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Clinical Randomisation of an Antifibrinolytic in Significant Head injury (CRASH-3)

Submission date
28/06/2011

Recruitment status
No longer recruiting

Registration date
19/07/2011

Overall study status
Completed

Last Edited
06/11/2024

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
Worldwide, about 10 million people die or are hospitalised following a sudden head injury. Bleeding into the brain at the time of injury, which can continue many hours afterwards, is associated with increased rates of death and disability. It is important to find better ways of treating patients who bleed into the brain after a head injury. A drug called tranexamic acid has been shown to reduce death from bleeding after other types of traumatic injury. In addition, it is often used to reduce bleeding after major surgery such as heart operations. The CRASH-3 study is being done to see if tranexamic acid can improve outcomes for people after traumatic brain injury. The main outcome we will assess is the effect on the number of people who die from this injury. Other important outcomes will also be assessed such as its effect on disability and complications.

Who can participate?
Adults within three hours of a head injury can take part in the CRASH-3 trial. Patients with significant bleeding outside of the head cannot take part. We plan to study 13,000 patients worldwide.

What does the study involve?
Patients with this problem will be admitted to hospital. Because this bleeding is an emergency situation, doctors will need to decide very quickly whether a patient is suitable for the trial or not (usually as soon as possible after the problem is identified). Brief information will be collected on an entry form to see if a patient is suitable. In this emergency situation it is difficult for patients to give written informed consent to take part. We will therefore ask the ethics committee for permission to put patients into the trial without written consent but where possible will get agreement from patients and relatives first, and we will explain to patients later what happened to them and how the information from the trial will be used. We have asked the opinions of members of the public about this and they agree that this is the only way we can do good research on life-threatening emergency problems. Everyone will get all the treatments that doctors usually give for this condition. In addition, they will get the trial treatment by an intravenous infusion (drip) for about 8 hours. Half of the patients will receive tranexamic acid and the other half a dummy medicine called a placebo. To make sure that the two groups are the same apart from tranexamic acid, we will decide who gets tranexamic acid

and who gets placebo using a computer programme, a modern equivalent of the toss of a coin (this is called randomisation). We will collect some information on the progress of patients and whether they have any side effects for up to 28 days after they receive treatment. Brain scan (CT Scan) are usually done routinely on admission to hospital in patients who are part of this trial to check for bleeding or any other damage. Scans are repeated whenever the doctors want to check the progress of a patient. We will collect information about bleeding and clotting from these routine scans in about 1000 patients who are part of the trial. This will provide information on how the drug tranexamic acid works.

What are the possible benefits and risks of participating?
We hope that tranexamic acid will help reduce the number of patients who die from this condition without increasing disability. The knowledge that we gain from this study will help other people with head injury in the future. Tranexamic acid is not a new drug. It has been used for years to reduce bleeding after operations and heavy menstruation and more recently to treat other types of serious injury. It works by stopping the breakdown of the blood clots which are needed to control bleeding. Studies have shown that it does not cause unwanted clotting and there are no serious side effects with short term use. However, patients will be monitored closely and doctors will report to the study organisers if there are any unexpected problems.

Where is the study run from?
The CRASH-3 trial is organised by the London School of Hygiene and Tropical Medicine (UK) and will involve hundreds of doctors and nurses worldwide.

When is the study starting and how long is it expected to run for?
September 2011 to January 2020

Who is funding the study?
The JP Moulton Charitable Trust, United Kingdom is funding the initial costs for this trial and the recruitment of up to 500 participants. Full funding for the main trial is provided by the Joint Global Health Trials scheme which is coordinated by provided by the United Kingdom’s National Institute for Health research -Health Technology Assessment (HTA) Programme and the Medical research Council.

Who is the main contact?
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Study website
http://crash3.lshtm.ac.uk/

Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

EudraCT/CTIS number
2011-003669-14

IRAS number

ClinicalTrials.gov number
NCT01402882

Secondary identifying numbers
PACTR20121000441277

Study information

Scientific Title
Tranexamic acid for the treatment of significant traumatic brain injury: an international randomised, double blind placebo controlled trial

Acronym
CRASH-3

Study objectives
The CRASH-3 trial will provide reliable evidence about the effect of tranexamic acid on mortality and disability in patients with traumatic brain injury. The effect of tranexamic acid on the risk of vascular occlusive events and seizures will also be assessed.

Protocol can be found at: http://crash3.lshtm.ac.uk/index.php/about/protocol/

Added 20/12/2016:
CRASH-3 Intracranial Bleeding Sub-study (CRASH-3 IBS)
The CRASH-3 IBS is nested in a cohort of CRASH-3 trial participants and aims to examine the effect of tranexamic acid on intracranial haemorrhage and cerebral ischaemia in a sample of CRASH-3 trial participants. Approximately 1,000 patients in the CRASH-3 trial, across several centres, will have their pre- and post-randomisation computed tomography scans examined for evidence of intracranial haemorrhage, cerebral ischaemia and other computed tomography endpoints.

