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Normothermic versus hypothermic cardiopulmonary bypass in paediatric open heart surgery

Submission date
19/12/2008

Recruitment status
No longer recruiting

Registration date
27/02/2009

Overall study status
Completed

Last Edited
07/05/2019

Condition category
Surgery

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

Plain English summary of protocol

Background and study aims
During open-heart surgery a patient is connected to a heart-lung bypass machine (cardiopulmonary bypass, CPB) which continues to pump blood around the body (perfusion) while the heart is stopped, allowing the surgeons to operate upon it. Typically the blood is cooled during this procedure (hypothermia) and re-warmed to normal body temperature again once the operation has been completed. This is standard practice at the Bristol Children's Hospital (BCH). However, there have been experiments in adult patients which suggest that there are benefits to keeping the blood at normal body temperature throughout surgery (normothermia) instead of cooling it. The main rationale for whole body cooling is to protect organs such as the brain, the kidneys, the lungs and the heart from injury during CPB by reducing the body's metabolic rate and thus decreasing oxygen consumption. However, hypothermic perfusion also has a number of disadvantages including detrimental effects on enzymatic function, energy generation and cellular integrity, which can all contribute towards an extended hospital stay after the operation. Given these factors, CPB with normothermic perfusion is gaining popularity as a viable alternative and research with adult patients has suggested a possible reduction in certain chemical markers of tissue injury as a result of using the normothermic technique, when compared against the hypothermic technique, which could help improve recovery time. The data from such research are helpful in informing paediatric surgeons. However, they cannot be applied directly to children undergoing cardiac surgery as very little is known about the effects of normothermic CPB on this patient group and the two techniques have not yet been extensively compared in children. The aim of this study is to compare normothermic and hypothermic CPB in children undergoing open heart surgery.

Who can participate?
Paediatric patients undergoing surgery for congenital cardiac defects.

What does the study involve?
Participants will be randomly allocated to receive either hypothermic perfusion or normothermic perfusion so that their respective effects on organs and patient welfare can be examined in detail.

What are the possible benefits and risks of participating?
Participants allocated to the hypothermic group will receive the same surgical procedure as patients not participating in the study and will be subject to the same benefits inherent in cardiac surgery. Participants allocated to the normothermic group will be subject to the same benefits, but it is believed that the perfusion of blood at normal body temperature will attenuate the whole body inflammatory response observed following hypothermic CPB; it is expected that this will reduce post-operative in-hospital recovery time. If the results of the research support the hypothesis that normothermic perfusion contributes to a reduction in postoperative hospitalisation, it is anticipated that the standard use of hypothermic perfusion during paediatric CPB could be reviewed. A general reduction in postoperative hospitalisation would benefit both patients and the NHS. It is not expected that patients will be at any greater risk of suffering harm by participating in this study.

Where is the study run from?
University of Bristol (UK).

When is the study starting and how long is it expected to run for?
From October 2011 to April 2016.

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

Who is the main contact?
Dr Massimo Caputo

Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
CH/2008/3052

Study information

Scientific Title
A randomised controlled trial to compare normothermic versus hypothermic cardiopulmonary bypass in children undergoing open heart surgery

Acronym
Thermic-2

Study objectives
The hypothesis for this trial is that the 'whole body inflammatory' response to the non-physiological cardiopulmonary bypass and its detrimental effects on different organ functions may be attenuated by implementing normothermic perfusion (35 - 37°C), rather than the standard hypothermic perfusion (28°C), during paediatric open heart surgery.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Not provided at time of registration

Study design
Single-centre two-group randomised 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 below to request a patient information sheet

Health condition(s) or problem(s) studied
Cardiopulmonary bypass procedure

Interventions

The hypothermic group will have their blood cooled to 28°C during CPB (standard practice). The normothermic group will have their blood temperature maintained at 35 - 37°C during CPB.

Duration of treatment for all groups is the duration of the surgery, i.e. 24 hours to cover the post-operative monitoring. Follow up will last for 12 months for eligible patients.

Intervention Type
Procedure/Surgery

Phase
Not Applicable

Primary outcome measure
Current primary outcome measures as of 15/05/2015:
Clinical outcome, in particular:
1. Duration of inotropic support
2. Intubation time
3. Postoperative hospital stay (from date of surgery to discharge from cardiac ward)

Previous primary outcome measures:
Clinical outcome, in particular duration of inotropic support, intubation time and post-operative stay. Measured in the period of post-operative hospitalisation, estimated to be 6 days on average.

