


BMJ Open Prompt closure versus gradual weaning of extraventricular drainage for hydrocephalus in adult patients with aneurysmal subarachnoid haemorrhage: a systematic review protocol with meta-analysis and trial sequential analysis

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ABSTRACT

Introduction In Neuro Intensive Care Units (NICU) and neurosurgical units, patients with an external ventricular drain (EVD) due to hydrocephalus following aneurysmal subarachnoid haemorrhage (SAH) are commonly seen. Cessation of the EVD involves the dilemma of either closing the EVD directly, or gradually weaning it before removal. Development of increased intracranial pressure (ICP) and acute hydrocephalus with subsequent need of a permanent shunt has been associated with prompt closure of the EVD, whereas increased risk of infection with possible spreading to the brain and subsequent patient fatality is suspected in connection to a longer treatment as seen in gradual weaning. Sparse data exist on the recommendation of cessation strategy and patients are currently being treated on the basis of personal experience and expert opinion. The objective of this systematic review is to assess the available evidence from clinical trials on the effects of prompt closure versus gradual weaning of EVD treatment for hydrocephalus in adult patients with SAH.

Methods and analysis We will search for randomised clinical trials in major international databases. Two authors will independently screen and select references for inclusion, extract data and assess the methodological quality of the included randomised clinical trials using the Cochrane risk of bias tool. Any disagreement will be resolved by consensus. We will analyse the extracted data using Review Manager and trial sequential analysis. To assess the quality of the evidence, we will create a 'Summary of Findings' table containing our primary and secondary outcomes using the GRADE assessment.

Ethics and dissemination Results will be published widely according to the interest of the society. No possible impact, harm or ethical concerns are expected doing this protocol.

Trial registration number PROSPERO CRD42018108801

INTRODUCTION

Background

Spontaneous subarachnoid haemorrhage (SAH) is a common and often devastating cerebrovascular disease accounting for

Strengths and limitations of this study

- Patient-centred outcomes (clinical relevance).
- Rigorous bias assessment of the risk of random errors/trial sequential analysis.
- GRADE assessment of 'overall quality of the evidence'.
- Expected few trials and thus few randomised patients.
- Recommendations from systematic reviews may suffer from the quality of the included trials.

approximately 7% of all strokes.¹ Most patients are younger than 60 years of age at the time they suffer from SAH. In 85% of cases, the cause of SAH is rupture of an intracranial aneurism, whereas non-aneurysmal perimesencephalic haemorrhage accounts for 10%, and a variety of other conditions for 5%.² In contrast to other types of stroke, the incidence of SAH has been stable at around 6 cases per 100,000 patient years throughout the last 30 years.^{2,3} Reported mortality from SAH is 27%–50%, with a third of survivors permanently dependent on daily care after the initial hospital admission.^{2,4} Because SAH occurs at a relatively young age and has high mortality and morbidity, both loss of productive life years in the general population as well as the economic burden per patient on public healthcare systems are considerable.^{5,6}

When rupture of an intracranial aneurysm occurs, arterial blood is shunted into the subarachnoid space at arterial pressure leading to a sudden rise in intracranial pressure.⁷ Hydrocephalus due to blockage of cerebrospinal fluid (CSF) circulation and absorption occurs as a common and serious

complication to SAH.^{4 8} In the acute and subacute course of SAH, hydrocephalus is of a high pressure obstructive type with bloody CSF, which is commonly treated by placing an EVD in the ventricular system, allowing management of ICP into a clinically safe range by external diversion of excessive CSF. Some patients proceed to require permanent diversion of CSF, because steps to discontinue CSF drainage result in unacceptable ICP increase and/or clinical deterioration. Two different strategies for drain closure can be followed: either prompt closure or weaning by gradually increasing resistance to outflow over a few days. It is not known if these two strategies result in different clinical outcomes, different probabilities for needing permanent shunt placement or different complication rates.

It seems both necessary and feasible to systematically review the evidence on the relationship between cessation strategy for hydrocephalus in SAH and such outcome measures.

Description of the condition

CSF is continually produced by filtration of the arterial blood from vessels in the choroid plexus lining the inside of the cerebral ventricles. It is generally accepted that the rate of adult CSF production is constant at approximately 500 mL per day. According to the classical bulk flow theory, CSF flows from the ventricular system, out through the fourth ventricle outlets into the subarachnoid space around the brain and the spinal cord before it is reabsorbed in the venous system through arachnoid granulations in (primarily) the sagittal sinus.⁹ Alternative theories for CSF circulation and absorption physiology are increasingly being expressed describing cerebral lymphatics and molecular transport of CSF and brain water along perivascular spaces in the brain parenchyma.^{10 11} Whether several routes coexist or one is more important is unresolved.

