. Death by 36 weeks postmenstrual age
2. Moderate or severe BPD at 36 weeks postmenstrual age
3. Severity of BPD at 36 weeks postmenstrual age
4. Incidence or duration of the following up to discharge:
 - 4.1. Severe intraventricular haemorrhage (IVH) (grade III/IV with ventricular dilatation or intraparenchymal abnormality)
 - 4.2. Cystic periventricular leukomalacia (PVL)
 - 4.3. Non-cystic PVL
 - 4.4. Hydrocephalus
 - 4.5. Babies treated for retinopathy of prematurity (ROP)
 - 4.6. Significant pulmonary haemorrhage (fresh blood in endotracheal tube with increase in respiratory support)
 - 4.7. Treated for pulmonary hypertension with pulmonary vasodilator
 - 4.8. NEC definitive and/or complicated (Bell stage II and above) confirmed by radiology and/or histopathology
 - 4.9. NEC requiring surgery
 - 4.10. Gastrointestinal bleeding (leading to investigation or clinical treatment) within 7 days of the first dose of trial drug administration
 - 4.11. Spontaneous intestinal perforation
 - 4.12. Closed or non-significant PDA ($<1.5\text{mm}$) at around 3 weeks of age (range of 18–24 days),

confirmed by ECHO

- 4.13. PDA ≥ 1.5 mm at around 3 weeks of age (range of 18–24 days)
- 4.14. Medical open-label treatment of a symptomatic PDA with a COX inhibitor
- 4.15. Open-label treatment of a symptomatic PDA by surgical treatment
- 4.16. Administration and duration of inotropic support
- 4.17. Total duration of respiratory support:
 - 4.17.1. Invasive ventilation through an endotracheal tube
 - 4.17.2. Non-invasive support through nasal CPAP, nasal ventilation, humidified high-flow nasal cannula therapy, or low-flow oxygen ≥ 1.1 L/min
- 4.18. Discharge home on oxygen
- 4.19. Duration of initial hospitalisation (birth to discharge home)
- 4.20. Postnatal steroid use for chronic lung disease
- 4.21. Tolerance of ibuprofen treatment within the foreseeable SAE reporting range
- 4.22. Weight gain: a change in z score between birth and discharge (or death if sooner)
- 4.23. Head circumference: a change in head size z score between randomisation and discharge (or death if sooner)

Long-term outcomes assessed at 2 years of age corrected for prematurity:

- 5. Survival without moderate or severe neurodevelopmental disability (main long-term outcome)
- 6. Survival
- 7. Individual components of survival without moderate or severe neurodevelopmental disability (in the four domains of motor, cognitive, hearing and visual function). Cognitive disability will be assessed by determining the standardised non-verbal cognitive subscale and language subscale scores obtained through the Parent Report of Cognitive Abilities–Revised (PARCA-R) assessment. The PARCA-R assessment will be adapted to include questions to assess gross motor, hearing and visual function.
- 8. Survival without respiratory morbidity. Respiratory morbidity will be assessed by the need for oxygen or respiratory support; presence of persistent cough and/or wheeze; need for regular treatment for respiratory illness; unscheduled attendances at hospital/GP; readmission to hospital for respiratory problems
- 9. Duration of oxygen supplementation from randomisation
- 10. A cost-effectiveness analysis will be conducted of deaths and BPD events avoided and national health services used up to 2 years of age corrected for prematurity

Process outcomes:

- 11. Number of doses of trial medication received
- 12. Adherence to protocol (e.g. protocol violations, incidence of non-symptomatic open-label treatment etc)
- 13. Study withdrawals

Previous secondary outcome measures as of 10/04/2014:

Secondary outcomes are divided into short- and long-term outcomes:

- 1. Short-term outcomes:
 - 1.1. Death before discharge
- 2. Incidence or duration of the following up to time of neonatal unit discharge:
 - 2.1. Severity of BPD at 36 weeks postmenstrual age
 - 2.2. Severe IVH (grade 3/4 with ventricular dilation or intraparenchymal bleeding)
 - 2.3. Cystic periventricular leukomalacia (PVL)
 - 2.4. Retinopathy of prematurity (ROP) requiring treatment
 - 2.5. Pulmonary haemorrhage

- 2.6. Pulmonary hypertension
- 2.7. NEC definitive and/or complicated (Bell stage II and above) confirmed by radiology or histopathology
- 2.8. NEC requiring surgery
- 2.9. Gastrointestinal bleeding within 7 days of the first dose of study drug administration
- 2.10. Spontaneous intestinal perforation
- 2.11. PDA closure at 3 weeks of age (or hospital discharge, if discharged before this age)
- 2.12. Medical rescue treatment with a COX inhibitor of a symptomatic PDA
- 2.13. Administration and duration of inotropic support
- 2.14. Duration of mechanical ventilation
- 2.15. Total duration of respiratory support (ventilation + nCPAP/high flow oxygen therapy)
- 2.16. Discharge home on oxygen
- 2.17. Duration of initial hospitalisation (birth to neonatal unit discharge home)
- 2.18. Postnatal steroid use
- 2.19. Safety and tolerability of ibuprofen treatment
- 2.20. Number of doses of trial medication received during intervention period
- 3. Secondary long-term clinical outcomes assessed at 2 years of age corrected for prematurity
 - 3.1. Survival without moderate or severe neurodevelopmental disability
 - 3.2. Individual components of survival without moderate or severe neurodevelopmental disability (in the four domains of motor, cognitive, hearing and visual function)
 - 3.3. Survival without respiratory morbidity
 - 3.4. A cost-effectiveness analysis will be conducted of deaths and BPD events avoided and national health services used up to 2 years of age corrected for prematurity

