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Brain injury depolarisations in patients with aneurysmal subarachnoid haemorrhage (aSAH)

Submission date 11/03/2009	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 17/06/2009	**Overall study status** Completed	
Last Edited 14/04/2022	**Condition category** Circulatory System	

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
DR 323/5-1

Study information

Scientific Title
Depolarisations in ISCHaemia after aneurysmal subARachnoid haemorrhaGE: a multicentre diagnostic phase III single-arm study

Acronym
DISCHARGE-1

Study objectives
Primary Objective:
To calculate (1) sensitivity and (2) specificity for a known cut-off value for the duration of cortical spreading depolarisation (CSD)-induced depression of high-frequency electrocorticography (ECoG) activity per 24-hour period that indicates delayed ischaemic stroke as assessed by magnetic resonance imaging (MRI) and (3) to estimate a new cut-off value with a predefined sensitivity and specificity (note: in the majority, delayed ischaemia after aneurysmal subarachnoid haemorrhage [aSAH] involves the aneurysm-bearing vascular territory where the electrode strip was placed several days before the development of delayed ischaemia. Moreover, the propagating nature of CSD implicates that even if the recording strip is placed remote from the actual ischaemic zone, CSDs from the ischaemic zone should spread to the recording strip).

Hypothesis:
Recording of CSDs allows real time detection of delayed ischaemia after aSAH at the bedside, thus, it becomes possible to stratify the population of aSAH patients into two groups at the earliest possible time point. This clinical trial would provide:
1. An immediate value in the near future for neurointensive care patients with aSAH in whom clinical assessment is often limited because of reduced consciousness (analgo-sedation, etc.) since aggressive treatment of delayed ischaemia with the currently established standard regimen (triple-H-therapy, see below) could be selectively started earlier
2. The basis for future proof of concept studies on neuroprotective strategies that allows for (a) selective treatment allocation to those patients developing ischaemia while ischaemic stroke is still in the phase of early development, plus (b) the option for aggressive neuroprotection that interferes with consciousness or even respiratory drive since delayed strokes develop on the intensive care unit under the eyes of the treating intensivist
3. The basis to develop automated detection systems for CSD and CSD-induced depression of high-frequency electrocorticographic (ECoG) activity in collaboration with physicists and mathematicians
4. A strong argument to target prolonged CSDs or disturbed neurovascular coupling between CSD and regional cerebral blood flow (rCBF) in the future development of novel neuroprotective strategies (see below)
5. The translation of the CSD concept from experimental research into clinical practice with implications far beyond aSAH for the whole class of neurological diseases that are characterised by development of cytotoxic oedema in the brain including ischaemic and haemorrhagic stroke, traumatic brain injury and hypoxia that place the highest health burden on our society in terms of mortality, morbidity and economic costs.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Ethics Committee of Campus Benjamin Franklin, Charité - University Medicine Berlin (Charité - Universitätsmedizin Berlin) approved on the 11th March 2009 (ref: EA4/022/09)

Study design
Multicentre diagnostic phase III single-arm study

Primary study design
Interventional

Secondary study design
Multi-centre

Study setting(s)
Hospital

Study type(s)
Diagnostic

Participant information sheet
Not available in web format, please use the contact details found in the interventions field to request a patient information sheet.

Health condition(s) or problem(s) studied
Aneurysmal subarachnoid haemorrhage (aSAH)

Interventions
Screening begins when a patient (less than 72 hours post-rupture of aneurysm) is seen in the emergency room (aneurysm treatment within 24 hours). If patient is eligible, electrode strip (Wyler, 5-mm diameter; Ad-Tech Medical, Racine, Wisconsin, USA) for cortical spreading depolarisation (CSD) monitoring, oxygen/temperature sensor (Licox, Integra Lifesciences Corporation, Plainsboro, NJ, USA) and microdialysis (MD) probe (CMA Microdialysis AB, Solna, Sweden) are placed either via craniotomy (clipped patients) or burr-hole (coiled patients). Patients will be admitted to intensive care unit where continuous bedside monitoring of local electrocorticogram (ECoG), tissue partial pressure of oxygen (ptiO2), MD and intracranial pressure (ICP) as well as systemic mean arterial blood pressure (MAP) will be started and continued until day 15 after aneurysmal subarachnoid haemorrhage (aSAH).