Regardless of the actual physiological mechanisms behind CSF, blood elements and coagula obstructing CSF circulation and absorption anywhere in the system will result in hydrocephalus.⁷ The reported prevalence of hydrocephalus following SAH varies widely; between 6% and 67%. Three stages are generally recognised: acute (0–3 days after SAH), subacute (4–13 days after SAH) and chronic (≥ 14 days after SAH).⁸

Description of the intervention

Acute hydrocephalus in SAH is treated by inserting a temporary external ventricular drain (EVD) into the brain's ventricular system. Excessive CSF is drained in a closed system into a sterile bag or container. The vertical placement of the inlet in the bag/container determines the drainage pressure.^{12 13} In some patients, reabsorption of CSF returns to normal within days permitting the EVD to be removed without ICP increase or further need for treatment of the hydrocephalus. In other patients, the EVD is needed much longer, before it can be removed, and in yet other patients, chronic hydrocephalus evolves with the need of an implanted permanent drainage

solution (most frequently a ventriculoperitoneal (VP) shunt¹⁴). There is no documentation to define the timing when to insert a permanent internal drainage weighted against further continuation of an EVD. Prolonged duration of EVD treatment (eg, in an attempt to await potential return of normal CSF reabsorption and avoid a permanent shunt) increases the risk of infection (ventriculitis, meningitis, cerebral abscess), which can be serious and potentially fatal.

In some patients, chronic hydrocephalus occurs late and following a non-hydrocephalic condition lasting several months (secondary normal pressure hydrocephalus).¹⁵ This type of hydrocephalus is not the scope of this review.

How the intervention might work

After SAH, some patients will experience only temporarily decreased reabsorption of CSF leading to hydrocephalus, while others develop chronic hydrocephalus requiring permanent CSF diversion. The process of identifying patients who will need a permanent VP shunt often involves a trial of CSF drainage cessation. The main argument in favour of prompt closure of the drain is to minimise EVD treatment period and thereby the risk of infection. The argument in favour of weaning by gradually increasing the drainage pressure is to allow more time for re-establishment of normal CSF reabsorption and thereby lower the need for a permanently implanted drainage system (VP shunt).

Why it is important to do this review

To our knowledge, previous reviews based on comprehensive literature searches have compared the two common cessation strategies of EVD treatment in patients with hydrocephalus following aneurysmal SAH without prepublished protocols containing predefined hypotheses and data extraction plans.^{16 17} It is our belief that a review which methodologically meets the rigorous demands for systematic reviews as defined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (and the 2015 Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement) is relevant in order to provide the highest possible impact for researchers to use in forthcoming work and evaluation of this medical issue.¹⁸

If there is a difference between treatment strategies, it is important to choose the strategy with the best outcomes. Insertion of a VP shunt in the present context is best defined as a surrogate outcome measure, as the procedure is associated with risks for the patient (ie, mechanical shunt dysfunction and shunt-related infections) and increased medical costs for society, as shunt complications frequently require hospitalisation and surgical interventions.

Objectives

The objective of this review is to summarise the evidence on benefits and harms of prompt closure versus gradual weaning of extraventricular drainage in patients with aneurysmal SAH, based on randomised clinical trials.

MATERIALS AND METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised clinical trials comparing prompt closure versus gradual weaning of extraventricular drainage. We will include randomised clinical trials without consideration of publication status, blinding status or language. We will contact the investigators and the authors in order to retrieve relevant data. We will only include unpublished trials if trial data and methodological descriptions are provided either in written form or by direct contact with the authors. We will exclude trials using quasi-randomisation and observational studies. However, we will establish an appendix enumerating the findings from observational studies regarding adverse effects.

Types of participants

We will include patients aged equal to or greater than 18 years with hydrocephalus in relation to aneurysmal SAH. However, we will establish an appendix enumerating the findings from studies of prompt closure versus gradual weaning of extraventricular drainage in other conditions, such as spontaneous intracranial haemorrhage.

Types of outcome measures

Primary outcomes

1. Death from any cause.
2. Patients with one or more serious adverse events (SAE) including all-cause mortality, defined according to International Conference of Harmonisation of Good Clinical Practice (ICH-GCP) for devices. Additionally, we will include complications and adverse events specific for extraventricular drainage and VP shunt systems: (i) Clinical and radiological signs of shunt obstruction. ii) Clinical and microbiological signs of ventriculitis or shunt infection.
As we expect the reporting of SAEs to be very heterogeneous and not strictly according to the ICH-GCP recommendations, we will estimate the number of patients with one or more SAE in two ways: (i) By adding all reported SAEs, assuming that patients only experience one SAE (the number of patients in each group will be a maximum) which will somehow be a worst-case scenario. (ii) By choosing the SAE with the highest proportion reported in each trial which will somehow be a best-case scenario. The true effect on the occurrence of SAEs will be between these extremes.
3. Rate of permanent VP shunt implantation.
4. Quality of life (QoL) measured with any score.

