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Protecting the heart with remote ischaemic preconditioning during children's heart surgery

Submission date
30/04/2016

Recruitment status
No longer recruiting

Registration date
25/05/2016

Overall study status
Completed

Last Edited
05/04/2024

Condition category
Circulatory System

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

Plain English summary of protocol

Background and study aims
Congenital heart disease is a general term used to describe a range of birth defects that affect the way the heart works. Children with congenital heart disease often need operations to correct the abnormality that they were born with to improve their chance of survival and quality of life. The surgery is complex and usually involves a period of support on a heart-lung machine (cardiopulmonary bypass) whilst the defect is repaired. The surgery puts a strain on the child's heart and may potentially cause a type of damage called ischaemia-reperfusion injury (tissue damage when the blood supply to the heart is interrupted and restored). Previous studies have found that using a blood pressure cuff to stop blood flow to one or more limbs (Remote ischemic preconditioning (RIPC)) for short periods immediately before surgery may reduce any damage to the heart during surgery and thereby make the surgery safer. This study is going to look at RIPC in children with two common types of congenital heart conditions, ventricular septal defect (in which there is a hole in the wall between the lower chambers of the heart) and tetralogy of Fallot (a condition which combines four defects in the heart muscle). The aim of this study is to find out whether RIPC improves heart protection in all or just some children.

Who can participate?
Children aged between three months and three years who are undergoing surgery due to a heart defect they were born with (Tetralogy of Fallot or Ventricular Septal Defect).

What does the study involve?
Children are randomly allocated to one of two groups. Those in the first group receive RIPC. This involves placing a tourniquet (precisely controlled blood pressure cuff) around the top of each leg once the child is asleep (under anaesthesia) and inflating it for 5 minutes to stop the blood supply, then deflating it for 5 minutes to allow the blood supply to resume. This is repeated three times to get the most accurate result. For those in the second group, the cuffs are placed beside the patient around a dummy limb for the inflation-deflation cycles. In all cases, the cuffs are covered with a drape to ensure that it is not known which procedure the children receive. For both groups, blood and muscle samples are taken during surgery to measure if there is a difference in how the heart cells make energy between children with normal or low blood oxygen levels and whether this is affected by using RIPC.

What are the possible benefits and risks of participating?
There may not be any benefit from participating as whilst some previous studies have shown that the blood pressure cuff technique helps to protect children’s hearts from injury during surgery, it is unknown whether it is beneficial to all children with all types of congenital heart disease. There are no notable risks of participating, as the technique being used is safe with no complications reported related to the technique in either children or adults undergoing any type of surgery.

Where is the study run from?
University of Birmingham (UK), Birmingham Children's Hospital (UK), and Leeds Children's Hospital (UK)

When is the study starting and how long is it expected to run for?
December 2014 to December 2020

Who is funding the study?
British Heart Foundation (UK)

Who is the main contact?
Mr Nigel Drury
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Contact information

Type(s)
Public, Principal Investigator

Contact name
Mr Nigel Drury

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Additional identifiers

EudraCT/CTIS number

IRAS number
200876

ClinicalTrials.gov number

Secondary identifying numbers
1845, IRAS 200876

Study information

Scientific Title
The Bilateral Remote Ischaemic Conditioning in Children trial

Acronym
BRICC

Study objectives
1. Remote ischemic preconditioning (RIPC) improves myocardial protection and reduces markers of IR injury in young children undergoing surgery; however, the benefits may be attenuated in those with chronic hypoxia
2. RIPC leads to a reduction in the accumulation of citric acid cycle intermediates during ischaemia; however, this effect may be reduced in those with chronic hypoxia
3. Succinate concentration is significantly higher in the chronically hypoxic myocardium than in the previously normoxic heart, both at the onset and at the end of surgical ischaemia

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 05/08/2016, West Midlands-Solihull NHS Research Ethics Committee (The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS; +44 0207 104 8019; NRESCommittee.WestMidlands-Solihull@nhs.net), ref: 16/WM/0309

Study design
Two-centre prospective double-blind randomized controlled trial

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 the contact details to request a patient information sheet

Health condition(s) or problem(s) studied

Prevention of ischaemia-reperfusion injury in children undergoing surgery for tetralogy of Fallot or ventricular septal defect

Interventions

On the day of surgery, participants will be randomised to either Remote Ischaemic Preconditioning (RIPC) or control in a 1:1 ratio using an online randomisation system. Patients will be stratified for the congenital heart defect undergoing repair (TOF or VSD) and the presence of a RVOT stent in patients with TOF. In all cases, the cuffs will be covered with a drape to maintain blinding.

RIPC group: After induction of anaesthesia but prior to sternotomy, participants will receive RIPC induced by 3 cycles of 5-minutes ischaemia and 5-minutes reperfusion. Ischaemia will be induced simultaneously in two limbs using the PTSii system (Delfi Medical, Vancouver), a state-of-the-art digital tourniquet with precise control of occlusion pressure. Age-appropriate PediFit cuffs, with Contour limb protection sleeves, will be placed around both thighs and inflated to at least 50mmHg above systolic pressure measured via the arterial line; if vascular access is problematic and the femoral route is required by the anaesthetist, one cuff will be placed on the thigh and the other on the upper arm.

