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A study examining the effects of cooling the body after severe brain injury

Submission date
30/04/2008

Recruitment status
No longer recruiting

Registration date
30/05/2008

Overall study status
Completed

Last Edited
03/09/2018

Condition category
Injury, Occupational Diseases, Poisoning

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

Plain English summary of protocol

Background and study aims
Following a blow to the head (traumatic brain injury), the brain can swell like a bruise, but is enclosed within the skull. If the brain swells, it can lead to a build-up of pressure that can cause damage to parts of the brain. Many patients who have suffered a traumatic brain injury are admitted to an Intensive Care Unit. This is usually because they have become unconscious as a result of the brain injury. These patients require specialised care and often cannot breathe well enough for themselves therefore they are sedated and attached to a breathing machine, called a ventilator. Cooling the body down to between 32-35°C within 10 days after brain injury may help to reduce brain swelling and prevent further brain damage. This study aims to find out if this treatment makes a difference to how well people with brain injury have recovered 6 months after the injury.

Who can participate?
Six hundred patients who have been admitted to an Intensive Care Unit following a traumatic brain injury will be enrolled.

What does the study involve?
Patients will be allocated by chance to receive one of the following two treatments: either the usual care given to people who have had a severe brain injury, or to the usual care with the added treatment of cooling the body to between 32-35°C for at least 48 hours. To compare the longer term recovery of patients in each group, each surviving patient will be sent a questionnaire by post 6 months after the injury. This is an 8-point questionnaire that will assess the patient's overall function since the brain injury.

What are the possible benefits and risks of participating?
We hope that the treatments given as part of this research study will help patients. They may be put into the cooling group and this treatment may help to reduce the swelling in the brain and so may or may not prevent further brain damage. As a result of the brain injury that the patient has suffered, there is a risk of permanent brain injury whether or not they take part in this study. This study allows normal care to be given to everyone that takes part. No matter which group the patient is put into, they will be closely monitored and will receive the normal care given to people with severe brain injury. Everyone who suffers a severe brain injury is at risk of a number

of complications such as chest infections whether or not they are cooled. Everyone who takes part in the study will be continually assessed and treated for any signs of chest infection. Cooling the body down to between 32-35°C can cause skin redness and can increase the chance of skin breaking down. If the skin becomes red, it may not be possible to remove the cooling treatment at the time, especially if there is still brain swelling. The nurses and doctors looking after each patient will check their skin regularly and try to minimise the risk of the skin breaking down. There is also an increased risk of having an irregular heartbeat, low blood pressure and problems with blood clotting during cooling. There is also a possibility of developing low blood pressure during warming. This is a reason why each patient will be warmed slowly (over 16-20 hours). These are all known side effects of cooling and the doctors and nurses involved in the trial are used to caring for patients who are being cooled. There are guidelines in place for people being cooled to minimise the risk of any side effects.

Where is the study run from?
Western General Hospital (UK).

When is the study starting and how long is it expected to run for?
From September 2009 to July 2017.

Who is funding the study?
The European Society of Intensive Care Medicine (Belgium) and The National Institute for Health Research Health Technology Assessment (NIHR HTA) Programme.

Who is the main contact?
Prof Peter Andrews
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Study website
http://www.eurotherm3235trial.eu

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
Protocol version 8 dated 9/5/12

Study information

Scientific Title
European Society of Intensive Care Medicine study of therapeutic hypothermia (32 - 35°C) for intracranial pressure (ICP) reduction after traumatic brain injury

Acronym
Eurotherm3235Trial

Study objectives
Current hypothesis as of 01/07/2009:
Patients treated with therapeutic hypothermia (32 - 35°C) will have reduced morbidity and mortality rates compared to those receiving standard care alone after traumatic brain injury (TBI).

Initial information at time of registration:
Does therapeutic hypothermia (33 - 35°C) reduce death and disability after intracranial hypertension due to traumatic brain injury?