Secondary outcomes

1. Patients with a shunt failure, defined as number of shunt interventions following the primary shunt insertion (surgical shunt interventions for any reason) within the longest follow-up in each trial.
2. Total hospital length of stay.
3. NICU length of stay.
4. EVD-related complications (ventriculitis defined as positive CSF culture, clinically relevant

intracranial haemorrhage requiring surgical evacuation or additional surgical procedure secondary to EVD misplacement).

Search methods for identification of studies

Electronic searches

1. U.S. National Library of Medicine premier bibliographic database (MEDLINE) (1946 to date) (Medical Library at Health First database (Ovid SP)), Excerpta Medica database (EMBASE) (1974 to date) (Ovid SP) and Latin American and Caribbean Health Sciences Literature (LILACS) (1982 to date) (BIREME).
2. Science Citation Index Expanded (1900 to November 2018) and Conference Proceedings Citation Index—Science (1990 to November 2018) (Web of Science)
3. The Cochrane Library's Central Register of Controlled trials (CENTRAL).

Additional separate searches will be run plus additional sources (such as the Chinese Biomedical Literature Database BIOSIS Previews) to ensure that the most up-to-date results are retrieved. The search strategy that will be used for the retrieval of reports of trials from MEDLINE (via the Ovid SP platform) can be seen in online supplementary appendix 1.

The searches will be performed without language or date restrictions.

Searching other resources

We will hand search the reference list of reviews, randomised and non-randomised studies, and editorials for additional studies. We will contact the main authors of studies to ask for any missed, unreported or ongoing trials.

Data collection and analysis

Selection of studies

Two authors (AL-C and TC) will independently evaluate all relevant trials and provide a detailed description of the included and excluded articles under the sections 'Characteristics of included studies' and 'Characteristics of excluded studies', respectively. We will also provide a detailed description of our search results.

Data extraction and management

We will screen the titles and abstracts in order to identify studies that are eligible. AL-C and TC will independently extract and collect the data using the Covidence software. We will not be blinded to the author, institution or the publication source of trials. We will resolve disagreements by discussion. We will approach all corresponding authors of the included trials for additional information relevant to the review's outcomes measures and risk of bias (ROB) components.

Assessment of ROB in included studies

The validity and design characteristics of each trial are to be evaluated. Two authors (AL-C and TC) will independently conduct the assessment of ROB. To draw conclusions about the overall ROB for an outcome it is necessary to evaluate the trials for major sources of bias,

also defined as domains (random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other sources of bias). The Cochrane Collaboration's recommended tool for assessing ROB is neither a scale nor a checklist but rather a domain-based evaluation. Any assessment of the overall ROB involves consideration of the relative importance of the different domains.

Even the most realistic assessment of the validity of a trial may involve subjectivity since it is impossible to know the extent of bias (or even the true ROB) in each trial. Some domains affect the ROB across outcomes in a trial, for example, sequence generation and allocation sequence concealment, while others such as blinding and incomplete outcome data may have different risks of bias for different outcomes within a trial. Thus, ROB is not the same for all outcomes in a trial. We will perform separate sensitivity analyses for patient-reported outcomes (subjective outcomes) and for mortality.¹⁹

We will define the trials as having low ROB only if they adequately fulfil the criteria listed in the Cochrane Handbook for Systematic reviews of Interventions and we will perform summary assessments of the ROB for each important outcome (across domains) within and across studies. We will apply a 'risk of bias graph' and a 'risk of bias summary figure'.¹⁹

We will present results for all outcomes including adverse events in a 'Summary of findings' (SOF) table with a GRADE (Grading of Recommendations Assessment, Development and Evaluation) assessment for the quality of evidence for the results on each outcome. As there is no sufficiently well designed formal statistical method to combine the results of trials with high and low ROB, the principle approach to incorporating ROB assessments in Cochrane reviews is to restrict meta-analyses to studies at low (or lower) ROB.¹⁹ We will use the ROB table described in the Cochrane Handbook, section 8.5 as a tool for assessing ROB in included studies.

Measures of treatment effect

We will report QoL as continuous outcomes and the intervention effect as a standardised mean difference with 98% CI. All other outcomes are dichotomous and will be reported as relative risks (RRs) with 98% CIs. For mortality, which we expect will be a rare outcome, the Peto OR (POR) will be calculated. We will also calculate the risk difference (RD) with 98% CI and subsequently numbers needed to treat, if possible.

Unit of analysis issues

Number of events in all binary meta-analyses, and QoL scores in the QoL analysis.

