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Does general anaesthesia and oxygen affect markers on DNA in children?

Submission date
12/11/2022

Recruitment status
Recruiting

Registration date
22/05/2023

Overall study status
Ongoing

Last Edited
09/06/2025

Condition category
Surgery

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
More than half a million children have an anaesthetic each year in the UK. Though anaesthesia in these children is usually thought to be safe, concerns remain about potential long-term health effects of the drugs used. During general anaesthesia children also require additional oxygen, but there remains uncertainty over the safest amount of oxygen to give. Evidence suggests that both too much and too little oxygen could cause harm.
Gene expression is the process by which instructions in DNA are used to make products such as proteins. Laboratory studies have shown that anaesthetic drugs and oxygen may both alter gene expression through a process called epigenetics.
This study will focus on children aged under 3 undergoing general anaesthesia for hip surgery at University Hospital Southampton and will run for up to 12 months. Participants will be given either 25% or 60% oxygen (chosen at random) during their operation – both values within the normal amounts of oxygen that may be used during anaesthesia. A small blood sample (between 1 and 2 teaspoons) will be collected at the start and end of their first anaesthetic and then again at the start of their second anaesthetic when their cast is changed. Blood samples will only be taken when the child is under anaesthetic. The samples from the different times will be analysed to look for any changes in signals on DNA (epigenetic changes) and other markers which may be associated with the anaesthetic drugs, and results from the two different oxygen levels will be compared.
There is relatively less medical research carried out in children and this work will show whether this type of study is possible in this age-group and provide information for future trials. It will help towards improving our understanding of the effects of anaesthesia ultimately help doctors and families make better informed decisions.

Who can participate?
Children aged under 3 undergoing general anaesthesia for hip surgery at University Hospital Southampton.

What does the study involve?
The trial randomises participants to a fixed level of additional oxygen during their anaesthetic as we want to see the effects of these two levels on markers within DNA. However, the levels being used were selected as these are within the normal ranges that patients may recieve at

different stages during an anaesthetic. In addition, the anaesthetist responsible for this case will closely monitor oxygen levels throughout the anaesthetic, as they do normally, and if they do drop below safe limits, they will treat this in exactly the same way as they normally would, including giving more oxygen if required.

What are the possible benefits and risks of participating?
Benefits:
Children are unlikely to benefit directly from taking part in this study, however, the knowledge gained from their participation may aid in developing a larger research study and will help improve our understanding of the effects of anaesthesia and oxygen on children's DNA. In the future this type of research may help us with decision making in relation to procedures such as theirs and improve the quality of care we can deliver.
Risks:
3 blood samples will be taken and then analysed to allow the team to look at the effects of oxygen and general anaesthesia on markers within the DNA of red blood cells. Collecting blood samples can be painful, therefore all blood samples in this study will be collected under anaesthesia to remove any distress this process may cause. As with all blood tests there is a risk of bruising, so where possible we will aim to collect the sample from their normal cannula to minimise the chances of a small bruise. This risk of a local infection from a blood test is very small.
There will be no additional hospital visits required as part of this trial, the protocol utilises planned/routine visits.
It is unlikely that a child's oxygen levels will drop too low during the surgery, but the anaesthetist will be closely monitoring these and if they do drop below safe levels, they will treat this in exactly the same way as they normally would, including giving more oxygen if required

Where is the study run from?
University Hospital Southampton National Health Service (NHS) Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
January 2022 to June 2027

Who is funding the study?
The National Institute for Health and Care Research (NIHR) will fund the salary of the Chief Investigator through the provision of an Academic Clinical Fellowship. The remaining cost of the trial will be met by an award from University Hospital Southampton's Research and Development department's small grants scheme.

