Trial Description

Title

Stereotactic Cisternal Lavage in Patients with Aneurysmal Subarachnoid Hemorrhage with Urokinase and Nimodipine for the Prevention of Secondary Brain Injury. A Randomized Controlled Trial.

Trial Acronym

SPLASH

URL of the trial

[---]*

Brief Summary in Lay Language

The present study deals with the improvement of the treatment of aneurysmal subarachnoid hemorrhage (aSAH), a bleeding caused by a rupture of a blood vessel (aneurysm) in the brain. The study is being conducted to investigate the effectiveness of the so-called "stereotactic cisternal lavage". In this procedure, a catheter is placed in the so-called "basal cisterns", a cavity filled with brain fluid on the undersurface of the brain. In the vast majority of cases, the aneurysm and thus the source of the cerebral hemorrhage can be found in this area. To place the catheter, a special high-precision surgical method (stereotaxy or stereotactic neurosurgery) is used. Via the catheter, drugs (urokinase, Ringer's solution and possibly nimodipine) can be administered directly into the basal cisterns of the brain. A second catheter can be used to drain the administered medication, thus creating an irrigation (= lavage) of the brain with urokinase, Ringer's solution and, if necessary, nimodipine. This study investigates whether this therapy can help to improve the survival rate of patients with aSAH and prevent neurological damage. In addition, the safety of the treatment will be investigated.

Brief Summary in Scientific Language

The aim of this randomized clinical trial is to assess whether intrathecal lavage therapy with urokinase, nimodipine and Ringer’s solution administered via a stereotactically implanted catheter into the basal cisterns (IT, Investigational Treatment) improves neurological outcome and is safe in patients with aneurysmal subarachnoid hemorrhage (aSAH).

Do you plan to share individual participant data with other researchers?

[---]*

Description IPD sharing plan

[---]*

Organizational Data

- DRKS-ID: **DRKS00015645**
- Date of Registration in DRKS: **2019/05/08**
- Date of Registration in Partner Registry or other Primary Registry: **[---]***
- Investigator Sponsored/Initiated Trial (IST/IIT): **yes**
- Ethics Approval/Approval of the Ethics Committee: **Approved**
- (leading) Ethics Committee Nr.: **394/18 , Ethik-Kommission der Albert-Ludwigs-Universität Freiburg**

Secondary IDs

- EudraCT-No.
  (for studies acc. to Drug Law): **2017-000868-15**

Health condition or Problem studied

- ICD10: **I60.7 - Subarachnoid haemorrhage from intracranial artery, unspecified**
- ICD10: **I67.80 - [generalization I67.8: Other specified cerebrovascular diseases]**

Interventions/Observational Groups

- Arm 1: **Standard-of-Care treatment of patients with aSAH according to recommendations from the “European Stroke Organization Guidelines for the Management of Intracranial Aneurysms and Subarachnoid Hemorrhage”.**
- Arm 2: **Standard-of-care treatment of patients with aSAH (see group 1) PLUS**
  - Stereotactic implantation of a catheter into the basal cisterns as soon as possible after aneurysm securing and randomization
  - Continuous cisternal lavage with urokinase, Ringer's solution and nidmodipine, starting from stereotactic catheter implantation until max. day 21

Characteristics

- Study Type: **Interventional**
- Study Type Non-Interventional: **[---]***
- Allocation: **Randomized controlled trial**
- Blinding: **[---]***
- Who is blinded: **[---]***
- Control: **Active control (effective treament of control group)**
- Purpose: **Treatment**
-

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Purpose: **Treatment**

Assignment: **Parallel**

- Phase: **II**
- Off-label use (Zulassungsüberschreitende Anwendung eines Arzneimittels): **Yes**

Primary Outcome

Neurological outcome: Proportion of subjects with a favorable outcome measured on the modified Rankin Scale (mRS) at 6 months after aSAH, assessed by an independent physician.