Dealing with missing data

We will contact all the first authors and contact persons of the trials that have missing data in order to retrieve the relevant data. A modified intention-to-treat (ITT) analysis will be performed. ITT analysis is recommended to minimise bias in the design, follow-up and analysis of the

efficacy of randomised clinical trials. It gives a pragmatic estimate of the benefit of a change in treatment policy rather than a measure of the potential benefit in patients who receive treatment exactly as planned.²⁰ Full application of ITT is possible only when complete outcome data are available for all randomised participants. Even though about half of all published reports of randomised clinical trials state that ITT analysis was used, handling of deviations from randomised allocation varies widely and many trials have missing data for the primary outcome variable. Methods used to deal with this are generally inadequate, potentially leading to bias.²¹ Performing an ITT analysis in a systematic review is not straightforward since review authors must decide how to handle outcome data missing from the contributing trials.²² No consensus exists about how missing data should be handled in ITT analyses and different approaches may be appropriate in different situations.^{19 20} In cases of missing data, for our primary outcomes we will use a 'complete-case analysis' by simply excluding from the analysis all participants with the outcome missing. Additionally, we will conduct sensitivity analyses for our primary outcomes by applying best-case and worst-case scenarios, please see section 2.4.4 on sensitivity analyses. The best-case scenario is: all patients lost to follow-up in the prompt closure group survived and all patients lost to follow-up in the gradual weaning group died; all patients lost to follow-up in the prompt closure group did not have an SAE and all patients lost to follow-up in the gradual weaning group did have an SAE. The worst-case scenario is: all patients lost to follow-up in the prompt closure group had an SAE and all patients lost to follow-up in the gradual weaning group did not have an SAE; all patients lost to follow-up in the prompt closure group had an SAE and all patients lost to follow-up in the gradual weaning group did not have an SAE. Selective outcome reporting occurs when non-significant results are selectively withheld from publication.²³ It is defined as the selection, on the basis of the results, of a subset of the original recorded variables for inclusion in the publication of a trial. The most important types of selective outcome reporting are: selective omission of outcomes from reports; selective choice of data for an outcome; selective reporting of analyses using the same data; selective reporting of subsets of the data; and selective under-reporting of data.¹⁹ Statistical methods to detect within-study selective reporting are still in their infant stage. We will explore selective outcome reporting by comparing publications with their protocols, if the latter are available.

Assessment of heterogeneity

The degree of heterogeneity observed in the results is quantified using diversity (D^2)²⁴ and inconsistency factor (I^2) statistics, which can be interpreted as the proportion of the total variation observed between the trials that is attributable to differences between trials rather than sampling error (chance).²⁵ A value of $p \leq 0.10$ indicates significant heterogeneity, and the suggested I^2 statistic

thresholds for low, moderate and high heterogeneity are 0% to 49%, 50% to 74% and $\geq 75\%$, respectively.²⁵ If $I^2=0$, we will report the results using the fixed-effect model only. In the case of $I^2>0$, we will report the results using both the random-effects and the fixed-effect models. However, we believe that there is little value in using a fixed-effect model in cases of substantial heterogeneity, which we suspect will be present in this review due to inclusion of various patient types and outcome reporting. So, we will emphasise the results from the random-effects model analysis unless a few trials dominate the meta-analysis (for example more than 50% of the cumulated fixed weight percentage). Additionally, in cases of $I^2>0$ (for the primary outcomes) we will seek to determine the cause of heterogeneity by performing relevant subgroup analyses and meta-regression. We aim to combine trial results in a meta-analysis only when clinical heterogeneity is low to moderate.

Assessment of reporting biases

Publication bias occurs when the publication of research results depends on their nature and direction.²⁶ We will examine this by providing funnel plots in order to detect either publication bias or a difference between smaller and larger studies (small study effects), expressed as asymmetry of the funnel plot.²⁷ Funding bias is defined as the biases in the design, outcome and reporting of industry-sponsored research in order to show that a drug has a favourable outcome.^{28 29} Relationships between industry, scientific investigators and academic institutions are widespread and often result in conflicts of interest.^{28 29}

Data synthesis

As we intend to analyse four primary outcomes we adjust the level of statistical significance and CIs due to statistical multiplicity to keep the familywise error rate (FWER) below 0.05. The adjustment will be done according to³⁰ halfway between a full Bonferroni adjustment, and no adjustment, to an $\alpha=0.02(0.05/((4+1)/2))$ and 98%, CIs, as our outcomes are surely not independent.

We will use Review Manager software (RevMan V.5.0) as the statistical software. We will calculate the RR with 98% CI for dichotomous variables (binary outcomes). We will also calculate the risk difference,³¹ if the results are similar we will only report the RR. Additionally, we will calculate mean difference as the measure of absolute change with 98% CI for continuous outcomes. We will use $D^2(24)$ and I^2 statistics²⁵ to describe heterogeneity among the included trials.