Who is the main contact?
Dr Joseph Larvin, j.larvin@soton.ac.uk

Contact information

Type(s)
Principal Investigator

Contact name
Dr Joseph Larvin

Contact details

Department of Anaesthesia
Southampton General Hospital
Southampton
United Kingdom
SO16 6YD
+44 7906390486
j.larvin@soton.ac.uk

Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
1006664

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CRI0427, GRT0717, IRAS 1006664

Study information

Scientific Title
The EPIgenetic consequences in children of Volatile-based anaesthesia and surgery, with high or low OXygen exposure (EPI-VOX) – A single centre, double-blinded, randomised, feasibility trial

Acronym
EPI-VOX feasibility trial

Study objectives
Primary objective:
To assess and determine the feasibility (whether it is possible) of conducting a study in which children are randomised to two levels of oxygen whilst under anaesthesia in order to look at how anaesthesia and oxygen affect markers within their DNA (epigenetics).
This is an important objective as we are not aware of any similar studies in this context and this aims to refine and strengthen the case for a larger clinical trial in this research area.

Secondary objectives:
1. Investigate whether there are changes in markers on DNA (epigenetic) associated with gas-based (volatile) anaesthesia in each patient group, and if present whether these changes are immediate, persistent, or delayed.
2. Investigate whether oxygen exposure impacts any changes observed, or whether it is independently associated with epigenetic changes in this patient group.
3. Identify which functional biological processes or pathways any changes may potentially be involved in.
These are important objectives as they target an unanswered clinical question - whether volatile-based anaesthesia may have an impact on the epigenetic profiles of paediatric patients.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 17/05/2023, London Central REC (3rd Floor, Barlow House, 4 Minshull Street, Manchester, M1 3DZ, UK; +44 (0)207 104 8225; londoncentral.rec@hra.nhs.uk), ref: 22/LO/0881

Study design
Interventional randomized controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet

Health condition(s) or problem(s) studied
Children aged under 3 years old and undergoing general anaesthesia and surgery for developmental dysplasia of the hip.

Interventions
Current intervention as of 16/06/2023:
Participants that meet the eligibility criteria will be randomised to either the high or low oxygen exposure group. This will take place after their legal representative/s have given their informed consent and prior to the induction of anaesthesia. ALEA (a web-based system designed for secure data storage and management) will provide an online randomisation service which will be used to allocate subjects in a 1:1 ratio between the groups in a similar way to previous studies performed by the University Hospital Southampton's Critical Care research group.

The participant's anaesthetist for the case will remain unblinded to this allocation in order to deliver the intervention and for safety reasons, however this individual will have no role in randomisation, or subsequent analysis. The participant, their legal representative/s and the members of the investigation team will remain blinded for the duration of the trial. Only the ALEA service administrators will have access to the randomisation sequence.

As is routine anaesthetic practice for this age-group, a gas induction using the volatile agent sevoflurane in combination with oxygen will be performed for both groups. Children in the high oxygen randomisation group will receive 60% oxygen from the point of gas induction. Children in the low oxygen group will receive 50% oxygen during gas induction until an endotracheal tube has been placed, at which point this will be changed to 25% oxygen. 60% oxygen and 25% oxygen will then be continued, for high and low oxygen exposure groups respectively, for the

entire duration of the surgical procedure unless there is a clinical need for the level to be altered. These levels are both within the range of oxygen that a patient could expect to be exposed to at different stages of a standard general anaesthetic.

For both groups, after induction of anaesthesia a baseline sample of blood (5-10 mls in total) will be taken from the intravenous cannula that is inserted as part of routine care. If an inadequate volume of blood is obtained through this method, the sample may be obtained either though peripheral venipuncture or a heel-prick. For both groups, the anaesthetic and surgical care will then follow routine practice, including insertion of a lumbar epidural and maintenance of anaesthesia with the volatile agent sevoflurane
After the surgical procedure has been completed, and prior to cessation of general anaesthesia and emergence, a further blood sample will be taken for analysis from both groups (5-10 mls). This will be obtained via the cannula (after withdrawing and discarding 5 mls). If an inadequate volume of blood is obtained through this method, then the sample may be obtained either though peripheral venipuncture or a heel-prick.

