Received: 12 April 2023 | Accepted: 29 April 2023

DOI: 10.1111/aas.14263

RESEARCH ARTICLE

acta Anaesthesiologica Scandinavica

Prompt closure versus gradual weaning of external ventricular drainage for hydrocephalus following aneurysmal subarachnoid haemorrhage: Protocol for the DRAIN randomised clinical trial

Tenna Capion[1] | Alexander Lilja-Cyron[1] | Markus Harboe Olsen[2,3] | Marianne Juhler[1,4] | Kirsten Møller[3,4] | Angelika Sorteberg[5] | Pål André Rønning[5] | Frantz Rom Poulsen[6,7] | Joakim Wismann[6,7] | Celina Ravlo[8,9] | Jørgen Isaksen[8,9] | Jane Lindschou[2] | Christian Gluud[2,10] | Tiit Mathiesen[1,4]

[1]Department of Neurosurgery, The Neuroscience Centre, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

[2]Copenhagen Trial Unit, Centre for Clinical Intervention Research, The Capital Region, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

[3]Department of Neuroanaesthesiology, The Neuroscience Centre, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

[4]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

[5]Department of Neurosurgery, Oslo University Hospital, Oslo, Norway

[6]Department of Neurosurgery, Odense University Hospital, Odense, Denmark

[7]BRIDGE (Brain Research—Inter Disciplinary Guided Excellence), University of Southern Denmark, Odense, Denmark

[8]Department of Neurosurgery, Ophthalmology and Otorhinolaryngology, Division of Clinical Neurosciences, University Hospital of North Norway, Tromsø, Norway

[9]Department of Clinical Medicine, Faculty of Health Sciences, UiT The Arctic University of Norway, Tromsø, Norway

[10]Department of Regional Health Research, The Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark

Correspondence
Tenna Capion, Department of Neurosurgery, the Neuroscience Centre, Copenhagen

Abstract

Background: Aneurysmal subarachnoid haemorrhage (aSAH) is a life-threatening disease caused by rupture of an intracranial aneurysm. A common complication following aSAH is hydrocephalus, for which placement of an external ventricular drain (EVD) is an important first-line treatment. Once the patient is clinically stable, the EVD is either removed or replaced by a ventriculoperitoneal shunt. The optimal strategy for cessation of EVD treatment is, however, unknown. Gradual weaning may increase the risk of EVD-related infection, whereas prompt closure carries a risk of acute hydrocephalus and redundant shunt implantations. We designed a randomised clinical trial comparing the two commonly used strategies for cessation of EVD treatment in patients with aSAH.

Methods: DRAIN is an international multi-centre randomised clinical trial with a parallel group design comparing gradual weaning versus prompt closure of EVD treatment in patients with aSAH. Participants are randomised to either gradual weaning which comprises a multi-step increase of resistance over days, or prompt closure of the EVD. The primary outcome is a composite outcome of VP-shunt implantation, all-cause mortality, or ventriculostomy-related infection. Secondary outcomes are serious adverse events excluding mortality, functional outcome (modified Rankin scale), health-related quality of life (EQ-5D) and Fatigue Severity Scale (FSS). Outcome assessment will be performed 6 months after ictus. Based on the sample size calculation (event proportion 80% in the gradual weaning group, relative risk reduction 20%, type I error 5%, power 80%), 122 patients are needed in each intervention group. Outcome assessment for the primary outcome, statistical analyses and conclusion drawing will be blinded.

University Hospital, Rigshospitalet, Inge Lehmanns Vej 8, 2100 Copenhagen, Denmark.
Email: tenna.baek.capion@regionh.dk

Funding information
Rigshospitalet

Trial Registration: ClinicalTrials.gov identifier: NCT03948256.