Meta-analysis

We will perform conventional meta-analysis of outcomes with comparable effect measures where more than one trial is included. If clinical and statistical heterogeneity are large or unexpected, we will reconsider performing the meta-analysis.

We will explore causes of substantial heterogeneity by subgroup analyses and meta-regression using

comprehensive meta-analysis V.1 and Stata V.9. We will use the χ^2 test to provide an indication of heterogeneity between studies, with $p\leq 0.10$ considered significant. Adverse effects may be rare but serious, and hence important³² when meta-analysis is applied for combining results from several trials that have binary outcomes (that is event or no event). First, we will apply the POR in the case of small event proportions. Most meta-analytical software packages do not include options for analyses to calculate RR when included trials have 'zero events' in both arms (intervention vs control). Exempting these trials from the calculation of RR and CI may lead to overestimation of a treatment effect as the control event proportion may be overestimated. Thus we will perform a sensitivity analysis by applying empirical continuity corrections to our zero event trials, as proposed by Sweeting *et al*^{31 33} by applying an imaginary small mortality in both arms.

Trial Sequential Analysis

Meta-analyses may result in type 1 errors due to sparse data and repeated significance testing when meta-analyses are updated with new trials.^{24 34-37} Systematic errors from trials with high ROB, outcome reporting bias, publication bias, early stopping for benefit and small trial bias may result in spurious p values. In a single trial, interim analysis increases the risk of type 1 errors. To avoid type 1 errors, group sequential monitoring boundaries³⁸ are applied to decide whether a trial could be terminated early because of a sufficiently small p value, that is the cumulative Z curve crosses the monitoring boundary. Sequential monitoring boundaries can be applied to meta-analyses as well and are called trial sequential monitoring boundaries (TSMBs). In 'Trial Sequential Analysis' (TSA) the addition of each trial in a cumulative meta-analysis is regarded as an interim meta-analysis and helps to decide whether additional trials are needed.^{36 37} Potentially a meta-analysis can be performed every time new trial results are added to a review and we will investigate whether the risk of increased type 1 error by multiple and early testing influences the level of statistical significance. It therefore seems appropriate to adjust new meta-analyses for multiple testing on accumulating data to control the overall type 1 error risk in cumulative meta-analysis.^{35-37 39 40} The idea in TSA is that if the cumulative Z curve crosses the boundary, a sufficient level of evidence is reached and no further trials may be needed. However, there is insufficient evidence to reach a conclusion if the Z curve does not cross the boundary or does not surpass the required information size. To construct the TSMB the required information size is needed and will be calculated as the least number of participants needed in a well-powered single trial.^{34 37 40} We will adjust the required information size for heterogeneity with the diversity adjustment factor.²⁴ We will apply TSA, since it prevents an increase in the risk of type 1 error ($<5\%$) due to potential multiple updating and early testing on accumulating data, whenever new trial results are included in a cumulative meta-analysis.^{39 40} This provides us with

important information in order to estimate the level of evidence on the experimental intervention.^{35 39 40} Additionally, TSA provides important information regarding the need for additional trials and their required sample size.^{24 37} We will apply TSMBs according to an information size suggested by an a priori 20% relative risk reduction (RRR) of the binary outcomes.^{24 37} Furthermore, we will perform an analysis using the intervention effect suggested by the CI limit closest to the null effect and the point estimate in a random-effects model of all the trials using a control event proportion suggested by large observational studies and by the pooled estimate of the event proportion in the included trials control groups. As mortality a priori seems low or very low in the trials conducted so far, and hence the ability to detect small intervention effects is low, we will perform a TSA with a diversity-adjusted required information size estimated based on an a priori 33% RRR of mortality.^{24 37} We will use an a priori anticipated diversity of 50% and a sensitivity analysis using the diversity suggested by all the included trials. We will present all analyses with TSA-adjusted (1- α) CI using $\alpha=0.02$ to preserve an FWER<0.05.

Subgroup analysis and investigation of heterogeneity

We will only make inferences from the subgroup analyses in terms of implications for clinical practice if the overall analysis of one of the co-primary outcomes becomes statistically significant. Where the analyses of the co-primary outcomes do not become statistically significant, we intend to reference them in 'Implications for research' to provide possible hypothesis generation for further research. We will compare intervention effects in subgroups using a test of interaction.⁴¹ We consider $p<0.05$ to be indicative of significant interaction between the prompt closure effect on one of the co-primary outcomes and the subgroup category.¹⁹

The following subgroup analyses will be conducted if data permit:

1. Comparing estimates of the pooled intervention effect in trials with overall high ROB versus trials with overall low ROB. Hypothesised direction of subgroup effect: increased beneficial intervention effect in the trials with overall high ROB.
2. Comparing estimates of the pooled intervention effect in the included subpopulations of adult patients with hydrocephalus following aneurysmal SAH: if different weaning strategies are used within the individual included trials, patients assessed differently will be analysed in groups according to the respectively used strategies. Hypothesised direction of subgroup effect: increased beneficial intervention effect in some subpopulation.
3. Comparing estimates of the pooled intervention effect in the included subpopulations of adult patients with hydrocephalus following aneurysmal SAH: patients with severe degree of SAH on modified Fisher's Scale (grades 3 and 4) versus patients with fair degree of SAH on modified Fisher's Scale (grades 1 and 2).