Previous secondary outcome measures:

- 1. Mortality
- 2. Complications of prematurity
- 3. Cardiovascular effects
- 4. Respiratory outcomes
- 5. Acute abdominal problems
- 6. Side effects of medicine
- 7. Length of hospital stay
- 8. Developmental outcome at 2 years

Overall study start date

01/07/2014

Completion date

31/08/2023

Eligibility

Key inclusion criteria

Current inclusion criteria as of 03/08/2023:

- 1. Born at 23+0 to 28+6 weeks of gestation
- 2. Less than 72 hours old
- 3. Confirmed by echocardiography to have a large PDA which is at least 1.5 mm in diameter (determined by gain optimised colour Doppler) AND has unrestrictive pulsatile (left to right) flow (ratio of flow velocity in PDA Maximum (Vmax) to Minimum (Vmin) > 2:1)) or, growing flow pattern (< 30% right to left), and no clinical concerns of pulmonary hypertension
- 4. The responsible clinician is uncertain about whether this baby might benefit from treatment

to close the PDA

5. Written informed consent has been obtained from the parent(s)

Previous inclusion criteria as of 10/04/2014:

1. Born at 23+0 to 28+6 weeks of gestation
 2. Less than 72 hours old
 3. Confirmed by echocardiography to have a large PDA which is at least 1.5 mm in diameter (determined by gain optimised colour Doppler) AND has unrestrictive pulsatile left to right flow
 4. The responsible clinician is uncertain about whether this baby might benefit from treatment to close the PDA
 5. Written informed consent has been obtained from the parent(s)
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Previous inclusion criteria:

1. Preterm infants born between 23+0 and 28+6 weeks gestation
2. Echocardiographic assessment within 24 hours of birth meeting the enrolment criteria
3. Signed parental consent

Participant type(s)

Patient

Age group

Neonate

Upper age limit

3 Days

Sex

Both

Target number of participants

730 infants

Total final enrolment

653

Key exclusion criteria

Current exclusion criteria as of 03/08/2023:

1. No realistic prospect of survival
 2. Severe congenital anomaly
 3. Clinical or echocardiography suspicion of congenital structural heart disease that contraindicates treatment with ibuprofen
 4. Other conditions that would contraindicate the use of ibuprofen (active bleeding especially intracranial or gastrointestinal bleeding, coagulopathy, thrombocytopenia (platelet count <50,000), renal failure, life threatening infection, pulmonary hypertension, known or suspected necrotising enterocolitis (NEC))
 5. Indomethacin, ibuprofen, or paracetamol administration after birth
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Previous exclusion criteria as of 10/04/2014:

1. No realistic prospect of survival
2. Severe congenital anomaly
3. Structural heart disease requiring treatment
4. Other conditions that would contraindicate the use of ibuprofen (clinically significant intracranial or gastrointestinal haemorrhage, coagulopathy, thrombocytopenia [platelet count <50,000], renal failure, pulmonary hypertension, known or suspected necrotising enterocolitis [NEC])
5. Antenatal exposure to cyclo-oxygenase (COX) inhibitors
6. Received indomethacin, ibuprofen or paracetamol administration after birth

Previous exclusion criteria:

1. Baby clinically unstable and not expected to survive
2. Congenital anomalies predicted to influence neurodevelopmental outcome
3. Structural heart disease
4. Contraindication to use of ibuprofen (platelet count <50,000)
5. Unlikely to commence first dose of treatment by 24 hours of age

Date of first enrolment

01/07/2014

Date of final enrolment

31/12/2020

Locations

Countries of recruitment

England

United Kingdom

Study participating centre

Professor of Neonatology

Stockton-on-Tees

United Kingdom

TS19 8PE

Sponsor information

Organisation

University of Oxford (UK)

Sponsor details

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Sponsor type

University/education

ROR

<https://ror.org/052gg0110>

Funder(s)

Funder type

Government

Funder Name

NIHR Health Technology Assessment Programme - HTA (UK)

Results and Publications

Publication and dissemination plan

Not provided at time of registration

Intention to publish date

01/09/2023

Individual participant data (IPD) sharing plan

The NPEU is committed to sharing data with the research community. Data will be shared in accordance with the National Perinatal Epidemiology Unit Data Sharing policy. Requests for access to the data will be considered by the National Perinatal Epidemiology Unit Data Sharing Committee. Access to anonymized data can be requested from ctu@npeu.ox.ac.uk.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	26/02/2021	01/03/2021	Yes	No
Statistical Analysis Plan	statistical analysis plan	26/05/2021	28/05/2021	No	No
Statistical Analysis Plan	version 1.0	20/04/2023	20/06/2023	No	No
Participant information sheet	version 7.0	10/07/2018	03/08/2023	No	Yes
Results article		25/01/2024	25/01/2024	Yes	No
Other files	2 year form version 2.0	10/07/2018	15/07/2024	No	No