Secondary Outcome

- Neuropsychological outcome at 6 months following aSAH:
--- Cognitive performance (Montreal Cognitive Assessment)
--- Health-related quality of life (SF-36)
--- Fatigue, anxiety and depressive symptoms (Frontal Systems Behavior Scale, Multidimensional Assessment of Fatigue, Hospital Anxiety and Depression Scale), Post-traumatic stress disorder (Impact of Event Scale – R)
--- Return-to-work parameters at 6 months
- Rate and severity of delayed cerebral infarction (DCI) according to the Vergouwen criteria
- Rate of delayed ischemic neurological deficit (DIND), defined as clinical deterioration caused by delayed cerebral ischemia (i.e. a new focal neurological deficit or decline on the Glasgow Coma Scale of 1 point not attributable to other causes) on days 3 – 21
- Delta mean flow velocities of both middle cerebral arteries – measured by transcranial Doppler-ultrasonography on days 3 – 21
- NIHSS score at days 3-21 and at 6 months
- Rates of shunt-dependent hydrocephalus at 6 months following aSAH
- Rate of endovascular interventions for the treatment of cerebral vasospasm
- Key parameters of intensive care medicine (Sequential Organ Failure Score)
- Key parameters of endocrinological dysfunction
- Morphological brain damage at 6 months after aSAH as assessed by MRI
- Key markers of neuronal injury and systemic inflammation in patient blood
- electroencephalographic patterns as measured by continuous EEG-monitoring during intensive care period (exploratory endpoint)
- Safety of IT: (Serious) Adverse Events related to the IT

Countries of recruitment

- DE **Germany**

Locations of Recruitment

- University Medical Center **Klinik für Neurochirurgie, Freiburg im Breisgau**

Recruitment

- Planned/Actual: **Planned**
- (Anticipated or Actual) Date of First Enrollment: **2019/06/17**
- Target Sample Size: **54**
- Monocenter/Multicenter trial: **Monocenter trial**
- National/International: **National**

Inclusion Criteria

- Gender: **Both, male and female**
- Minimum Age: **18 Years**
- Maximum Age: **80 Years**

Additional Inclusion Criteria

1. Male or female patients aged ≥18 years and <80 years
2. Modified Fisher grade 3 or 4
3. Cisternal/Ventricular blood amount according to Hijdra Score ≥ 20
4. Admission WFNS grade ≥ 3 (if grade 5 only with fixed dilated pupil due to raised ICP for less than 45 minutes)
5. External ventricular drain (EVD) in situ or indication for placement of EVD
6. Disease duration ≤96 hours before randomization
7. Written informed consent, either by patient or by patient’s legally authorized representative
8. Cerebral aneurysm as definitive source of subarachnoid hemorrhage
9. Patients in whom the cerebral aneurysm has been safely treated via open surgical or endovascular technique

Exclusion criteria

1. Pregnancy
2. Surgical contraindications according to the opinion of the investigator
3. Inability to administer study medication (known allergy to urokinase or nimodipine)
4. Presence of a severe illness prior to aSAH (e.g. progressive cancer, terminal organ failure, severe neurological disorder, life expectancy <1 year)
5. Known and persistent abuse of medication or drugs
6. Presence of severe cerebral infarction related to the aSAH or medical procedures prior to randomization

7. Presence of intracerebral hematoma that is ≥ 30ml (assessed using the AxBxC/2 method) or in eloquent location prior to randomization
8. Presence of a condition or abnormality that in the opinion of the investigator would compromise safety of the patient
9. Known severe complications during aneurysm securing (e.g. dissections of blood vessels, vessel occlusions, re-hemorrhage)
10. Clinical signs of brain stem / midbrain compression (dilated pupil not reacting to light) persisting for more than 45 minutes at any time between aSAH onset and randomization
11. Persons who are in a relationship of dependence/employment with the sponsor or the investigator
12. For MRI follow-up: cardiac pacemaker and/or cardiac defibrillator. Stent implantation within the last 6 weeks prior to MRI, claustrophobia

Addresses

- **Primary Sponsor**

  Universitätsklinikum Freiburg
  Breisacher Str. 153
  79110 Freiburg
  Germany

  Telephone: **[---]***
  Fax: **[---]***
  E-mail: **[---]***
  URL: **[---]***

- **Contact for Scientific Queries**

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Sources of Monetary or Material Support

- **Private sponsorship (foundations, study societies, etc.)**

  Else Kröner-Fresenius-Stiftung
  Am Pilgerrain 15
  61352 Bad Homburg v.d.H.
  Germany

  Telephone: **[---]***
  Fax: **[---]***
  E-mail: **[---]***
  URL: **https://www.ekfs.de/**
- **Institutional budget, no external funding (budget of sponsor/PI)**

  Universitätsklinikum FreiburgKlinik für NeurochirurgieAbteilung Stereotaktische und Funktionelle Neurochirurgie
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Status

- Recruitment Status: **Recruiting ongoing**
- Study Closing (LPLV): **[---]***

Trial Publications, Results and other documents

** This entry means the parameter is not applicable or has not been set.*

**** This entry means that data is not displayed due to insufficient data privacy clearing.*