Each patient will undergo the following treatment:
Step 1: Screening includes history (from patient or by proxy, protocol of emergency doctor, clinical notes, neuroimages) with documentation of initial symptoms, risk factors (such as hypertension, smoking etc.) and complications (such as hydrocephalus) followed by detailed neurological examination.
Step 2: Assessment of eligibility and informed consent.
Step 3: Monitoring of vital signs every 1 hour, arterial blood gas (ABG)/neurological status (Glasgow Coma Scale [GCS]) every 4 hours, documentation of new delayed ischaemic neurological deficit (DIND) (with detailed description, time of onset, further clinical course), detailed examination once daily including modified National Institutes of Health Stroke Scale (NIHSS), transcranial doppler (TCD) of basal cerebral arteries, digital subtraction angiography (DSA) on day 7. MRI1 will be performed 24 - 48 hours after aneurysm treatment in order to assess initial structural brain injury and MRI2 around day 7 to assess possible perfusion deficit and screen for new delayed ischaemic stroke. MRI3 on the day of electrode withdrawal (approximately day 15) will be compared to MRI1 and MRI2 for the assessment of new delayed ischaemic stroke that occurred during the ECoG monitoring period. During the study period at least one computed tomography (CT) will be performed to locate the electrode strip.

Step 4: MRI4 after 6 months will be performed for follow-up (step 3). Clinical outcome assessment will be performed after 6 months including Glasgow Outcome Scale Extended (GOSE) and modified Rankin Scale (mRS).

Treatment:
No experimental treatment. Patients will be treated according to standard care guidelines of aSAH (e.g., oral nimodipine). Patients with DIND will receive triple-H therapy (aiming at hypertension: MAP 100 - 120 mmHg, hyper-volaemia: central venous pressure greater than 10 mmHg and haemodilution: haematocrit approximately 30%) using hydroxyethyl starch (10%), crystalloids and catecholamines [note: although triple-H-therapy is the standard treatment for DINDs worldwide, its efficacy is limited and there is a need for more effective treatment options. In general, all therapeutic approaches including triple-H therapy face a high risk of side effects, thus a better risk stratification of patients is urgently needed].

Duration of intervention per patient: 15 minutes of electrode implantation added to the regular operative time in clipped patients. In patients undergoing coiling, the recording devices will be implanted via an extended burr-hole when the ventricular drain is established. Monitoring will continue until day 15 after aSAH. Use of a single, narrow linear electrode strip allows withdrawal at the bedside.

Control intervention:
This is a diagnostic study of phase III in the systematics of Sackett and Haynes.4 In this phase no control group is requested. In a randomised study ECoG efficacy might be proved subsequently (phase IV).

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Intervention Type
Other

Phase
Phase III

Primary outcome measure
Occurrence of a new delayed ischaemia infarct (comparison between MRI 48 hours after event and MRI 15 days after event).

Secondary outcome measures
1. Location of a new delayed ischaemic infarct in the recording area, ipsilateral lobe adjacent to electrode strip, ipsilateral hemisphere and whole brain (comparison of MRI1 and MRI3). Total duration of follow-up: 6 months.
2. In unsedated patients, occurrence of clinical delayed ischaemic neurological deficit (DIND) defined by delayed decrease of consciousness (greater than or equal to 2 Glasgow Coma Scale

[GCS] levels) and/or new focal neurological deficit with onset between 48 hours and 14 days after aSAH and at least 24 hours following surgery or coiling that cannot be attributed to rebleeding, systemic or post-operative complications, or hydrocephalus
3. Death related to delayed ischaemic infarcts/death of other causes. Total duration of follow-up: 6 months.
4. Clinical outcome on day 15 post-aSAH (mRS) and at 6 months (modified Rankin scale [mRS], Glasgow Outcome Score-Extended [GOSE])