KEYWORDS
aneurysm, aneurysmal subarachnoid haemorrhage, external ventricular drain, hydrocephalus, protocol, randomised clinical trial, weaning

1 | BACKGROUND

The incidence of aneurysmal subarachnoid haemorrhage (aSAH) is 6–7 per 100,000 patient-years in most populations.[1–4] Symptoms of aSAH include acute intense headache, nausea, seizures, loss of consciousness, and sudden death.[5] Most patients are below 60 years at the time of insult and mortality is 27%–50%, with one-third of survivors becoming permanently dependent on daily care after the initial hospital admission.[1,6] As aSAH occurs at a relatively young age and has high mortality and morbidity, the loss of productive life years in the general population is considerable, as is the economic burden per patient on health care systems.[7,8]

aSAH often causes acute hydrocephalus.[9] Symptoms of acute hydrocephalus include headache, nausea, vomiting, confusion, loss of consciousness, and ultimately death.[10] The primary treatment of acute hydrocephalus is the placement of an external ventricular drain (EVD) which allows diversion of excessive cerebrospinal fluid (CSF) to reduce the associated increase in intracranial pressure (ICP), which, if untreated, can lead to reduced cerebral blood flow and subsequent brain damage.[11,12] In some patients, the CSF circulation returns to normal within days or weeks after the aSAH, which allows the EVD to be removed. In other patients, however, chronic hydrocephalus evolves. This requires permanent drainage—usually in the form of a ventriculoperitoneal (VP) shunt which diverts CSF from the brain ventricles to the abdomen.[12] This procedure is associated with risks for the patient and increased medical costs for society, as complications to shunt treatment including obstruction and shunt-related infection, frequently require hospitalisation and surgical intervention.[6,12] In everyday clinic, patients in need of a VP-shunt are identified by a trial of EVD closure, typically, by one of two different strategies: gradual weaning or prompt closure. Weaning is done by gradually increasing the EVD outflow resistance over days. In theory, weaning compared to prompt closure may reduce the risk of shunt dependency or brain injury as a result of acute hydrocephalus. Conversely, weaning may increase the risk of EVD-related infection secondary to the longer duration of EVD treatment.[13] However, none of these questions have been resolved.

Guidelines from The American Stroke Association for management of patients with aSAH include a class I-recommendation for treatment of aSAH-associated acute hydrocephalus with CSF diversion (EVD treatment), and a class I-recommendation for permanent CSF diversion (VP shunt) for chronic hydrocephalus.[5] The strategy for weaning the EVD, however, has a class III recommendation (level of evidence B), stating that weaning of external ventricular drainage for more than 24 h 'does not appear to be effective in reducing the need for ventricular shunting'.[5] This recommendation is based specifically on the results from a single randomised clinical trial from 2004.[5,14] A systematic review from 2020 confirms that only one trial assessing strategy of EVD weaning has been conducted to this date.[15] Nonetheless, two recent surveys amongst North American and Scandinavian neurosurgeons revealed that most neurosurgical centres and neurosurgeons prefer gradual weaning, even though the best available evidence and current guidelines suggest that prompt closure is safe and can reduce the length of stay in the Neurointensive Care Unit (NICU) and hospital.[15,16] This lack of consensus and adherence to the guidelines reflects a lack of trust in the currently available evidence concerning the strategy for cessation of EVD treatment and calls for further solid investigation within the field.

2 | OBJECTIVE

The primary objective is to investigate the beneficial and harmful effects of gradual weaning versus prompt closure of EVD treatment in patients with aSAH.

3 | METHODS

The DRAIN trial is an international multi-centre, 1:1 randomised, parallel group, superiority clinical trial investigating gradual weaning vs. prompt closure of external ventricular drainage in patients with hydrocephalus following aSAH. The trial was registered at ClinicalTrials.gov with identifier no. NCT03948256 before inclusion of the first patient.

All adult patients with a diagnosis of aSAH admitted to one of the participating neurosurgical departments will be screened for enrolment. A complete list of participating trial sites can be seen in Supplementary material.

After successful treatment of the ruptured aneurysm, eligible participants will have the EVD resistance set to 10 cm H_2O before randomisation. An increase of drainage resistance to 15 cm H_2O may be done to ensure a uniform drainage production prior to intervention. When the participant fulfils all the all the inclusion criteria, and none of the exclusion criteria, they will be randomised, and the intervention (gradual weaning or prompt closure) will be initiated immediately hereafter. Participants who do not fulfil the inclusion criteria within 18 days after ictus are not included in the trial.