On 01/07/2009 this record was extensively updated to reflect recent protocol changes. All changes can be found under the relevant field with the above update date. Please note that at this time, the overall trial dates were also been updated; the initial trial dates were as follows:
Overall trial start date: 01/01/2009
Overall trial end date: 30/07/2013

On 14/08/2012 this record was extensively updated. All changes can be found under the relevant field with the above update date. The following changes were also made:
1. The scientific title was changed from 'European Society of Intensive Care Medicine study of therapeutic hypothermia (32 - 35°C) for intracranial pressure (ICP) reduction after traumatic brain injury' to 'European study of therapeutic hypothermia (32-35˚C) for intracranial pressure reduction after traumatic brain injury'
2. The target number of participants was changed from 1800 to 600
3. The overall trial end date was changed from 07/02/2013 to 31/07/2017
4. France, the Netherlands and Poland were removed from the countries of recruitment, and Belguim, Estonia, Greece, Hungary, India, Ireland, Russian Federation, Spain and United Arab Emirates were added to the countries of recruitment

On 13/04/2015 Netherlands, Portugal and Saudi Arabia were added to the countries of recruitment.

Ethics approval required
Old ethics approval format

Ethics approval(s)
All trial centres will seek ethical approval before recruiting patients. Ethical approval has been obtained in the United Kingdom, Belgium, Estonia, Germany, Greece, Hungary, India, Ireland, Netherlands, Portugal, Russia, Saudi Arabia, Spain, United Arab Emirates
1. Scotland A REC, 09/MRE00/34 (Lead)
2. NRES Committee Yorkshire and The Humber – Bradford Leeds, 09/H1302/44

Study design
Prospective randomised controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Patient information can be found at http://www.eurotherm3235trial.eu/information/index.phtml

Health condition(s) or problem(s) studied
Traumatic brain injury complicated by increased intracranial pressure

Interventions
Current information as of 01/07/2009:
Intervention Group: Usual traumatic brain injury management with therapeutic hypothermia (32 - 35°C) for at least 48 hours. The depth of hypothermia will be dependent on ICP control with a higher ICP warranting a lower target temperature. Hypothermia will be induced rapidly using 20 - 30 ml/kg refrigerated saline (0.9%) over 20 - 30 minutes. Hypothermia will then be maintained by using the cooling technique that is routinely used at each recruiting centre.

Control Group: Usual traumatic brain injury management.

Total duration of follow up: 6 months

Initial information at time of registration:
Intervention group: Traumatic brain injury management (Brain Trauma Foundation guidelines) + hypothermia (33 - 35°C) for 48 hours (at least) and guided by ICP response to slow rewarming at 0.3°C/hour. Each centre will use 20 ml per kg of Hartman's solution at 4°C and then a cooling technique available at that centre (a priori sub group analysis may be effectiveness of device type on outcome) and previous experience of the use of hypothermia will be essential.

Control group: Traumatic brain injury management in line with the Brain Trauma Foundation guidelines.

Total duration of follow-up: 6 months

Intervention Type
Other

Phase
Not Applicable

Primary outcome measure
Outcome at 6 months using the extended Glasgow Outcome Score (GOSE) questionnaire

Secondary outcome measures
Current information as of 01/07/2009:
1. 6-month mortality rate
2. Intracranial pressure (ICP) control
3. Incidence of Pneumonia across both groups
4. Length of stay in the Intensive Care Unit (ICU) and Hospital
5. Modified Oxford Handicap Scale score at one month, discharge from the randomising hospital or death, whichever occurs first
6. Correlation between the predicted outcome using the modified Oxford handicap scale at hospital discharge and the GOSE Score at 6 months post injury
7. Health economics (dependent on additional external funding)

Other planned analyses:
A priori sub group analysis will be presented testing the relationship between minimisation factors including; age < 45 years, admission post resuscitation GCS motor score <2, time from injury <12 hours and outcome. The analysis will test for interaction effects, and stricter levels of statistical significance (p<0.01) will be sought, reflecting the exploratory nature of these subgroup analyses. Only the primary outcome measure will be used in these analyses.

Other exploratory and observational studies will be conducted by some centres. These sub-studies will be run by local Investigators and will require approval by the trial management and steering committees together with further ethical approval. All sub-studies must also have secured external funding.