Control group: The cuffs will be placed beside the patient for sham inflation-deflation cycles on a dummy limb.

Following surgery, all patients will be followed-up until discharge from hospital or 30 days, whichever is sooner.

Intervention Type

Procedure/Surgery

Primary outcome measure

Myocardial injury, determined by area under the time-concentration curve (AUC) for high-sensitivity troponin-T in the first 24 hours, measured at baseline, 3, 6, 12 and 24 hours after aortic cross-clamp release (reperfusion).

Secondary outcome measures

Current secondary outcome measures as of 24/03/2020:
1. Myocardial injury, measured by peak hs-troponin-T in the first 12 hours, measured at baseline, 3, 6 and 12 hours after reperfusion
2. Inotropic support, determined by vasoactive inotrope score over the first 12 hours after reperfusion
3. Metabolic debt, measured by serum lactate concentration and mixed venous oxygen saturations over the first 12 hours after reperfusion
4. Length of stay, determined by the period of time required in the paediatric intensive care unit and the hospital following surgery
5. Exploratory outcome: myocardial function, measured by cardiac index using the ICON device over the first 12 hours after reperfusion

Previous secondary outcome measures:
1. Myocardial injury, measured by peak hs-troponin-T in the first 12 hours, measured at baseline, 3, 6, 12 and 24 hours after reperfusion
2. Myocardial function, measured by cardiac index using the ICON device over the first 12 hours after reperfusion

3. Inotropic support, determined by inotrope score over the first 12 hours after reperfusion
4. Metabolic debt, measured by serum lactate concentration and mixed venous oxygen saturations over the first 12 hours after reperfusion
5. Length of stay, determined by the period of time required in the paediatric intensive care unit and the hospital following surgery

Overall study start date
11/12/2014

Completion date
21/12/2020

Eligibility

Key inclusion criteria
Current participant inclusion criteria as of 24/03/2020:
1. Aged 3 months to 3 years at the time of surgery
2. Undergoing elective primary repair of Tetralogy of Fallot (TOF) or Ventricular Septal Defect (VSD), with or without a concomitant atrial septal defect (ASD) or pulmonary artery repair /augmentation, at Birmingham Children's Hospital or Leeds Children's Hospital.

Previous participant inclusion criteria:
1. Aged 3 months to 3 years at the time of surgery
2. Undergoing elective primary repair of Tetralogy of Fallot (TOF) or Ventricular Septal Defect (VSD), with or without a concomitant atrial septal defect (ASD)

Participant type(s)
Patient

Age group
Child

Lower age limit
3 Months

Upper age limit
3 Years

Sex
Both

Target number of participants
120

Total final enrolment
120

Key exclusion criteria
Current participant exclusion criteria as of 24/03/2020:
1. Those requiring an additional procedure (other than ASD closure) at the time of primary repair

e.g. aortic arch repair
2. Those with significant airway or parenchymal lung disease, bleeding disorder or recent ischaemic event
3. Those who have undergone a previous cardiac surgical procedure with cardioplegic arrest.
4. Those presenting in a critical condition and requiring emergency cardiac surgery
5. Those for whom the parents are unwilling or unable to give informed consent

Previous participant exclusion criteria:
1. Those requiring an additional procedure (other than ASD closure) at the time of primary repair e.g. aortic arch repair
2. Those with a known major chromosomal defect, significant airway or parenchymal lung disease, bleeding disorder or recent ischaemic event
3. Those presenting in a critical condition and requiring emergency cardiac surgery
4. Those for whom the parents are unable to give informed consent

Date of first enrolment
15/08/2016

Date of final enrolment
08/12/2020

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Birmingham Children's Hospital
Steelhouse Lane
Birmingham
United Kingdom
B4 6NH

Study participating centre
Leeds Children's Hospital
Clarendon Wing
Leeds General Hospital
Leeds
United Kingdom
LS1 3EX

Sponsor information

Organisation
University of Birmingham

Sponsor details
Edgbaston
Birmingham
England
United Kingdom
B15 2TT

Sponsor type
University/education

Website
https://intranet.birmingham.ac.uk/finance/accounting/Research-Support-Group/Research-Governance/index.aspx

ROR
https://ror.org/03angcq70

Funder(s)

Funder type
Charity

Funder Name
British Heart Foundation

Alternative Name(s)
the_bhf, The British Heart Foundation, BHF

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Publication and dissemination plan

The findings of this clinical trial and metabolomics studies will be submitted for presentation at national and international meetings. Manuscripts will be prepared for submission to leading journals.

Intention to publish date
04/03/2024

Individual participant data (IPD) sharing plan
Requests for access to data should be addressed to the Chief Investigator Nigel Drury (nigel.drury@nhs.net). Individual participant data collected during the trial (including the data dictionary) will be available, after deidentification, when the article has been published with no end date. All proposals requesting data access must specify how the data will be used, and all proposals will need the approval of the Trial Management Committee before data release.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	07/10/2020	14/10/2020	Yes	No
Other publications	Qualitative substudy results	23/02/2021	25/02/2021	Yes	No
HRA research summary			28/06/2023	No	No
Results article		05/03/2024	05/04/2024	Yes	No