3.1 | Inclusion criteria

- ≥18 years of age.
- Diagnosis of aneurysmal subarachnoid haemorrhage (aSAH).
- External ventricular drain (EVD) for ≥6 days.
- Drain output of ≤220 mL/day.
- Drain resistance of 10 or 15 cm H_2O.
- Stable or improving Glasgow Coma Scale (GCS) ≥ 9 during the last 24 h.
- Signed informed consent (from patient or next-of-kin).

3.2 | Exclusion criteria

- None-tolerability of an increase of resistance to 10 cm H_2O due to clinical deterioration or an increase in ICP.
- Severe pre-existing (physical or mental) disability or severe co-morbidity that would lead to poor outcome even if the patient made a full recovery from the aSAH.
- Life expectancy shorter than 48 h after admission.

3.3 | Randomisation

Eligible participants are randomised 1:1 according to a computer-generated allocation sequence list generated by the data manager at the Copenhagen Trial Unit using concealed and varying block size and the following stratification variables:

1. Fisher grade ≤3 compared to >3,
2. age in years <60 years compared to ≥60 years, and
3. clinical site.

The allocation sequence list will be unknown to the investigators to allow immediate and concealed allocation of trial participants. Each trial participant is allocated a unique patient screening number.

3.4 | Blinding

Due to the nature of the intervention, blinding of participants and clinicians is not possible. Investigators, statisticians, and conclusion drawers will be blinded to the allocation when they carry out analysis and interpret the results. Assessment of the primary composite outcome will be carried out by blinded outcome assessors (see Section 5.4). The remaining outcomes will be assessed by unblinded trial investigators.

After completion of the clinical trial, blinded data will be analysed by two independent statisticians blinded to the intervention, where 'A' and 'B' refers to the two intervention groups. The statistical report with the analyses chosen for the manuscript is tracked using a version control system, and both statistical reports will be published as Supplementary material. Based on the final statistical report, two blinded conclusions will be drawn by the Steering Group before unblinding.

4 | INFORMED CONSENT FOR TRIAL PARTICIPATION

Signed informed consent from every participant, or from next-of-kin in case of temporarily incompetent patient.

4.1 | Trial interventions

4.1.1 | Gradual weaning

Gradual weaning comprises a stepwise increase of resistance to outflow ending with complete closure of the EVD. The drainage resistance is increased by 5 cm H_2O daily, beginning at the level where the patient is clinically stable, that is, when the decision to randomise and initiate intervention is made (at either 10 or 15 cm H_2O). The EVD is closed at the step where the resistance would reach 25 cm H_2O. The resistance is measured at the level of the external acoustic meatus according to standard clinical practice.[17] Finally, if closure is tolerated, the EVD is removed after 24 h of observation.

If the EVD resistance is decreased during the gradual weaning attempt, one additional attempt with a following monitoring period is initiated when the patient is clinically stable, that is, when he/she fulfils the inclusion criteria again. The participants are allowed two attempts of gradual weaning and if both attempts fail, the intervention is classified as a failure.

4.1.2 | Prompt closure

Prompt closure involves direct closure of the EVD at time of randomisation. If closure is tolerated, the EVD is removed after 48 h of observation. If the intervention is not tolerated, the EVD is reopened at the level from which closure was done. The participants are allowed two attempts of prompt closure of the EVD. If the participant fails two attempts of prompt closure, rescue intervention of gradual weaning is implemented.

4.1.3 | Discontinuation

Participants fail the trial intervention and are classified as needing a VP-shunt if:

1. They fail two attempts of gradual weaning, or
2. they fail two attempts of prompt closure, directly followed by two attempts of gradual weaning.

In both groups, an attempt of intervention fails if:

1. ICP rises above 20 mmHg for 20 consecutive minutes, or
2. GCS drops by two points or more, or
3. the patient clinically deteriorates otherwise (intolerable headache, nausea, etc.).