Hypothesised direction of subgroup effect: increased beneficial intervention in patients with fair degree of SAH on modified Fisher's Scale.

4. Comparing estimates of the pooled intervention effect in the included subpopulations of adult patients with hydrocephalus following aneurysmal SAH: patients with a severe degree of SAH on the Hunt and Hess Scale (grades 3, 4 and 5) versus patients with a fair degree of SAH on the Hunt and Hess Scale (grades 1 and 2). Hypothesised direction of subgroup effect: increased beneficial intervention in patients with a fair degree of SAH on the Hunt and Hess Scale.
5. Comparing estimates of the pooled intervention effect in the included subpopulations of adult patients with hydrocephalus following aneurysmal SAH: patients <60 years of age versus patients >60 years of age. Hypothesised direction of subgroup effect: increased beneficial intervention in patients <60 years of age.
6. Comparing estimates of the pooled intervention effect in the included subpopulations of adult patients with hydrocephalus following aneurysmal SAH: patients with late (>48 hours after SAH) versus early (≤ 48 hours after SAH) EVD implantation.

Sensitivity analysis

To assess the potential impact of the missing data for dichotomous outcomes, the following two analyses will be performed:

1. 'Best-worst-case' scenario: It will be assumed that all participants lost to follow-up in the experimental group survived, had no SAE and had no morbidity; and all those with missing outcomes in the control group did not survive, had an SAE and had morbidity.
2. 'Worst-best-case' scenario: It will be assumed that all participants lost to follow-up in the experimental group did not survive, had an SAE and had morbidity; and all those with missing outcomes in the control group did survive, had no SAE and had no morbidity.

Results from both scenarios will be presented in the review.

To assess the potential impact of the missing data for continuous outcomes, the following two analyses will be performed:

1. 'Best-worst-case' scenario: It will be assumed that all participants lost to follow-up in the experimental group had mean (from patients with follow-up)+2 \times SD; and all those with missing outcomes in the control group had mean (from patients with follow-up)-2 \times SD.
2. 'Worst-best-case' scenario: It will be assumed that all participants lost to follow-up in the experimental group had mean (from patients with follow-up)-2 \times SD; and all those with missing outcomes in the control group had mean (from patients with follow-up)+2 \times SD.

To assess the potential impact of missing SDs for continuous outcomes, the following sensitivity analyses will be performed: where SDs are missing and not possible to calculate, SDs will be imputed from trials with similar populations and low ROB. If no such trials can be found,

SDs will be imputed from trials with a similar population. As the final option SDs will be imputed from all trials.

We will perform sensitivity analyses to assess the potential impact of missing data by performing best-worst-case and worst-best-case scenarios. We will calculate RR with 98% CI and apply a complete case analysis, if possible, for the sensitivity and subgroup analyses based on the mortality and SAE primary outcomes.

Grade

SOF tables will be produced summarising the results of the trials with overall low ROB and for all trials, separately. Reasons for downgrading the quality of the available evidence are: ROB evaluation of the included bias domains, publication bias, heterogeneity, imprecision and indirectness (eg, length of stay is a surrogate outcome measure). We will compare the imprecision assessed according to GRADE with that of TSA.⁴²

Patient and public involvement

Patients and public were not involved in the making of this systematic review protocol.

Ethics and dissemination

The evidence on the benefits and harms of the two common strategies for cessation of EVD treatment in patients with hydrocephalus following SAH is sparse, and no methodologically thorough systematic review has been conducted so far.

Results from this review will be published in an international journal according to the interest of the society. No possible impact, harm or ethical concerns are expected doing this review.

The choice to publish the protocol separately is based on current PRISMA guidelines (and 2015 PRISMA-P statement) which recommends that systematic reviews are build on a separate protocol that describes rationale, hypothesis and planned methods of the review, and that this protocol is made public (besides PROSPERO registration) before data search and extraction are carried out, in order to avoid data-driven analysis.¹⁸

This will, in addition, make it possible for future peer reviewers and editors to be able to measure the completeness and transparency of the review with a predefined methodological approach, outlined in an associated protocol, which we find of significant methodological importance.