Participants will then be followed up on their return to hospital approximately 6 weeks later for a cast change which is conducted under general anaesthesia, as is routine practice. On this occasion, one further blood sample of 6mls will be taken after induction of anaesthesia, as per the process discussed above for each group for the first sample taken at the time of the initial surgery. On this occasion, after the sample is successfully obtained post-induction, no further data will be recorded.

Of the procedures described above, the deviations from routine clinical practice are:
1. The delivery of a fixed level of oxygen, which are both within the range that children are typically exposed to during general anaesthesia. The high oxygen exposure will receive 60% throughout and the low oxygen exposure group will receive 50% during gas induction and intubation, then 25% for the duration of the surgery
2. The peripheral sampling of blood at 3 time points which, where possible, will be taken from the intravenous cannula that is inserted as part of routine practice. Each will be conducted whilst the child is under general anaesthesia.

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Previous intervention:
Participants that meet the eligibility criteria will be randomised to either the high or low oxygen exposure group. This will take place after their legal representative/s have given their informed consent and prior to the induction of anaesthesia. ALEA (a web-based system designed for secure data storage and management) will provide an online randomisation service which will be used to allocate subjects in a 1:1 ratio between the groups in a similar way to previous studies performed by the University Hospital Southampton's Critical Care research group.

The participant's anaesthetist for the case will remain unblinded to this allocation in order to deliver the intervention and for safety reasons, however this individual will have no role in randomisation, or subsequent analysis. The participant, their legal representative/s and the members of the investigation team will remain blinded for the duration of the trial. Only the ALEA service administrators will have access to the randomisation sequence.

As is routine anaesthetic practice for this age-group, a gas induction using the volatile agent sevoflurane in combination with oxygen will be performed for both groups. Children in the high oxygen randomisation group will receive 70% oxygen from the point of gas induction. Children in the low oxygen group will receive 50% oxygen during gas induction until an endotracheal tube

has been placed, at which point this will be changed to 30% oxygen. 70% oxygen and 30% oxygen will then be continued, for high and low oxygen exposure groups respectively, for the entire duration of the surgical procedure unless there is a clinical need for the level to be altered. These levels are both within the range of oxygen that a patient could expect to be exposed to at different stages of a standard general anaesthetic.

For both groups, after induction of anaesthesia a baseline sample of blood (6 mls in total) will be taken from the intravenous cannula that is inserted as part of routine care. If an inadequate volume of blood is obtained through this method, the sample may be obtained either though peripheral venipuncture or a heel-prick. For both groups, the anaesthetic and surgical care will then follow routine practice, including insertion of a lumbar epidural and maintenance of anaesthesia with the volatile agent sevoflurane
After the surgical procedure has been completed, and prior to cessation of general anaesthesia and emergence, a further blood sample will be taken for analysis from both groups (6 mls). This will be obtained via the cannula (after withdrawing and discarding 5 mls). If an inadequate volume of blood is obtained through this method, then the sample may be obtained either though peripheral venipuncture or a heel-prick.

Participants will then be followed up on their return to hospital approximately 6 weeks later for a cast change which is conducted under general anaesthesia, as is routine practice. On this occasion, one further blood sample of 6mls will be taken after induction of anaesthesia, as per the process discussed above for each group for the first sample taken at the time of the initial surgery. On this occasion, after the sample is successfully obtained post-induction, no further data will be recorded.

Of the procedures described above, the deviations from routine clinical practice are:
1. The delivery of a fixed level of oxygen, which are both within the range that children are typically exposed to during general anaesthesia. The high oxygen exposure will receive 70% throughout and the low oxygen exposure group will receive 50% during gas induction and intubation, then 30% for the duration of the surgery
2. The peripheral sampling of blood at 3 time points which, where possible, will be taken from the intravenous cannula that is inserted as part of routine practice. Each will be conducted whilst the child is under general anaesthesia.