Initial information at time of registration:
1. ICP control, assessed by use of additional stage 2 therapies and/or escalation to stage three therapies, episodes of ICP >20 mmHg and duration ICP >20 mmHg
2. Length of intensive care unit (ICU) and hospital stay
3. Head Injury Related Early Outcome Scale (HIREOS) at 21 days
4. Mortality

Other planned analyses:
A priori sub group analysis will be testing the relationship between minimisation factors, including age less than and age older than 45 years, presence of cerebral contusion on CT scanning, admission post resuscitation GCS <5, gender, cooling technology, and outcome. Stricter levels of statistical significance (p <0.01) will be sought, reflecting the exploratory nature of these subgroup analyses. Primary outcome measure only will be used in these analyses.

Other exploratory, observational studies will be conducted by some centres and will include assessment of the genetics of responsiveness to hypothermia (to be lead by Professor Menon), modulation of inflammation (including response to intercurrent infection) and effect upon cerebral vascular autoregulation. There are likely to be other sub-studies run by centre PIs and all will require approval by the steering committee and will have identified external funding.

Overall study start date
01/09/2009

Completion date
31/07/2017

Eligibility

Key inclusion criteria
Current inclusion criteria as of 14/08/2012:
1. Believed to be legal age for consent to take part in research, either sex
2. Primary closed traumatic brain injury
3. Raised ICP greater than 20 mmHg for greater than or equal to 5 minutes after first line treatments with no obvious reversible cause e.g. patient position, coughing, inadequate sedation
4. Less than or equal to 10 days from the initial head injury
5. Cooling device or technique available for greater than 48 hours
6. Core temperature greater than or equal to 36°C (at the time of randomisation)
7. An abnormal computed tomography (CT) scan of the brain. This is defined as one that shows haematoma, contusion, swelling, herniation or compressed basal cisterns.

Previous inclusion criteria as of 01/07/2009 and until 14/08/2012:
1. Believed to be legal age for consent to take part in research to 65 years of age, either sex
4. Less than or equal to 72 hours from the initial head injury

Initial information at time of registration (2008):
1. Adults aged 16 - 65 years, both males and females
2. Primary, closed traumatic brain injury
3. An abnormal computed tomography (CT) scan of brain, Marshall grade greater than 1
4. Refractory increased intracranial pressure (ICP) greater than 20 mmHg for at least 30 minutes (refractory to first line interventions including mechanical ventilation, sedation, analgesia ± muscle relaxant, head of bed elevation, with monitoring of CVP and invasive arterial pressure)
5. Core temperature greater than 36°C (at the time of randomisation)
6. Cooling device or technique available for greater than 48 hours

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants

600

Key exclusion criteria
Current information as of 01/07/2009:
1. Patient already receiving therapeutic hypothermia treatment
2. Administration of barbiturate infusion prior to randomisation
3. Unlikely to survive for the next 24 hours in the opinion of the ICU Consultant or Consultant Neurosurgeon treating the patient
4. Temperature less than or equal to 34°C at hospital admission
5. Pregnancy

Initial information at time of registration:
1. Patients with bilateral fixed and dilated pupils
2. Unable to monitor ICP or patients with ICP less than 20 mmHg
3. Patients who have received barbiturates prior to randomisation
4. Where there is documented brainstem involvement
5. Moribund condition on admission

Date of first enrolment
01/09/2009

Date of final enrolment
31/07/2016

Locations

Countries of recruitment
Belgium

Estonia

Germany

Greece

Hungary

India

Ireland

Italy

Netherlands

Portugal

Russian Federation

Saudi Arabia

Scotland

Spain

United Arab Emirates

United Kingdom

Study participating centre
Western General Hospital
Edinburgh
United Kingdom
EH4 2XU

Sponsor information

Organisation
University of Edinburgh and NHS Lothian (UK)

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47 Little France Crescent
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Sponsor type
University/education

Website
http://www.accord.ed.ac.uk

ROR
https://ror.org/03q82t418

Funder(s)

Funder type
Research organisation

Funder Name
The European Society of Intensive Care Medicine (Belgium)

Funder Name
The National Institute for Health Research Health Technology Assessment (NIHR HTA) Programme

Results and Publications

Publication and dissemination plan
Manuscript preparation summer 2015, with publication and dissemination thereafter

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	12/01/2011		Yes	No
Results article	results	03/09/2013		Yes	No
Results article	results	17/12/2015		Yes	No
Results article	results	01/08/2018		Yes	No