DISCUSSION

Placement of an EVD in patients with hydrocephalus following aneurysmal SAH is an important first-line treatment and is scientifically well substantiated. Risks related to cessation strategy on the other hand remain unclear. To our knowledge, previous comprehensive literature searches have compared the two common cessation strategies of EVD treatment in patients with hydrocephalus following aneurysmal SAH without republished

protocols. It is our belief that a review which methodologically meets the rigorous demands for systematic reviews as defined by the PRISMA guidelines (and 2015 PRISMA-P statement) is relevant in order to provide the highest possible impact for researchers to use in the forthcoming work and evaluation of this medical issue, as well as provide reliable and powered evidence to better inform clinicians on the choice of cessation strategy, or for the initiation of upcoming trials within the field.

The objective is to conduct a systematic review with meta-analysis and TSA as well as GRADE assessments comparing the benefits and harms of prompt closure versus gradual weaning of EVD treatment in adult patients with hydrocephalus following aneurysmal SAH. We will primarily base our conclusions on meta-analyses of trials with overall low ROB. However, if pooled point-estimates of all trials are similar to pooled point-estimates of trials with overall low ROB and there is lack of a statistically significant interaction between estimates from trials with overall high ROB and trials with overall low ROB, we will consider the precision achieved in all trials as the result of our meta-analyses.

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Contributors Conception or design of the work: TC, AL-C, MJ, TIM, JW. Data collection: TC, AL-C, JW. Data analysis and interpretation: TC, JW. Drafting the article: TC, AL-C, JW. Critical revision of the article: TC, AL-C, MJ, TIM, JW. Final approval of the version to be published: TC, AL-C, MJ, TIM, JW.

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Competing interests JW is a member of the taskforce at Copenhagen Trial Unit which develops theory, manual and software for doing Trial Sequential Analysis presently freeware at www.ctu.dk/tsa.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement There are no data in this work.

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REFERENCES

1. Qian C, Yu X, Chen J, *et al*. Effect of the drainage of cerebrospinal fluid in patients with aneurysmal subarachnoid hemorrhage: a meta-analysis. *Medicine* 2016;95:e5140.
2. van Gijn J, Rinkel GJ. Subarachnoid haemorrhage: diagnosis, causes and management. *Brain* 2001;124:249–78.
3. Ellmore TM, Rohlfes F, Khursheed F. fMRI of working memory impairment after recovery from subarachnoid hemorrhage. *Front Neurol* 2013;4:1–13.
4. Xie Z, Hu X, Zan X, *et al*. Predictors of Shunt-dependent hydrocephalus after aneurysmal subarachnoid hemorrhage? A systematic review and meta-analysis. *World Neurosurg* 2017;106:844–60.