Secondary outcome measures
Current secondary outcome measures as of 15/05/2015:
1. In-hospital mortality and morbidity.
2. Blood loss and transfusion requirements.
3. Pre-operative and post-operative echocardiographic (ECG) findings.
4. Routine blood gas and blood test results.
5. Renal function as measured by urinary albumin, urinary creatinine, retinal binding protein (RBP), N-acetyl-β-glucosaminidase (NAG) and neutrophil gelatinase-associated lipocalin (NGAL). All markers of renal damage will be measured pre-operatively, and at several time-points post-operatively.
6. Cerebral function as measured by Glial Fibrillary Acidic Protein (GFAP), a serum marker of traumatic brain injury. GFAP levels will be measured of GFAP pre-operatively and at several time-points mid- and post-operatively.
7. Regional oxygen saturation of blood in the cerebral cortex, measured at approximately 15-minute intervals during the operative period using Near Infra-Red Spectroscopy (NIRS).
8. Neuropsychological development, assessed using the NEPSY-II psychometric tool. Neuropsychological assessments will be performed on patients aged between 3-16 years, pre-operatively and at 3- and 12-months post-operatively. These tests are intended as a tool to allow the assessment of both basic and complex aspects of cognition across six functional domains: attention and executive functions, language, memory and learning, sensorimotor functions, social perception and visual-spatial processing.
9. Cardiac tissue biopsies from heart tissue discarded during the surgical procedure and considered clinical waste will be analysed for biochemical markers and RNA analysis on a subset of 32 patients. If available, four samples will be collected from each patient in this subset; two samples will be collected immediately after institution of CPB and a further two samples 10-15 minutes after reperfusion. Biochemical tests will be performed on the biopsies to determine the presence of a range of important proteins and metabolites and transcriptional profiling by RNA

extraction will be performed with the aim to help establish whether any genomic expression changes associated with hypothermia could be prevented by using normothermic techniques.

Previous secondary outcome measures:
1. In-hospital mortality and other standard measures of morbidity as used in previous randomised controlled trials, e.g. blood loss and transfusion requirement, abnormal echocardiographic findings, abnormal post-operative blood tests results. Measured in the period of post-operative hospitalisation, estimated to be 6 days on average.
2. Post-operative cerebral function as assessed by presence of marker protein S100 relative to baseline, measured peri-operatively and up to 24 hours post-operatively (routine)
3. Post-operative renal function as assessed by presence of retinol binding protein, N-acetyl-ß-D-glucosaminidase, creatinine, albumin and total protein concentrations relative to baseline, measured peri-operatively and up to 72 hours post-operatively (routine)
4. Peri-operative myocardial function as assessed through biochemical and DNA analysis of biopsies, measured peri-operatively (once at the start of CPB, once after end of CPB)
5. Post-operative personal and social development assessed with the Vineland Adaptive Behaviour Scales (second edition, VABS-II), measured 3 and 12 months post-operatively

Secondary outcomes 2, 3 and 5 will be compared with baseline data collected pre-operatively.

Overall study start date
31/10/2011

Completion date
01/04/2016

Eligibility

Key inclusion criteria
Current inclusion criteria as of 15/05/2015:
Participant may enter study if ALL of the following apply:
1. Patients undergoing congenital heart operations not requiring deep hypothermic circulatory arrest
2. Patients aged ≤17 years of age

Previous inclusion criteria:
1. Female and male patients from birth upwards (there is no upper age limit, per se)
2. Treated at the Bristol Royal Hospital for Children
3. Undergoing congenital heart operations not requiring deep hypothermic circulatory arrest

Participant type(s)
Patient

Age group
Child

Upper age limit
17 Years

Sex
Both

Target number of participants
110

Key exclusion criteria
Participant may not enter study if ANY of the following apply
1. Emergency operations (patients with haemodynamic instability who require immediate surgical intervention)
2. Patients requiring hypothermic circulatory arrest

Date of first enrolment
01/11/2011

Date of final enrolment
02/10/2014

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
University of Bristol
Bristol
United Kingdom
BS2 8HW

Sponsor information

Organisation
University Hospitals Bristol NHS Foundation Trust (UK)

Sponsor details
Research and Effectiveness Department
Education Centre, Level 3
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Sponsor type
Hospital/treatment centre

Website
http://www.uhbristol.nhs.uk

ROR
https://ror.org/04nm1cv11

Funder(s)

Funder type
Charity

Funder Name
British Heart Foundation (BHF) (UK)

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
We intend to publish the protocol and the results

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	25/05/2015	27/05/2015	Yes	No
Results article	results	01/03/2019	07/05/2019	Yes	No