Intervention Type
Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)
Medical oxygen

Primary outcome measure
This is a feasibility trial, with feasibility as the primary endpoint. This will comprise of several outcome measures as listed below measured at completion of the trial (target 10 patient recruitment):
1. Number of eligible patients screened – those meeting the eligibility criteria who were approached to take part
2. Recruitment rate – number of participants randomized divided by the number screened
3. Retention/withdrawal rate – number of participants that complete the study divided by the

number who start it
4. Protocol compliance – number of deviations from trial protocol for each patient (and details)
5. Acceptability for participants and clinical staff – formal and informal feedback
6. Success of data management system - recorded issues with randomisation blinding and confidential storage. Opinion of research team on ease of use.
7. Additional resource requirements – List of time, costs and equipment not discussed in protocol

Secondary outcome measures
The secondary endpoints will be 'epigenetic changes' which will be assessed by ‘DNA methylation’ at CpG sites present throughout the human genome through the use of the Illumina Infinium HumanMethylation 850K array. This will include both the level and location of change at at different time-points and between the two oxygen exposure groups. This will be evaluated once all samples for all recruited participants have been collected and undergone HumanMethylation 850K array analysis.

Overall study start date
01/01/2022

Completion date
06/06/2027

Eligibility

Key inclusion criteria
1. Age ≥6 months and ≤3 years at time of initial operation
2. Undergoing surgical management of DDH (unilateral or bilateral)
3. Completed informed consent form (ICF) from legal representative (LR (this is the person who is empowered to give informed consent on behalf of a participant. For most children this will be one or both parents. This may also be a guardian or custodian with legal custody)).

Participant type(s)
Patient

Age group
Child

Lower age limit
6 Months

Upper age limit
3 Years

Sex
Both

Target number of participants
10

Key exclusion criteria

1. Legal representative (LR) unable to provide completed ICF
2. Withdrawal of consent at any stage
3. Previous exposure to general anaesthesia at any stage of life, including in-utero (through maternal exposure at any stage until delivery)
4. Neurodevelopmental/neurodisability diagnosis (given or under investigation) from a paediatric service including autistic spectrum disorder (ASD), attention deficit disorder (ADHD), traumatic brain injury (TBI), down's syndrome, cerebral palsy, epilepsy
5. Chronic respiratory diagnosis (given or under investigation) from a paedatric service, including bronchopulmonary dysplasia and cystic fibrosis with pulmonary manifestations, but excluding asthma
6. Clinical opinion that randomising the child's oxygen exposure would be unsafe
7. Clinical opinion that the use of a volatile anaesthesic agent would be unsafe

Date of first enrolment
01/09/2023

Date of final enrolment
29/12/2025

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Southampton General Hospital
University Hospital Southampton NHS Foundation Trust
Tremona Road
Southampton
United Kingdom
SO16 6YD

Sponsor information

Organisation
University Hospital Southampton NHS Foundation Trust

Sponsor details
Level E, Laboratory & Pathology Block
Southampton General Hospital
Tremona Rd
Southampton
England

United Kingdom
SO16 6YD
-
sponsor@uhs.nhs.uk

Sponsor type
Hospital/treatment centre

Website
http://www.uhs.nhs.uk/home.aspx

ROR
https://ror.org/0485axj58

Funder(s)

Funder type
Government

Funder Name
National Institute for Health and Care Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Peer reviewed scientific journals
Internal report
Conference presentation
Data will be rendered anonymous before sharing and this is acknowledged within the informed consent form.

Requests can be made to the research team by other researchers wishing to access this data and these will be reviewed by the trial management group and the R&D department of the host institution before sharing.

Intention to publish date
30/06/2027

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be available upon request from Dr Joseph Larvin - j.larvin@soton.ac.uk, this will include the baseline characteristics of patients, feasibility results, and the results of the 850k microarray analysis. This data will be made available from the point of first publication of the results, or 2 years after recruitment is closed. Requests for access to the datasets will be discussed by the study's trial management group before any information is shared and data will remain anonymised at all stages. Age at time of recruitment in years and months will be provided as opposed to date of birth will not be. As part of the informed consent process, the legal representatives of each participant are asked to confirm that they "understand that my child's anonymised data, including the level of markers on their DNA (epigenetic results), may be shared with other researchers to analyse, in line with the principles of research transparency."

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			20/09/2023	No	No