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Effects of systemic erythropoietin therapy on cerebral autoregulation and incidence of delayed ischemic deficits in patients with aneurysmal subarachnoid haemorrhage

Submission date 29/09/2006	**Recruitment status** No longer recruiting	[_] Prospectively registered [_] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 29/09/2006	**Overall study status** Completed	
Last Edited 28/09/2011	**Condition category** Circulatory System	

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

Contact name
Mr Peter John Kirkpatrick

Contact details
Box 167, Department of Neurosurgery, Addenbrooke's Hospital
Hills Road
Cambridge
United Kingdom
CB2 2QQ
+44 01223 217214
pjk21@medschl.cam.ac.uk

Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
N0544163605

Study information

Scientific Title

Study objectives
Can a short-term systemic treatment with erythropoietin, a red blood cell producing human hormone, prevent strokes caused by bleeding on the brain (subarachnoid haemorrhage)?

Ethics approval required
Old ethics approval format

Ethics approval(s)
Not provided at time of registration

Study design
Randomised controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Not specified

Study type(s)
Treatment

Participant information sheet

Health condition(s) or problem(s) studied
Cardiovascular: Stroke

Interventions
Randomisation procedure:
Following informed consent patients will be randomised to receive either intravenous r-HuEPO 30,000IU or placebo (0.9% saline) 50ml/30min, three times in the first week after SAH (total dose 100,000IU). The number in each group will be 40. For blinding, the Pharmacy Manufacture Unit (PMU) will prepare and number identical vials containing either saline (0.9% NaCl) or r-HuEPO reconstituted in saline. The vials will be randomly assigned to patients upon enrollment with the contents of each vial known only by the PMU. Trial medication will be started as soon as possible within 72 hours of the ictus. As approximately 70% of aneurysms will be treated with open clipping, and the remainder with endovascular coils, we do not consider the method of

treatment to represent a contaminating factor, but it will be included in the final analysis. Location, size, and morphology of the culprit aneurysm are not believed to affect outcome in our institution.

Following randomisation and start of trial therapy the clinical management of each patient will be as routine. Arterial blood pressure will be continuously monitored (Finapress, or via radial arterial line).

Safety:
The full blood cell count, reticulocyte count, blood viscosity, coagulation profile, serum biochemistry, serum iron levels, and C-reactive protein (CRP) at the time of admission will be checked as baseline data and repeated alternate days for the duration of the trial drug administration. Although r-HuEPO has effects of erythropoiesis and thrombopoiesis, associated deterioration or adverse events have not been observed in short-term treatment However, in the face of any abnormalities the trial drug will be stopped and the safety committee informed. A safety committee (chaired by Dr Ken Smith, Consultant nephrologist) will review the safety data at monthly intervals or, if concerns arise, on a patient-by-patient basis.

Trial patients will be examined daily with TCD (DWL, Germany) using a 2-MHz probe mounted on a purposed head frame for two weeks since SAH ictus. The systolic, diastolic, and mean FV will be recorded (trans-temporal) by a single user (MT). Vasospasm will be defined as mean FV > 120 cm/sec and Lindegaard ratio >3. The regression index (Mx) between mean FV and spontaneous changes in ABP will be calculated. Two carotid compressions lasting 5 seconds will be performed. The criteria for an acceptable THRT includes a sudden decrease in middle cerebral artery FV at the onset of compression, a stable TCD signal during compression, and a minimum of 30% decrease in FV with no blood pressure instability. The THRT ratio (THRR) is calculated using the formula: THRR = FVs (hyperaemia) / FVs(baseline), where FVs denotes systolic FV. THRR is classified as normal (=l.10) or impaired (<1.10), and will be repeated 2 minutes later. The average value of the two tests will be recorded. Quality issues concerning the THRT response have been extensively evaluated in this laboratory.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
erythropoietin

Primary outcome measure
Vasospasm and abnormal cerebral autoregulation shown on transcranial Doppler.
Trial patients will be examined daily with TCD (DWL, Germany) using a 2-MHz probe mounted on a purposed head frame for two weeks since SAH ictus. The systolic, diastolic, and mean FV will be recorded (trans-temporal) by a single user (MT). Vasospasm will be defined as mean FV > 120 cm/sec and Lindegaard ratio >3. The regression index (Mx) between mean FV and spontaneous changes in ABP will be calculated. Two carotid compressions lasting 5 seconds will be performed. The criteria for an acceptable THRT includes a sudden decrease in middle cerebral artery FV at the onset of compression, a stable TCD signal during compression, and a minimum of 30% decrease in FV with no blood pressure instability. The THRT ratio (THRR) is calculated using the formula: THRR = FVs (hyperaemia) / FVs(baseline), where FVs denotes systolic FV.

THRR is classified as normal (=l.10) or impaired (<1.10), and will be repeated 2 minutes later. The average value of the two tests will be recorded. Quality issues concerning the THRT response have been extensively evaluated in this laboratory.

Secondary outcome measures
Development of DID. The clinical progress of each patient will be monitored daily. The development of a focal neurological deficit and/or a drop in the GCS by 2 points or more will be the criteria adopted to define an episode of DID [Pickard 1989]. Clinical and radiological outcomes will be assessed at the time of discharge. Durations of hospitalisation and NCCU stay will be observed.

Overall study start date
01/01/2005

Completion date
30/04/2006

Eligibility

Key inclusion criteria
Patients >= 18 years old with suspected aneurysmal SAH admitted to the Addenbrooke's Neurosurgical Department will be approached.

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Not Specified

Target number of participants
80

Key exclusion criteria
Uncontrolled systemic hypertension (systolic blood pressure >220 mmHg), time after SAH ictus has been 7 days, traumatic or angiography-negative SAH. Patients over 65 years will have carotid duplex examinations to exclude those with significant carotid atheroma.

Date of first enrolment
01/01/2005

Date of final enrolment
30/04/2006

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Box 167, Department of Neurosurgery, Addenbrooke's Hospital
Cambridge
United Kingdom
CB2 2QQ

Sponsor information

Organisation
Record Provided by the NHSTCT Register - 2006 Update - Department of Health

Sponsor details
The Department of Health, Richmond House, 79 Whitehall
London
United Kingdom
SW1A 2NL
+44 (0)20 7307 2622
dhmail@doh.gsi.org.uk

Sponsor type
Government

Website
http://www.dh.gov.uk/Home/fs/en

Funder(s)

Funder type
Government

Funder Name
Cambridge Consortium - Addenbrooke's (UK) NHS R&D Support Funding

Results and Publications

Publication and dissemination plan
Not provided at time of registration

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	01/07/2009		Yes	No