5. de Rooij NK, Linn FHH, van der Plas JA, *et al.* Incidence of subarachnoid haemorrhage: a systematic review with emphasis on region, age, gender and time trends. *J Neurol Neurosurg Psychiatry* 2007;78:1365–72.
6. Dodel R, Winter Y, Ringel F, *et al.* Cost of illness in subarachnoid hemorrhage: a German longitudinal study. *Stroke* 2010;41:2918–23.
7. van Gijn J, Kerr RS, Rinkel GJE. Subarachnoid haemorrhage. *The Lancet* 2007;369:306–18.
8. Dorai Z, Hynan LS, Kopitnik TA, *et al.* Factors related to hydrocephalus after aneurysmal subarachnoid hemorrhage. *Neurosurgery* 2003;52:763–71.
9. Golanov EV, Bovshik EI, Wong KK, *et al.* Subarachnoid hemorrhage - Induced block of cerebrospinal fluid flow: Role of brain coagulation factor III (tissue factor). *J Cereb Blood Flow Metab* 2018;38:793–808.
10. Iliff JJ, Nedergaard M. Is there a cerebral lymphatic system? *Stroke* 2013;44(6 Suppl 1):S93–5.
11. Louveau A, Plog BA, Antila S, *et al.* Understanding the functions and relationships of the glymphatic system and meningeal lymphatics. *J Clin Invest* 2017;127:3210–9.
12. Esposito DP, Goldenberg FD, Frank JI, *et al.* Permanent cerebrospinal fluid diversion in subarachnoid hemorrhage: influence of physician practice style. *Surg Neurol Int* 2011;2:117.
13. Klopfenstein JD, Kim LJ, Feiz-Erfan I, *et al.* Comparison of rapid and gradual weaning from external ventricular drainage in patients with aneurysmal subarachnoid hemorrhage: a prospective randomized trial. *J Neurosurg* 2004;100:225–9.
14. Woernle CM, Winkler KML, Burkhardt J-K, *et al.* Hydrocephalus in 389 patients with aneurysm-associated subarachnoid hemorrhage. *J Clin Neurosci* 2013;20:824–6.
15. Yamada S, Ishikawa M, Yamamoto K. Fluid distribution pattern in adult-onset congenital, idiopathic, and secondary normal-pressure hydrocephalus: implications for clinical care. *Front Neurol* 2017;8:1–8.
16. Fried HI, Nathan BR, Rowe AS, *et al.* The insertion and management of external ventricular drains: an evidence-based consensus statement. *Neurocrit Care* 2016;24:61–81.
17. Chung DY, Mayer SA, Rordorf GA. External ventricular drains after subarachnoid hemorrhage: is less more? *Neurocrit Care* 2018;28:157–61.
18. Moher D, Liberati A, Tetzlaff J, *et al.* Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009;62:1006–12.
19. Higgins J, Green S. *Cochrane Handbook for systematic reviews of interventions* version 5.1.0; 2011. <http://handbook.cochrane.org>
20. Gamble C, Hollis S. Uncertainty method improved on best-worst case analysis in a binary meta-analysis. *J Clin Epidemiol* 2005;58:579–88.
21. Fergusson D, Aaron SD, Guyatt G, *et al.* Post-Randomisation exclusions: the intention to treat principle and excluding patients from analysis. *BMJ* 2002;325:652–4.
22. Jakobsen JC, Wetterslev J, Winkel P, *et al.* Thresholds for statistical and clinical significance in systematic reviews with meta-analytic methods. *BMC Med Res Methodol* 2014;14:1–13.
23. Chan A-W, Karmela Krieža-Jerić, Schmid I. Outcome reporting bias in randomized trials funded by the Canadian Institutes of health research. *Can Med Assoc J* 2004;171:735–40.
24. Wetterslev J, Thorlund K, Brok J, *et al.* Estimating required information size by quantifying diversity in random-effects model meta-analyses. *BMC Med Res Methodol* 2009;9:1–12.
25. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539–58.
26. Dickersin K. The existence of publication bias and risk factors for its occurrence. *JAMA* 1990;263:1385–9.
27. Stuck AE, Rubenstein LZ, Wieland D, *et al.* Bias in meta-analysis detected by a simple, graphical. *BMJ* 1998;316:469–70.
28. Bekelman JE, Li Y, Gross CP. Scope and impact of financial conflicts of interest in biomedical research: a systematic review. *JAMA* 2003;289:454–65.
29. Rasmussen K, Bero L, Redberg R, *et al.* Collaboration between Academics and industry in clinical trials: cross sectional study of publications and survey of lead academic authors. *BMJ* 2018;363.
30. Jakobsen JC, Wetterslev J, Lange T, *et al.* Viewpoint: taking into account risks of random errors when analysing multiple outcomes in systematic reviews. *Cochrane Database Syst Rev* 2016;3:ED000111.
31. Keus F, Wetterslev J, Gluud C, *et al.* Robustness assessments are needed to reduce bias in meta-analyses that include zero-event randomized trials. *Am J Gastroenterol* 2009;104:546–51.
32. Sutton AJ, Cooper NJ, Lambert PC, *et al.* Meta-analysis of rare and adverse event data. *Expert Rev Pharmacoecon Outcomes Res* 2002;2:367–79.
33. Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? use and avoidance of continuity corrections in meta-analysis of sparse data. *Stat Med* 2004;23:1351–75.
34. Brok J, Thorlund K, Gluud C, *et al.* Trial sequential analysis reveals insufficient information size and potentially false positive results in many meta-analyses. *J Clin Epidemiol* 2008;61:763–9.
35. Brok J, Thorlund K, Wetterslev J, *et al.* Apparently conclusive meta-analyses may be inconclusive--Trial sequential analysis adjustment of random error risk due to repetitive testing of accumulating data in apparently conclusive neonatal meta-analyses. *Int J Epidemiol* 2009;38:287–98.
36. Wetterslev J, Jakobsen JC, Gluud C. Trial sequential analysis in systematic reviews with meta-analysis. *BMC Med Res Methodol* 2017;17:1–18.
37. Wetterslev J, Thorlund K, Brok J, *et al.* Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. *J Clin Epidemiol* 2008;61:64–75.
38. Lan DeMets discrete sequential boundaries 1983.
39. Pogue JM, Yusuf S. Cumulating evidence from randomized trials: utilizing sequential monitoring boundaries for cumulative meta-analysis. *Control Clin Trials* 1997;18:580–93.
40. Pogue J, Yusuf S. Overcoming the limitations of current meta-analysis of randomised controlled trials. *The Lancet* 1998;351:47–52.
41. Altman DG, Bland JM. Interaction revisited: the difference between two estimates. *BMJ* 2003;326:219.
42. Guyatt GH, Oxman AD, Kunz R, *et al.* GRADE guidelines 6. Rating the quality of evidence--imprecision. *J Clin Epidemiol* 2011;64:1283–93.