The hypothesis is that the administration of tranexamic acid will reduce intracranial haemorrhage volume in patients with traumatic brain injury.

Ethics approval required
Old ethics approval format

Ethics approval(s)
LSHTM has approved the trial as the lead institution on 17/11/2011 (ref: 6060). All sites taking part will have the relevant approvals before recruitment starts.

Study design
Large pragmatic randomised double-blind placebo-controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
https://ctu-web.lshtm.ac.uk/c3w/index.php/patient-information/

Health condition(s) or problem(s) studied
Traumatic Brain Injury

Interventions
1. Tranexamic acid versus placebo
2. Patients will be randomised to either tranexamic acid (loading dose 1 gram over 10 minutes then infusion of 1 gram over 8 hours) or matching placebo

Added 20/12/2016:
CRASH-3 Intracranial Bleeding Sub-study (CRASH-3 IBS)
Information about bleeding and clotting from routine CT scans is collected in about 1000 patients who are part of the trial. This will provide information on how the drug tranexamic acid works.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Tranexamic acid

Primary outcome measure
Death in hospital within 28 days of injury (Added 22/01/2018: among patients randomised within 3 hours of injury) (cause of death will be described)

Added 20/12/2016:
CRASH-3 IBS primary outcome:
The primary outcome is the total volume of intracranial haemorrhage after randomisation, adjusting for the baseline volume of haemorrhage.

Secondary outcome measures
1. Vascular occlusive events (myocardial infarction, stroke, pulmonary embolism, clinical evidence of deep vein thrombosis)
2. Disability assessed using the Disability Rating Scale and Patient Orientated Outcomes
3. Seizures
4. Neurosurgical intervention
5. Days in intensive care
6. Other adverse events will be described

Added 20/12/2016:
CRASH-3 IBS secondary outcome:

Secondary outcomes will include: frequency of progressive haemorrhage (number of patients with a post-randomisation CT scan with total haemorrhage volume of more than 25% of the volume of the pre-randomisation scan); frequency of delayed haemorrhage (number of patients with haemorrhage on the post-randomisation CT scan when there was not one on the pre-randomisation scan); new focal ischaemic lesions (ischaemic lesions which appear on the post-randomisation CT scan but not on the pre-randomisation scan); total volume of intracranial bleeding after randomisation in patients who undergo surgical evacuation of haemorrhage, adjusting for volume of baseline bleeding.

Overall study start date
01/09/2011

Completion date
31/08/2019

Eligibility

Key inclusion criteria
1. Adult
2. Traumatic brain injury
3. Within 8 hours of injury (Added 22/01/18: limited to within 3 hours from September 2016)
4. Any intracranial bleeding on CT scan OR a GCS of 12 or less
5. No significant extra-cranial haemorrhage
6. Where the responsible clinician is substantially uncertain as to the appropriateness of antifibrinolytic agents in the patient

Participant type(s)
Patient

Age group
Adult

Lower age limit

18 Years

Sex
Both

Target number of participants
13,000 patients with head injury

Total final enrolment
12737

Key exclusion criteria
The fundamental eligibility criterion is the responsible clinician's 'uncertainty' as to whether or not to use an antifibrinolytic agent in a particular patient with traumatic brain injury

Date of first enrolment
01/12/2011

Date of final enrolment
31/01/2019

Locations

Countries of recruitment
Afghanistan

Albania

Cambodia

Cameroon

Canada

Colombia

Egypt

El Salvador

England

Georgia

Indonesia

Iraq

Ireland

Italy

Jamaica

Kenya

Malaysia

Mexico

Myanmar

Nepal

Nigeria

Pakistan

Papua New Guinea

Romania

Spain

United Arab Emirates

United Kingdom

Zambia

Study participating centre
London School of Hygiene and Tropical Medicine
London
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Sponsor information

Organisation
London School of Hygiene and Tropical Medicine (UK)

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Sponsor type
University/education

Website
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ROR
https://ror.org/00a0jsq62

Funder(s)

Funder type
University/education

Funder Name
London School of Hygiene and Tropical Medicine

Alternative Name(s)
London School of Hygiene & Tropical Medicine, LSHTM

Funding Body Type
Private sector organisation

Funding Body Subtype
Universities (academic only)

Location
United Kingdom

Funder Name
J P Moulton Charitable Foundation (UK)

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date
31/08/2020

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study are stored in a publically available repository: https://ctu-app.lshtm.ac.uk/freebird/

IPD sharing plan summary

Stored in repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	21/06/2012		Yes	No
Results article	results	09/11/2019	21/10/2019	Yes	No
Results article	sub-study results	01/12/2020	07/12/2020	Yes	No
Results article		01/04/2021	05/05/2021	Yes	No
Results article		03/09/2024	06/11/2024	Yes	No