Overall study start date
01/05/2009

Completion date
31/12/2019

Eligibility

Key inclusion criteria
Current inclusion criteria as of 09/08/2011:

1. Male or female patients aged 18 or older (inclusive)
2. World Federation of Neurosurgery (WFNS) grade I V unless the clinical state suggests an unfavourable prognosis such as wide, non-reactive pupils for more than 1h
3. Ruptured saccular aneurysm demonstrated by CT-angiography or digital subtraction angiography (DSA)
4. Onset of aSAH clinical symptoms within the preceding 72 hours
5. Treatment of aneurysm (clip ligation or endovascular coil embolisation)
6. Indication for a ventricular drain or oxygen sensor in coiled patients
7. Informed consent is obtained from the patient or a legal representative

Previous inclusion criteria:

1. Male or female patients aged 18 to 70 years (inclusive)
2. World Federation of Neurosurgery (WFNS) grade III - IV, and grade V patients who improve within 24 hours after ventriculostomy
3. Diffuse thick or localised thick subarachnoid clot on baseline computerised tomography (CT)
4. Ruptured saccular aneurysm demonstrated by CT-angiography or digital subtraction angiography (DSA)
5. Onset of aSAH clinical symptoms within the preceding 72 hours
6. Treatment of aneurysm (clip ligation or endovascular coil embolisation)
7. Indication for a ventricular drain in coiled patients
8. Informed consent is obtained from the patient or a legal representative

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
200

Total final enrolment
205

Key exclusion criteria
Current exclusion criteria as of 09/08/2011:

1. ASAH due to other causes (e.g., trauma, fusiform or mycotic aneurysm)
2. Admission in a clinical state with unfavourable prognosis (e.g., wide, nonreactive pupils for more than 1 hour)
3. Bleeding diasthesis
4. Cytostatic therapy in patients with malignant disease
5. Pregnancy
6. Special exclusion criteria for MRI such as non-MRI-compatible, non-removable metals, artificial joints etc., electronic devices (pacemaker, pumps etc.)
7. Interruption of monitoring for more than 48h during days 3-5, or 24h during days 6-8 or 24h during days 9-11 unless the patient dies after day 5 or develops an MRI documented delayed ischemic stroke during the monitoring period and recording is only interrupted after those events
8. Respiratory/haemodynamic instability does not allow MR transport (i.e. transport of the patient to the magentic resonance tomogram, patient monitoring during imaging, transport back to the ward)

Previous exclusion criteria:

1. ASAH due to other causes (e.g., trauma, fusiform or mycotic aneurysm)
2. Only a thin diffuse layer or no visible subarachnoid blood in the initial CT
3. Admission in a clinical state with unfavourable prognosis (e.g., wide, nonreactive pupils for more than 1 hour)
4. Significant disturbance of coagulation (thrombocytes less than 60/nl, quick value less than 60%, partial thromboplastin time greater than 45 seconds)
5. Cytostatic therapy in patients with malignant disease
6. Pregnancy
7. Special exclusion criteria for MRI such as non-removable metals, artificial joints etc., electronic devices (pacemaker, pumps etc.)
8. Interruption of monitoring for more than 24 hours during days 4 - 6 or days 7 - 9
9. Respiratory/haemodynamic instability does not allow MR transport (i.e. transport of the patient to the magentic resonance tomogram, patient monitoring during imaging, transport back to the ward)

Date of first enrolment
01/09/2009

Date of final enrolment
31/03/2018

Locations

Countries of recruitment
Germany

Study participating centre
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10117

Sponsor information

Organisation
Charité - University Medicine Berlin (Charité - Universitätsmedizin Berlin) (Germany)

Sponsor details
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Sponsor type
University/education

Website
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ROR
https://ror.org/001w7jn25

Funder(s)

Funder type
Research council

Funder Name
German Research Council (Deutsche Forschungsgemeinschaft [DFG]) (Germany) (ref: DR 323/5-1)

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date
31/12/2021

Individual participant data (IPD) sharing plan
Not provided at time of registration

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		12/04/2022	14/04/2022	Yes	No