ISRCTN84264977 https://doi.org/10.1186/ISRCTN84264977

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

Registration date
15/09/2010

Last Edited
24/11/2026

Recruitment status
No longer recruiting

Overall study status
Completed

Condition category
Neonatal Diseases

[X] Prospectively registered
[X] Protocol
[X] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol
https://www.npeu.ox.ac.uk/baby-oscar

Contact information

Type(s)
Scientific

Contact name
Prof Samir Gupta

Contact details
Durham University
University Hospital of North Tees
Hardwick Road
Stockton-on-Tees
United Kingdom
TS19 8PE
+974 (0)31000586; +44 (0)7584905920
samir.gupta@durham.ac.uk

Additional identifiers

Clinical Trials Information System (CTIS)
2013-005336-23

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.

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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.

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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

Primary study design
Interventional

Study design
Multicentre randomized placebo-controlled trial

Study type(s)
Treatment

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

Phase
Not Applicable

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

Primary outcome(s)
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 22–29% oxygen, or 0.01–1.0 L/min
Severe BPD: FiO2 ≥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 ≥ 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 ≥91% whilst breathing in air or at a given minimum FiO2. 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 <1.1L/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.

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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.

Key secondary outcome(s)

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 (<1.5mm) at around 3 weeks of age (range of 18–24 days), confirmed by ECHO
4.13. PDA ≥1.5mm 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 ≥1.1L/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

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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

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)

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

Healthy volunteers allowed
No

Age group
Neonate

Lower age limit
0 Days

Upper age limit
3 Days

Sex
All

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

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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
United Kingdom

England

Study participating centre
Professor of Neonatology
-
Stockton-on-Tees
England
TS19 8PE

Sponsor information

Organisation
University of Oxford (UK)

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Government

Funder Name
NIHR Health Technology Assessment Programme - HTA (UK)

Results and Publications

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?
Results article	Short-term outcomes	25/01/2024	25/01/2024	Yes	No
Results article	2-year outcomes	20/08/2025	04/09/2025	Yes	No
Results article	NIHR report	01/02/2026	09/02/2026	Yes	No
Protocol article		26/02/2021	01/03/2021	Yes	No
HRA research summary			24/11/2026	No	No
Other files	2-year form version 2.0	10/07/2018	15/07/2024	No	No
Participant information sheet	version 7.0	10/07/2018	03/08/2023	No	Yes
Preprint results	Health economic outcomes	24/06/2025	13/01/2026	No	No
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
Study website		11/11/2025	11/11/2025	No	Yes