In case of discontinuation, the participant stays in the allocated intervention group and all outcomes are collected at follow-up.

4.1.4 | Concomitant interventions

All other aspects of the treatment, for example, securing of the aneurysm, treatment of vasospasm/delayed neurological deficits, control CT scans, sedation, and respiratory support, etc. follow departmental guidelines and are thus comparable in the two groups and not affected by participation in the DRAIN trial.

5 | OUTCOMES

5.1 | Primary outcome

The primary outcome is a composite outcome of VP-shunt implantation, all-cause mortality, or EVD-related infection.

EVD-related infection is defined as a positive CSF culture, use of intrathecal or systemic antibiotics for an EVD-related infection, or both.

5.2 | Secondary outcomes

Secondary outcomes are:

- Number of serious adverse events (SAE) not including death as defined according to International Conference of Harmonisation of Good Clinical Practice (ICH-GCP) at 6 months (*count outcome*).
- Health-related quality of life (EQ-5D-5L) at 6 months[18] with the primary assessment being self- assessment of own health (EQ VAS; 0–100 point scale) (*continuous outcome*).

5.3 | Exploratory outcomes

Each component of the primary outcome will be analysed as exploratory outcomes measures.

Further exploratory outcome measures are:

- Functional outcome according to mRS at 6 months[19,20] (1–6 scale) (*ordered categorical outcome*).
- The remaining dimensions of EQ-5D-5L (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) at 6 months[18] (1–5 levels) (*count outcome*).
- Fatigue Severity Scale (FSS) at 6 months[21] (1–7 scale) (*ordered categorical outcome*).
- Glasgow Outcome Scale Extended (GOSE) at 6 months[22] (1–8 scale) (*ordered categorical outcome*).
- Reason for failure of EVD cessation (ICP elevation, drop in GCS by two points or more, and/or clinical deterioration).
- GCS on discharge from the Neuro Intensive Care Unit and Neurosurgical department
- Length of stay in Neuro Intensive Care Unit and hospital.

5.4 | Outcome assessment

Outcome assessment will take place 6 months after ictus.

Recording of the primary outcome will be done by one blinded outcome assessor who will be given access to parts of the patient medical record which contains information regarding the three parts of the composite outcome (mortality, VP-shunt implantation, and EVD-related infection). The assessor will not have access to information regarding randomisation group or type of intervention. One assessor will perform the evaluation of all randomised participants to ensure uniform handling.

Recording of secondary and explorative outcomes will be done by assessment of the electronic patient medical record by an investigator or specialised nurse. Assessment of functional outcome (mRS), health-related quality of life (EQ-5D), and Fatigue Severity Scale (FSS) for secondary outcomes will happen via contact to the participant (if capable) or next-of-kin via telephone. If the participant is not able to answer for him-/herself, data for health-related quality of life (EQ-5D-5L) and Fatigue Severity Scale will not be provided as these scales are not approved for use by proxy. Allocation to group of intervention will not be sought for in the electronic patient journal, nor asked for or mentioned in the telephone interviews.

5.5 | Data handling and record keeping

Data will be collected from medical files by trial personnel and saved in an electronically, web-based eCRF.[23] Each participant will receive a unique trial identification number. Trial investigators will receive personal usernames and passwords to access the randomisation system and the eCRF. Data will be handled according to the National Data Protection Agency, the General Data Protection Regulation (GDPR), and will be protected by the Danish national law.

5.6 | Safety

Gradual weaning may increase the risk of drain-related infections and pro-longed stay in the NICU due to prolonged drain treatment (e.g. in an attempt to await potential return of normal CSF circulation and thereby avoid a permanent VP shunt). Superficial infection can spread to the brain and ventricular system and cause ventriculitis and in rare

cases meningitis and cerebral abscess with potential patient fatality. Gradual weaning may moreover be ineffective at preventing acute or chronic hydrocephalus with a subsequent need for a permanent shunt solution.

Prompt closure carries a risk of acute hydrocephalus, might increase the risk of chronic hydrocephalus (requiring VP-shunt treatment) in a longer timeframe, and might carry an unknown risk of brain injury from increased ICP.

An early decision to implant a VP-shunt carries the risk of implanting a permanent device in a patient who might not need it, and thus exposing the patients to risks associated with the primary operation (bleeding, infection, and in rare cases bowel injury), frequent hospitalisation and repeated surgeries due to shunt-dysfunction. Conversely, waiting too long before VP shunt insertion in hopes that it may not become necessary may increase the risk of a drain-related infection.

6 | STATISTICS

Continuous outcomes will be analysed by linear regression; dichotomous outcomes by logistic regression; ordered categorical data by proportional odds logistic regression[24] and count data by using van Elteren test. In the primary analysis, we will include the intention-to-treat population and the analysis will be adjusted for the stratification variables used in the randomisation. A two-sided *p* value of less than 0.05 will be considered statistically significant.

A detailed statistical analysis plan will be published before the follow-up of the last trial participant.

6.1 | Sample size and power justification

6.1.1 | Sample size estimation

Data from the only randomised clinical trial suggest a VP shunt wimplantation rate of 63% in patients with acute need of CSF diversion following aSAH.[14] The mortality of aSAH is commonly quoted to be 27%–50%, whilst 5.8% develop an EVD-related infection.[1,25] Assuming an incidence of either of the three components of the composite primary outcome (VP-shunt implantation, all-cause mortality, and EVD-related infection) at 6 months of 80%, an $\alpha = 0.05$ (two-sided), and a $\beta = 0.20$, 2×122 participants are required to detect a 20% relative risk reduction or increase calculated using R (R Core Team, Vienna, Austria).

6.1.2 | Power estimations

Based on the estimated sample of 244 participants and an unadjusted alpha of 0.05, we used R (R Core Team) to calculate the power for the secondary outcomes:

- Previous assessments of SAE in aSAH have not seemed to adhere to ICH-GCP as unlikely low incidences have been reported and seemed defined as probably related to the intervention.[26,27] Thus, we pragmatically presumed an average of three SAEs in the control group with an *SD* of 1.5 and the minimum clinical difference is pragmatically chosen as 1, which would result in a power of 100%[28]
- Based on previous assessments we presume an average of 49.5[29] in self-assessment of own health of health-related quality of life (EQ-5D-5L) in the control group with an *SD* of 26.2[29] and the minimum clinical difference is pragmatically chosen as 11[30] which would result in a power of 90%

The exploratory outcomes of mRS and FSS was initially planned as secondary outcomes given their importance to patients (NCT03948256). As the trial is insufficient powered to detect the minimal relevant clinical importance for these two outcomes, we have consequently reclassified them as exploratory outcomes.[31]

6.2 | Interim analysis

Considering a relatively small trial population of 244 participants and a follow-up period of 6 months, the probability of finding a significant difference between the intervention groups in an interim analysis is very slim. Thus, no interim analysis will be performed.

6.3 | Data sharing

Results whether positive, negative, or neutral will be submitted for peer-reviewed publication to a major clinical journal. The paper will be written in accordance with the CONSORT Statement for Randomized Trials of Non-pharmacologic Treatments.[32] Authorship will be determined according to the Vancouver definitions.[33] Anonymised data will be shared upon reasonable request.

7 | DISCUSSION

In this randomised clinical trial, we compare two common strategies for cessation of EVD treatment in adult patients with hydrocephalus following aSAH. It is the first randomised clinical trial with a pre-published protocol and statistical analysis plan with sufficient power to determine outcomes investigating this scientific matter.

A systematic review published at the initiation of this trial concluded that it is not possible, based on currently available scientific evidence, to favour any of the two strategies used for cessation of EVD treatment in patients with aSAH.[34] Despite this, current guidelines from the American Heart Association[5] for management of patients with hydrocephalus following aSAH base its recommendations on the only available trial investigating this matter,[14] even though thorough evaluation of the evidence suggests that a high risk of bias, and thus lack of certainty, makes it less reliable.[34]

Patients with aSAH constitute a heterogeneous and clinically complicated patient group with neurosurgical challenges such as treatment of the ruptured aneurysm and placement of an EVD, as well as medical complications such as delayed neurological deficits (DND), vasospasm, infections, electrolyte imbalances and respiratory distress. This makes it challenging to implement a one-size-fits-all for timing and initiation of the randomisation process, as the clinical course will vary considerably from patient to patient.

The investigators behind DRAIN have previously conducted a survey amongst Scandinavian neurosurgeons, asking them how they manage treatment and discontinuation of the EVD in patients with aSAH.[15] Decisions regarding timing of randomisation and interventions in DRAIN are based upon answers from this survey, and thus display the opinions and experience of a broad spectrum of neurosurgical clinicians. This is done to ensure that the randomisation and intervention process is as close to everyday clinical practice as possible.

DRAIN will provide results for adult patients with an EVD due to hydrocephalus following aSAH who regain consciousness (GCS ≥9) within an 18-day window (possibly extended due to treatment of medical conditions, e.g. DND or infection). This trial will not allow for conclusions on patients with a GCS below 9, or patients with a continuous very high drainage production (>220 mL/day) which does not decline within the time frame. The same applies for patients who received an EVD due to other pathologies than aSAH; intraparenchymal haemorrhage, traumatic brain injury, and so on.

7.1 | Strengths

DRAIN is the first investigator-initiated, international, multi-centre, randomised, controlled trial of prompt closure vs. gradual weaning of EVD treatment in adult patients with hydrocephalus following aSAH. The trial design is based on a stringent methodology, which includes concealed sequence generation for randomisation, allocation concealment, blinding to the outcome assessors and the trial statistician.

Sample size estimations and trial design are based on the only available trial within the field and on recent surveys amongst treating clinicians, making the trial relevant and representative of current clinical practice.

Completion of a randomised trial with independent outcomes and multiple exploratory clinical outcomes will contribute with important data for the future patient treatment.

7.2 | Limitations

DRAIN allows for randomisation of patients with a GCS of nine or above as outcomes are primarily clinical, and thus comatose patients who during their stay in the ICU do not regain assessable consciousness are not within the scope of this trial. Furthermore, blinding of patients, relatives, and treating physicians has not been possible due to the nature of the intervention.

8 | CONCLUSION

There is a need for a high-quality, randomised clinical trial to assess and compare the strategies used in everyday clinical work for EVD cessation in patients with hydrocephalus following aSAH.

8.1 | Trial status

The protocol is registered at www.clinicaltrials.gov (NCT03948256; registered 4 April 2019). The first participant was enrolled in June 2019. Four departments of neurosurgery across Norway and Denmark currently include patients, and the anticipated date of final participant inclusion is end of 2023.

AUTHOR CONTRIBUTIONS

Tenna Capion and Markus Harboe Olsen drafted the first version of the manuscript and the statistical report. All other authors revised the manuscript. All authors approved the final version.

ACKNOWLEDGEMENT

The authors declare that they have no competing interests.

FUNDING INFORMATION

TC has received funding from the Research Council at Copenhagen University Hospital Rigshospitalet (grant no. E-23565-02 and E-23565-03).

DATA AVAILABILITY STATEMENT

After end of follow up, statistical analyses, submission of manuscripts, and publication anonymised trial data will be shared through Zenodo.

ORCID

Tenna Capion https://orcid.org/0000-0002-6968-1938
Alexander Lilja-Cyron https://orcid.org/0000-0003-2915-249X
Kirsten Møller https://orcid.org/0000-0003-3058-1072

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Capion T, Lilja-Cyron A, Olsen MH, et al. Prompt closure versus gradual weaning of external ventricular drainage for hydrocephalus following aneurysmal subarachnoid haemorrhage: Protocol for the DRAIN randomised clinical trial. *Acta Anaesthesiol Scand*. 2023;1-7. doi:10.1111/aas.14263